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STAFF REPORT to the NIDA DIRECTOR

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RESEARCH FINDINGS

BASIC AND BEHAVIORAL RESEARCH

Visualizing Hypothalamic Network Dynamics For Appetitive and Consummatory Behaviors
Jennings JH, Ung RL, Resendez SL, Stamatakis AM, Taylor JG, Huang J, Veleta K, Kantak PA, Aita M, Shilling-Scrivo K, Ramakrishnan C, Deisseroth K, Otte S, Stuber GD. Cell 2015; 160(3): 516-527.
Optimally orchestrating complex behavioral states, such as the pursuit and consumption of food, is critical for an organism's survival. The lateral hypothalamus (LH) is a neuroanatomical region essential for appetitive and consummatory behaviors, but whether individual neurons within the LH differentially contribute to these interconnected processes is unknown. Here, the authors show that selective optogenetic stimulation of a molecularly defined subset of LH GABAergic (Vgat-expressing) neurons enhances both appetitive and consummatory behaviors, whereas genetic ablation of these neurons reduced these phenotypes. Furthermore, this targeted LH subpopulation is distinct from cells containing the feeding-related neuropeptides, melanin-concentrating hormone (MCH), and orexin (Orx). Employing in vivo calcium imaging in freely behaving mice to record activity dynamics from hundreds of cells, we identified individual LH GABAergic neurons that preferentially encode aspects of either appetitive or consummatory behaviors, but rarely both. These tightly regulated, yet highly intertwined, behavioral processes are thus dissociable at the cellular level.

Integrative Analysis Of 111 Reference Human Epigenomes Roadmap Epigenomics Consortium, Kundaje A, Meuleman W, Ernst J, Bilenky M, Yen A, Heravi-Moussavi A, Kheradpour P, Zhang Z, Wang J, Ziller MJ, Amin V, Whitaker JW, Schultz MD, Ward LD, Sarkar A, Quon G, Sandstrom RS, Eaton ML, Wu Y-C, Pfenning AR, Wang X, Claussnitzer M, Liu Y, Coarfa C, Harris RA, Shoresh N, Epstein CB, Gjoneska E, Leung D, Xie W, Hawkins RD, Lister R, Hong C, Gascard P, Mungall AJ, Moore R, Chuah E, Tam A, Canfield TK, Hansen RS, Kaul R, Sabo PJ, Bansal MS, Carles A, Dixon JR, Farh K-H, Feizi S, Karlic R, Kim A-R, Kulkarni A, Li D, Lowdon R, Elliott G, Mercer TR, Neph SJ, Onuchic V, Polak P, Rajagopal N, Ray P, Sallari RC, Siebenthall KT, Sinnott-Armstrong NA, Stevens M, Thurman RE, Wu J, Zhang B, Zhou X, Beaudet AE, Boyer LA, De Jager PL, Farnham PJ, Fisher SJ, Haussler D, Jones SJM, Li W, Marra MA, McManus MT, Sunyaev S, Thomson JA, Tlsty TD, Tsai L-H, Wang W, Waterland RA, Zhang MQ, Chadwick LH, Bernstein BE, Costello JF, Ecker JR, Hirst M, Meissner A, Milosavljevic A, Ren B, Stamatoyannopoulos JA, Wang T, Kellis M. Nature 2015; 518(7539): 317-330.
The reference human genome sequence set the stage for studies of genetic variation and its association with human disease, but epigenomic studies lack a similar reference. To address this need, the NIH Roadmap Epigenomics Consortium generated the largest collection so far of human epigenomes for primary cells and tissues. Here the authors describe the integrative analysis of 111 reference human epigenomes generated as part of the programme, profiled for histone modification patterns, DNA accessibility, DNA methylation and RNA expression. They establish global maps of regulatory elements, define regulatory modules of coordinated activity, and their likely activators and repressors. They show that disease- and trait-associated genetic variants are enriched in tissue-specific epigenomic marks, revealing biologically relevant cell types for diverse human traits, and providing a resource for interpreting the molecular basis of human disease. These results

demonstrate the central role of epigenomic information for understanding gene regulation, cellular differentiation and human disease.

Effects of Fatty Acid Amide Hydrolase (FAAH) Inhibitors in Non-Human Primate Models of Nicotine Reward and Relapse Justinova Z, Panlilio LV, Moreno-Sanz G, Redhi GH, Auber A, Secci ME, Mascia P, Bandiera T, Armirotti A, Bertorelli R, Chefer SI, Barnes C, Yasar S, Piomelli D, Goldberg SR. Neuropsychopharmacology. 2015 Mar 10. [Epub ahead of print].
Inhibition of the enzyme fatty acid amide hydrolase (FAAH) counteracts reward-related effects of nicotine in rats, but has not been tested for this purpose in non-human primates. Therefore, the authors studied the effects of the first- and second-generation O-arylcarbamate-based FAAH inhibitors, URB597 (cyclohexyl carbamic acid 3'-carbamoyl-3-yl ester) and URB694 (6-hydroxy-[1,1'-biphenyl]-3-yl-cyclohexylcarbamate), in squirrel monkeys. Both FAAH inhibitors: 1) blocked FAAH activity in brain and liver, increasing levels of endogenous ligands for cannabinoid and alpha-type peroxisome proliferator-activated (PPAR-α) receptors; 2) shifted nicotine self-administration dose-response functions in a manner consistent with reduced nicotine reward; 3) blocked reinstatement of nicotine seeking induced by re-exposure to either nicotine priming or nicotine-associated cues; and 4) had no effect on cocaine or food self-administration. The effects of FAAH inhibition on nicotine self-administration and nicotine priming-induced reinstatement were reversed by the PPAR-α antagonist, MK886. Unlike URB597, which was not self-administered by monkeys in an earlier study, URB694 was self-administered at a moderate rate. URB694 self-administration was blocked by pretreatment with an antagonist for either PPAR-α (MK886) or cannabinoid CB_1 receptors (rimonabant). In additional experiments in rats, URB694 was devoid of THC-like or nicotine-like interoceptive effects under drug-discrimination procedures, and neither FAAH inhibitor induced dopamine release in the nucleus accumbens shell-consistent with their lack of robust reinforcing effects in monkeys. Overall, both URB597 and URB694 show promise for the initialization and maintenance of smoking cessation, due to their ability to block the rewarding effects of nicotine and prevent nicotine priming-induced and cue-induced reinstatement.

Optogenetic Excitation Of Central Amygdala Amplifies and Narrows Incentive Motivation To Pursue One Reward Above Another Robinson MJF, Warlow SM, Berridge KC. J Neurosci 2014; 34(50): 16567-16580.
Choosing one reward above another is important for achieving adaptive life goals. Yet hijacked into excessive intensity in disorders such as addiction, single-minded pursuit becomes maladaptive. Here, the authors report that optogenetic channelrhodopsin stimulation of neurons in central nucleus of amygdala (CeA), paired with earning a particular sucrose reward in rats, amplified and narrowed incentive motivation to that single reward target. Therefore, CeA rats chose and intensely pursued only the laser-paired sucrose reward while ignoring an equally good sucrose alternative. In contrast, reward-paired stimulation of basolateral amygdala did not hijack choice. In a separate measure of incentive motivation, CeA stimulation also increased the progressive ratio breakpoint or level of effort exerted to obtain sucrose reward. However, CeA stimulation by itself failed to support behavioral self-stimulation in the absence of any paired external food reward, suggesting that CeA photo-excitation specifically transformed the value of its external reward (rather than adding an internal reinforcement state). Nor did CeA stimulation by itself induce any aversive state that motivated escape. Finally, CeA stimulation also failed to enhance 'liking' reactions elicited by sucrose taste and did not simply increase the general motivation to eat. This pattern suggests that

CeA photo-excitation specifically enhances and narrows incentive motivation to pursue an associated external reward at the expense of another comparable reward.

Large-Scale Topology and The Default Mode Network In the Mouse Connectome Stafford JM, Jarrett BR, Miranda-Dominguez O, Mills BD, Cain N, Mihalas S, Lahvis GP, Lattal KM, Mitchell SH, David SV, Fryer JD, Nigg JT, Fair DA. Proc Natl Acad Sci USA 2014; 111(52): 18745-18750.
Noninvasive functional imaging holds great promise for serving as a translational bridge between human and animal models of various neurological and psychiatric disorders. However, despite a depth of knowledge of the cellular and molecular underpinnings of atypical processes in mouse models, little is known about the large-scale functional architecture measured by functional brain imaging, limiting translation to human conditions. Here, the authors provide a robust processing pipeline to generate high-resolution, whole-brain resting-state functional connectivity MRI (rs-fcMRI) images in the mouse. Using a mesoscale structural connectome (i.e., an anterograde tracer mapping of axonal projections across the mouse CNS), the authors show that rs-fcMRI in the mouse has strong structural underpinnings, validating our procedures. They next directly show that large-scale network properties previously identified in primates are present in rodents, although they differ in several ways. Last, they examine the existence of the so-called default mode network (DMN)--a distributed functional brain system identified in primates as being highly important for social cognition and overall brain function and atypically functionally connected across a multitude of disorders. The authors show the presence of a potential DMN in the mouse brain both structurally and functionally. Together, these studies confirm the presence of basic network properties and functional networks of high translational importance in structural and functional systems in the mouse brain. This work clears the way for an important bridge measurement between human and rodent models, enabling us to make stronger conclusions about how regionally specific cellular and molecular manipulations in mice relate back to humans.

Structural Basis For Bifunctional Peptide Recognition At Human δ-Opioid Receptor Fenalti G, Zatsepin NA, Betti C, Giguere P, Han GW, Ishchenko A, Liu W, Guillemyn K, Zhang H, James D, Wang D, Weierstall U, Spence JCH, Boutet S, Messerschmidt M, Williams GJ, Gati C, Yefanov OM, White TA, Oberthuer D, Metz M, Yoon CH, Barty A, Chapman HN, Basu S, Coe J, Conrad CE, Fromme R, Fromme P, Tourwe D, Schiller PW, Roth BL, Ballet S, Katritch V, Stevens RC, Cherezov V. Nat Struct Mol Biol 2015; 22(3): 265-268.
Bifunctional μ- and δ-opioid receptor (OR) ligands are potential therapeutic alternatives, with diminished side effects, to alkaloid opiate analgesics. The authors solved the structure of human δ-OR bound to the bifunctional δ-OR antagonist and μ-OR agonist tetrapeptide H-Dmt-Tic-Phe-Phe-NH2 (DIPP-NH2) by serial femtosecond crystallography, revealing a cis-peptide bond between H-Dmt and Tic. The observed receptor-peptide interactions are critical for understanding of the pharmacological profiles of opioid peptides and for development of improved analgesics.

Mutations at Tyrosine 88, Lysine 92 and Tyrosine 470 of Human Dopamine Transporter Result in an Attenuation of HIV-1 Tat-Induced Inhibition of Dopamine Transport Midde NM, Yuan Y, Quizon PM, Sun W-L, Huang X, Zhan C-G, Zhu J. J Neuroimmune Pharmacol 2015; 10(1): 122-135.
HIV-1 transactivator of transcription (Tat) protein disrupts the dopamine (DA) neurotransmission by inhibiting DA transporter (DAT) function, leading to increased neurocognitive impairment in HIV-1 infected individuals. Through integrated computational modeling and pharmacological

studies, the authors have demonstrated that mutation of tyrosine470 (Y470H) of human DAT (hDAT) attenuates Tat-induced inhibition of DA uptake by changing the transporter conformational transitions. The present study examined the functional influences of other substitutions at tyrosine470 (Y470F and Y470A) and tyrosine88 (Y88F) and lysine92 (K92M), two other relevant residues for Tat binding to hDAT, in Tat-induced inhibitory effects on DA transport. Y88F, K92M and Y470A attenuated Tat-induced inhibition of DA transport, implicating the functional relevance of these residues for Tat binding to hDAT. Compared to wild type hDAT, Y470A and K92M but not Y88F reduced the maximal velocity of [(3)H]DA uptake without changes in the Km. Y88F and K92M enhanced IC50 values for DA inhibition of [(3)H]DA uptake and [(3)H]WIN35,428 binding but decreased IC50 for cocaine and GBR12909 inhibition of [(3)H]DA uptake, suggesting that these residues are critical for substrate and these inhibitors. Y470F, Y470A, Y88F and K92M attenuated zinc-induced increase of [(3)H]WIN35,428 binding. Moreover, only Y470A and K92M enhanced DA efflux relative to wild type hDAT, suggesting mutations of these residues differentially modulate transporter conformational transitions. These results demonstrate Tyr88 and Lys92 along with Tyr470 as functional recognition residues in hDAT for Tat-induced inhibition of DA transport and provide mechanistic insights into identifying target residues on the DAT for Tat binding.

Endocannabinoid Catabolic Enzymes Play Differential Roles in Thermal Homeostasis in Response to Environmental or Immune Challenge Nass SR, Long JZ, Schlosburg JE, Cravatt BF, Lichtman AH, Kinsey SG. J Neuroimmune Pharmacol. 2015 Feb 27. [Epub ahead of print].
Cannabinoid receptor agonists, such as Δ9-THC, the primary active constituent of Cannabis sativa, have anti-pyrogenic effects in a variety of assays. Recently, attention has turned to the endogenous cannabinoid system and how endocannabinoids, including 2-arachidonoylglycerol (2-AG) and anandamide, regulate multiple homeostatic processes, including thermoregulation. Inhibiting endocannabinoid catabolic enzymes, monoacylglycerol lipase (MAGL) or fatty acid amide hydrolase (FAAH), elevates levels of 2-AG or anandamide in vivo, respectively. The purpose of this experiment was to test the hypothesis that endocannabinoid catabolic enzymes function to maintain thermal homeostasis in response to hypothermic challenge. In separate experiments, male C57BL/6J mice were administered a MAGL or FAAH inhibitor, and then challenged with the bacterial endotoxin lipopolysaccharide (LPS; 2 mg/kg ip) or a cold (4 °C) ambient environment. Systemic LPS administration caused a significant decrease in core body temperature after 6 h, and this hypothermia persisted for at least 12 h. Similarly, cold environment induced mild hypothermia that resolved within 30 min. JZL184 exacerbated hypothermia induced by either LPS or cold challenge, both of which effects were blocked by rimonabant, but not SR144528, indicating a CB1 cannabinoid receptor mechanism of action. In contrast, the FAAH inhibitor, PF-3845, had no effect on either LPS-induced or cold-induced hypothermia. These data indicate that unlike direct acting cannabinoid receptor agonists, which elicit profound hypothermic responses on their own, neither MAGL nor FAAH inhibitors affect normal body temperature. However, these endocannabinoid catabolic enzymes play distinct roles in thermoregulation following hypothermic challenges.

Dopamine-Associated Cached Values Are Not Sufficient As the Basis For Action Selection Hollon NG, Arnold MM, Gan JO, Walton ME, Phillips PEM. Proc Natl Acad Sci USA 2014; 111(51): 18357-18362.
Phasic dopamine transmission is posited to act as a critical teaching signal that updates the stored (or "cached") values assigned to reward-predictive stimuli and actions. It is widely hypothesized that these cached values determine the selection among multiple courses of action, a premise that

has provided a foundation for contemporary theories of decision making. In the current work the authors used fast-scan cyclic voltammetry to probe dopamine-associated cached values from cue-evoked dopamine release in the nucleus accumbens of rats performing cost-benefit decision-making paradigms to evaluate critically the relationship between dopamine-associated cached values and preferences. By manipulating the amount of effort required to obtain rewards of different sizes, the authors were able to bias rats toward preferring an option yielding a high-value reward in some sessions and toward instead preferring an option yielding a low-value reward in others. Therefore, this approach permitted the investigation of dopamine-associated cached values in a context in which reward magnitude and subjective preference were dissociated. The authors observed greater cue-evoked mesolimbic dopamine release to options yielding the high-value reward even when rats preferred the option yielding the low-value reward. This result identifies a clear mismatch between the ordinal utility of the available options and the rank ordering of their cached values, thereby providing robust evidence that dopamine-associated cached values cannot be the sole determinant of choices in simple economic decision making.

Evolutionary Genomics. Evolutionary Changes In Promoter and Enhancer Activity During Human Corticogenesis Reilly SK, Yin J, Ayoub AE, Emera D, Leng J, Cotney J, Sarro R, Rakic P, Noonan JP. Science 2015; 347(6226): 1155-1159.
Human higher cognition is attributed to the evolutionary expansion and elaboration of the human cerebral cortex. However, the genetic mechanisms contributing to these developmental changes are poorly understood. The authors used comparative epigenetic profiling of human, rhesus macaque, and mouse corticogenesis to identify promoters and enhancers that have gained activity in humans. These gains are significantly enriched in modules of coexpressed genes in the cortex that function in neuronal proliferation, migration, and cortical-map organization. Gain-enriched modules also showed correlated gene expression patterns and similar transcription factor binding site enrichments in promoters and enhancers, suggesting that they are connected by common regulatory mechanisms. These results reveal coordinated patterns of potential regulatory changes associated with conserved developmental processes during corticogenesis, providing insight into human cortical evolution.

13-Methylarachidonic Acid Is A Positive Allosteric Modulator Of Endocannabinoid Oxygenation By Cyclooxygenase Kudalkar SN, Nikas SP, Kingsley PJ, Xu S, Galligan JJ, Rouzer CA, Banerjee S, Ji L, Eno MR, Makriyannis A, Marnett LJ. J Biol Chem. 2015 Mar 20; 290(12): 7897-7909.
Cyclooxygenase-2 (COX-2) oxygenates arachidonic acid (AA) and the endocannabinoids 2-arachidonoylglycerol (2-AG) and arachidonylethanolamide to prostaglandins, prostaglandin glyceryl esters, and prostaglandin ethanolamides, respectively. A structural homodimer, COX-2 acts as a conformational heterodimer with a catalytic and an allosteric monomer. Prior studies have demonstrated substrate-selective negative allosteric regulation of 2-AG oxygenation. Here the authors describe AM-8138 (13(S)-methylarachidonic acid), a substrate-selective allosteric potentiator that augments 2-AG oxygenation by up to 3.5-fold with no effect on AA oxygenation. In the crystal structure of an AM-8138·COX-2 complex, AM-8138 adopts a conformation similar to the unproductive conformation of AA in the substrate binding site. Kinetic analysis suggests that binding of AM-8138 to the allosteric monomer of COX-2 increases 2-AG oxygenation by increasing kcat and preventing inhibitory binding of 2-AG. AM-8138 restored the activity of COX-2 mutants that exhibited very poor 2-AG oxygenating activity and increased the activity of COX-1 toward 2-AG. Competition of AM-8138 for the allosteric site prevented the inhibition of COX-2-

dependent 2-AG oxygenation by substrate-selective inhibitors and blocked the inhibition of AA or 2-AG oxygenation by nonselective time-dependent inhibitors. AM-8138 selectively enhanced 2-AG oxygenation in intact RAW264.7 macrophage-like cells. Thus, AM-8138 is an important new tool compound for the exploration of allosteric modulation of COX enzymes and their role in endocannabinoid metabolism.

Which Foods May Be Addictive? The Roles Of Processing, Fat Content, and Glycemic Load
Schulte EM, Avena NM, Gearhardt AN. PLoS One 2015; 10(2): e0117959.
The authors propose that highly processed foods share pharmacokinetic properties (e.g. concentrated dose, rapid rate of absorption) with drugs of abuse, due to the addition of fat and/or refined carbohydrates and the rapid rate the refined carbohydrates are absorbed into the system, indicated by glycemic load (GL). The current study provides preliminary evidence for the foods and food attributes implicated in addictive-like eating. This was a cross-sectional study conducted in a University (Study One) and a community (Study Two). 120 undergraduates participated in Study One and 384 participants recruited through Amazon MTurk participated in Study Two. In Study One, participants (n = 120) completed the Yale Food Addiction Scale (YFAS) followed by a forced-choice task to indicate which foods, out of 35 foods varying in nutritional composition, were most associated with addictive-like eating behaviors. Using the same 35 foods, Study Two utilized hierarchical linear modeling to investigate which food attributes (e.g., fat grams) were related to addictive-like eating behavior (at level one) and explored the influence of individual differences for this association (at level two). In Study One, processed foods, higher in fat and GL, were most frequently associated with addictive-like eating behaviors. In Study Two, processing was a large, positive predictor for whether a food was associated with problematic, addictive-like eating behaviors. BMI and YFAS symptom count were small-to-moderate, positive predictors for this association. In a separate model, fat and GL were large, positive predictors of problematic food ratings. YFAS symptom count was a small, positive predictor of the relationship between GL and food ratings. The current study provides preliminary evidence that not all foods are equally implicated in addictive-like eating behavior, and highly processed foods, which may share characteristics with drugs of abuse (e.g. high dose, rapid rate of absorption) appear to be particularly associated with "food addiction."

Fatty Acid Binding Proteins (FABPs) are Intracellular Carriers for Δ9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) Elmes MW, Kaczocha M, Berger WT, Leung K, Ralph BP, WangL, Sweeney JM, Miyauchi JT, Tsirka SE, Ojima I, Deutsch DG. J Biol Chem. 2015 Feb 9. [Epub ahead of print].
Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) occur naturally in marijuana (Cannabis) and may be formulated, individually or in combination in pharmaceuticals such as Marinol or Sativex. While it is known that these hydrophobic compounds can be transported in blood by albumin or lipoproteins, intracellular carrier have not been identified. Recent reports suggest that CBD and THC elevates the levels of the endocannabinoid anandamide (AEA) when administered to humans, suggesting that phytocannabinoids target cellular proteins involved in endocannabinoid clearance. Fatty acid binding proteins (FABPs) are intracellular proteins that mediate AEA transport to its catabolic enzyme fatty acid amide hydrolase (FAAH). By computational analysis and ligand displacement assays, the authors show that at least three human FABPs bind THC and CBD and they demonstrate that THC and CBD inhibit the cellular uptake and catabolism of AEA by targeting FABPs. Furthermore, they show that in contrast to rodent FAAH, CBD does not inhibit the

enzymatic actions of human FAAH, and thus FAAH inhibition cannot account for the observed increase in circulating AEA in humans following CBD consumption. Using computational molecular docking and site-directed mutagenesis the authors identify key residues within the active site of FAAH that confer the species-specific sensitivity to inhibition by CBD. Competition for FABPs may in part or wholly explain the increased circulating levels of endocannabinoids reported after consumption of cannabinoids. These data shed light on the mechanism of action of CBD in modulating the endocannabinoid tone in vivo and may explain, in part, its reported efficacy towards epilepsy and other neurological disorders.

Knockdown Of Ventral Tegmental Area Mu-Opioid Receptors In Rats Prevents Effects Of Social Defeat Stress: Implications For Amphetamine Cross-Sensitization, Social Avoidance, Weight Regulation and Expression Of Brain-Derived Neurotrophic Factor Johnston CE, Herschel DJ, Lasek AW, Hammer Jr RP, Nikulina EM. Neuropharmacology 2015; 89: 325-334.
Social defeat stress causes social avoidance and long-lasting cross-sensitization to psychostimulants, both of which are associated with increased brain-derived neurotrophic factor (BDNF) expression in the ventral tegmental area (VTA). Moreover, social stress upregulates VTA mu-opioid receptor (MOR) mRNA. In the VTA, MOR activation inhibits GABA neurons to disinhibit VTA dopamine neurons, thus providing a role for VTA MORs in the regulation of psychostimulant sensitization. The present study determined the effect of lentivirus-mediated MOR knockdown in the VTA on the consequences of intermittent social defeat stress, a salient and profound stressor in humans and rodents. Social stress exposure induced social avoidance and attenuated weight gain in animals with non-manipulated VTA MORs, but both these effects were prevented by VTA MOR knockdown. Rats with non-manipulated VTA MOR expression exhibited cross-sensitization to amphetamine challenge (1.0 mg/kg, i.p.), evidenced by a significant augmentation of locomotion. By contrast, knockdown of VTA MORs prevented stress-induced cross-sensitization without blunting the locomotor-activating effects of amphetamine. At the time point corresponding to amphetamine challenge, immunohistochemical analysis was performed to examine the effect of stress on VTA BDNF expression. Prior stress exposure increased VTA BDNF expression in rats with non-manipulated VTA MOR expression, while VTA MOR knockdown prevented stress-induced expression of VTA BDNF. Taken together, these results suggest that upregulation of VTA MOR is necessary for the behavioral and biochemical changes induced by social defeat stress. Elucidating VTA MOR regulation of stress effects on the mesolimbic system may provide new therapeutic targets for treating stress-induced vulnerability to substance abuse.

Examination Of the Metabolite Hydroxybupropion In the Reinforcing and Aversive Stimulus Effects Of Nicotine In Rats Malcolm E, Carroll FI, Blough B, Damaj MI, Shoaib M. Psychopharmacology (Berl). 2015 Mar 13. [Epub ahead of print].
Preclinical studies with bupropion in rodent models of nicotine dependence have generated equivocal findings with regard to translating the clinical efficacy of the antidepressant as a smoking cessation agent. Given that rats are poor metabolizers of bupropion, the present experiments examined (2S,3S)-hydroxybupropion, the major active metabolite, on the positive reinforcing and aversive stimulus properties of nicotine in rats. In male hooded Lister rats, (2S,3S)-hydroxybupropion (1.0-10.0 mg/kg IP) was tested on intravenous nicotine (0.03 mg/kg/inf) self-administration behaviour for three sessions (n = 8), and in another experiment, the same doses of (2S,3S)-hydroxybupropion were tested in a conditioned taste aversion procedure to assess the aversive stimulus properties of nicotine, a function implicated in the regulation of nicotine intake.

(2S,3S)-hydroxybupropion attenuated nicotine intake in a manner similar to that produced by mecamylamine pretreatment (1.0 mg/kg SC). This effect on nicotine-taking was specific since these doses had no effect on responding maintained by sucrose presented orally (200 µl of 5 % w/v). (2S,3S)-hydroxybupropion (1, 3 and 10 mg/kg IP) pretreatment failed to modify the aversive effects produced by a small dose of nicotine (0.1 mg/kg SC). These results demonstrate this metabolite to specifically modify the positive reinforcing effects of nicotine without affecting its aversive motivational effects. We propose that the clinical efficacy of bupropion may be due to a combination of effects produced by bupropion and/or its active metabolite (2S,3S)-hydroxybupropion involving the inhibition of reuptake of dopamine and noradrenaline in reward centres of the brain and the noncompetitive antagonism of neuronal nicotinic receptors.

Locus-Specific Epigenetic Remodeling Controls Addiction- and Depression-Related Behaviors Heller EA, Cates HM, Pena CJ, Sun H, Shao N, Feng J, Golden SA, Herman JP, Walsh JJ, Mazei-Robison M, Ferguson D, Knight S, Gerber MA, Nievera C, Han M-H, Russo SJ, Tamminga CS, Neve RL, Shen L, Zhang HS, Zhang F, Nestler EJ. Nat Neurosci 2014; 17(12): 1720-1727.
Chronic exposure to drugs of abuse or stress regulates transcription factors, chromatin-modifying enzymes and histone post-translational modifications in discrete brain regions. Given the promiscuity of the enzymes involved, it has not yet been possible to obtain direct causal evidence to implicate the regulation of transcription and consequent behavioral plasticity by chromatin remodeling that occurs at a single gene. The authors investigated the mechanism linking chromatin dynamics to neurobiological phenomena by applying engineered transcription factors to selectively modify chromatin at a specific mouse gene in vivo. They found that histone methylation or acetylation at the Fosb locus in nucleus accumbens, a brain reward region, was sufficient to control drug- and stress-evoked transcriptional and behavioral responses via interactions with the endogenous transcriptional machinery. This approach allowed us to relate the epigenetic landscape at a given gene directly to regulation of its expression and to its subsequent effects on reward behavior.

Sign-Tracking Predicts Increased Choice Of Cocaine Over Food In Rats Tunstall BJ, Kearns DN. Behav Brain Res 2015; 281: 222-228.
The purpose of this study was to determine whether the tendency to sign-track to a food cue was predictive of rats' choice of cocaine over food. First, rats were trained on a procedure where insertion of a retractable lever was paired with food. A sub-group of rats - sign-trackers - primarily approached and contacted the lever, while another sub-group - goal-trackers - approached the site of food delivery. Rats were then trained on a choice task where they could choose between an infusion of cocaine (1.0 mg/kg) and a food pellet (45 mg). Sign-trackers chose cocaine over food significantly more often than did goal-trackers. These results support the incentive-salience theory of addiction and add to a growing number of studies which suggest that sign-trackers may model an addiction-prone phenotype.

Epigenetic Basis Of Opiate Suppression Of BDNF Gene Expression In the Ventral Tegmental Area Koo JW, Mazei-Robison MS, LaPlant Q, Egervari G, Braunscheidel KM, Adank DN, Ferguson D, Feng J, Sun H, Scobie KN, Damez-Werno DM, Ribeiro E, Pena CJ, Walker D, Bagot RC, Cahill ME, Anderson SAR, Labonte B, Hodes GE, Browne H, Chadwick B, Robison AJ, Vialou VF, Dias C, Lorsch Z, Mouzon E, Lobo MK, Dietz DM, Russo SJ, Neve RL, Hurd YL, Nestler EJ. Nat Neurosci 2015; 18(3): 415-422.

Brain-derived neurotrophic factor (BDNF) has a crucial role in modulating neural and behavioral plasticity to drugs of abuse. The authors found a persistent downregulation of exon-specific BDNF expression in the ventral tegmental area (VTA) in response to chronic opiate exposure, which was mediated by specific epigenetic modifications at the corresponding BDNF gene promoters. Exposure to chronic morphine increased stalling of RNA polymerase II at these BDNF promoters in VTA and altered permissive and repressive histone modifications and occupancy of their regulatory proteins at the specific promoters. Furthermore, the authors found that morphine suppressed binding of phospho-CREB (cAMP response element binding protein) to BDNF promoters in VTA, which resulted from enrichment of trimethylated H3K27 at the promoters, and that decreased NURR1 (nuclear receptor related-1) expression also contributed to BDNF repression and associated behavioral plasticity to morphine. These findings suggest previously unknown epigenetic mechanisms of morphine-induced molecular and behavioral neuroadaptations.

Cannabinoid Receptor-Interacting Protein 1a Modulates CB1 Receptor Signaling and Regulation Smith TH, Blume LC, Straiker A, Cox JO, David BG, McVoy JRS, Sayers KW, Poklis JL, Abdullah RA, Egertova M, Chen C-K, Mackie K, Elphick MR, Howlett AC, Selley DE. Mol Pharmacol 2015; 87(4): 747-765.
Cannabinoid CB1 receptors (CB1Rs) mediate the presynaptic effects of endocannabinoids in the central nervous system (CNS) and most behavioral effects of exogenous cannabinoids. Cannabinoid receptor-interacting protein 1a (CRIP1a) binds to the CB1R C-terminus and can attenuate constitutive CB1R-mediated inhibition of Ca(2+) channel activity. The authors now demonstrate cellular colocalization of CRIP1a at neuronal elements in the CNS and show that CRIP1a inhibits both constitutive and agonist-stimulated CB1R-mediated guanine nucleotide-binding regulatory protein (G-protein) activity. Stable overexpression of CRIP1a in human embryonic kidney (HEK)-293 cells stably expressing CB1Rs (CB1-HEK), or in N18TG2 cells endogenously expressing CB1Rs, decreased CB1R-mediated G-protein activation (measured by agonist-stimulated [(35)S]GTPγS (guanylyl-5'-[O-thio]-triphosphate) binding) in both cell lines and attenuated inverse agonism by rimonabant in CB1-HEK cells. Conversely, small-interfering RNA-mediated knockdown of CRIP1a in N18TG2 cells enhanced CB1R-mediated G-protein activation. These effects were not attributable to differences in CB1R expression or endocannabinoid tone because CB1R levels did not differ between cell lines varying in CRIP1a expression, and endocannabinoid levels were undetectable (CB1-HEK) or unchanged (N18TG2) by CRIP1a overexpression. In CB1-HEK cells, 4-hour pretreatment with cannabinoid agonists downregulated CB1Rs and desensitized agonist-stimulated [(35)S]GTPγS binding. CRIP1a overexpression attenuated CB1R downregulation without altering CB1R desensitization. Finally, in cultured autaptic hippocampal neurons, CRIP1a overexpression attenuated both depolarization-induced suppression of excitation and inhibition of excitatory synaptic activity induced by exogenous application of cannabinoid but not by adenosine A1 agonists. These results confirm that CRIP1a inhibits constitutive CB1R activity and demonstrate that CRIP1a can also inhibit agonist-stimulated CB1R signaling and downregulation of CB1Rs. Thus, CRIP1a appears to act as a broad negative regulator of CB1R function.

GABAergic Transmission and Enhanced Modulation By Opioids and Endocannabinoids In Adult Rat Rostral Ventromedial Medulla Li MH, Suchland KL, Ingram SL. J Physiol. 2015 Jan 1; 593(1): 217-230.
Electrical stimulation of the rostral ventromedial medulla (RVM) facilitates pain behaviours in neonates but inhibits these behaviours in adults. The cellular mechanisms underlying these changes in RVM modulation of pain behaviours are not known. The authors optimized whole-cell patch-clamp recordings for RVM neurons in animals older than postnatal day 30 and compared the results to postnatal day 10-21 animals. Their results demonstrate that the γ-aminobutyric acid (GABA) release is lower and opioid effects are more evident in adult rats compared to early postnatal rats. A cannabinoid receptor antagonist significantly increased GABA release in mature but not in immature RVM neurons suggesting the presence of local endocannabinoid tone in mature RVM. Neurons in the rostral ventromedial medulla (RVM) play critical and complex roles in pain modulation. Recent studies have shown that electrical stimulation of the RVM produces pain facilitation in young animals (postnatal (PN) day < 21) but predominantly inhibits pain behaviours in adults. The cellular mechanisms underlying these changes in RVM modulation of pain behaviours are not known. This is in part because whole-cell patch-clamp studies in RVM to date have been in young (PN day < 18) animals because the organization and abundance of myelinated fibres in this region make the RVM a challenging area for whole-cell patch-clamp recording in adults. Several neurotransmitter systems, including GABAergic neurotransmission, undergo developmental changes that mature by PN day 21. Thus, the authors focused on optimizing whole-cell patch-clamp recordings for RVM neurons in animals older than PN day 30 and compared the results to animals at PN day 10-21. These results demonstrate that the probability of GABA release is lower and that opioid and endocannabinoid effects are more evident in adult rats (mature) compared to early postnatal (immature) rats. Differences in these properties of RVM neurons may contribute to the developmental changes in descending control of pain from the RVM to the spinal cord.

Pharmacological Manipulation Of Glucocorticoid Receptors Differentially Affects Cocaine Self-Administration In Environmentally Enriched and Isolated Rats Hofford RS, Prendergast MA, Bardo MT. Behav Brain Res 2015; 283: 196-202.
Social isolation rearing (isolated condition, IC) is used as a model of early life stress in rodents. Rats raised in this condition are often compared to rats raised in an environmentally enriched condition (EC). However, EC rats are repeatedly exposed to forced novelty, another classic stressor in rodents. These studies explored the relationship between cocaine self-administration and glucocorticoid receptor (GR) activation and measured total levels of GR protein in reward-related brain regions (medial prefrontal cortex, orbitofrontal cortex, nucleus accumbens, amygdala) in rats chronically exposed to these conditions. For Experiment 1, rats were housed in EC or IC and were then trained to self-administer cocaine. Rats raised in these housing conditions were tested for their cocaine responding after pretreatment with the GR antagonist, RU486, or the GR agonist, corticosterone (CORT). For Experiment 2, levels of GR from EC and IC rats were measured in brain regions implicated in drug abuse using Western blot analysis. Pretreatment with RU486 (20mg/kg) decreased responding for a low unit dose of cocaine (0.03mg/kg/infusion) in EC rats only. IC rats were unaffected by RU486 pretreatment, but earned significantly more cocaine than EC rats after pretreatment with CORT (10mg/kg). No difference in GR expression was found between EC and IC rats in any brain area examined. These results, along with previous literature, suggest that enrichment enhances responsivity of the HPA axis related to cocaine reinforcement, but

this effect is unlikely due simply to differential baseline GR expression in areas implicated in drug abuse.

Kappa Opioid Receptor Activation Potentiates the Cocaine-Induced Increase In Evoked Dopamine Release Recorded In Vivo In the Mouse Nucleus Accumbens Ehrich JM, Phillips PEM, Chavkin C. Neuropsychopharmacology 2014; 39(13): 3036-3048.
Behavioral stressors increase addiction risk in humans and increase the rewarding valence of drugs of abuse including cocaine, nicotine and ethanol in animal models. Prior studies have established that this potentiation of drug reward was mediated by stress-induced release of the endogenous dynorphin opioids and subsequent kappa opioid receptor (KOR) activation. In this study, the authors used in vivo fast scan cyclic voltammetry to test the hypothesis that KOR activation before cocaine administration might potentiate the evoked release of dopamine from ventral tegmental (VTA) synaptic inputs to the nucleus accumbens (NAc) and thereby increase the rewarding valence of cocaine. The KOR agonist U50488 inhibited dopamine release evoked by either medial forebrain bundle (MFB) or pedunculopontine tegmental nucleus (PPTg) activation of VTA inputs to the shell or core of the mouse NAc. Cocaine administration increased the dopamine response recorded in either the shell or core evoked by either MFB or PPTg stimulation. Administration of U50488 15 min before cocaine blocked the conditioned place preference (CPP) to cocaine, but only significantly reduced the effect of cocaine on the dopamine response evoked by PPTg stimulation to NAc core. In contrast, administration of U50488 60 min before cocaine significantly potentiated cocaine CPP and significantly increased the effects of cocaine on the dopamine response evoked by either MFB or PPTg stimulation, recorded in either NAc shell or core. Results of this study support the concept that stress-induced activation of KOR by endogenous dynorphin opioids may enhance the rewarding valence of drugs of abuse by potentiating the evoked dopamine response.

Conserved Higher-Order Chromatin Regulates NMDA Receptor Gene Expression and Cognition Bharadwaj R, Peter CJ, Jiang Y, Roussos P, Vogel-Ciernia A, Shen EY, Mitchell AC, Mao W, Whittle C, Dincer A, Jakovcevski M, Pothula V, Rasmussen TP, Giakoumaki SG, Bitsios P, Sherif A, Gardner PD, Ernst P, Ghose S, Sklar P, Haroutunian V, Tamminga C, Myers RH, Futai K, Wood MA, Akbarian S. Neuron 2014; 84(5): 997-1008.
Three-dimensional chromosomal conformations regulate transcription by moving enhancers and regulatory elements into spatial proximity with target genes. Here the authors describe activity-regulated long-range loopings bypassing up to 0.5 Mb of linear genome to modulate NMDA glutamate receptor GRIN2B expression in human and mouse prefrontal cortex. Distal intronic and 3' intergenic loop formations competed with repressor elements to access promoter-proximal sequences, and facilitated expression via a "cargo" of AP-1 and NRF-1 transcription factors and TALE-based transcriptional activators. Neuronal deletion or overexpression of Kmt2a/Mll1 H3K4- and Kmt1e/Setdb1 H3K9-methyltransferase was associated with higher-order chromatin changes at distal regulatory Grin2b sequences and impairments in working memory. Genetic polymorphisms and isogenic deletions of loop-bound sequences conferred liability for cognitive performance and decreased GRIN2B expression. Dynamic regulation of chromosomal conformations emerges as a novel layer for transcriptional mechanisms impacting neuronal signaling and cognition.

Implication Of Delta Opioid Receptor Subtype 2 But Not Delta Opioid Receptor Subtype 1 In the Development Of Morphine Analgesic Tolerance In A Rat Model Of Chronic Inflammatory Pain Beaudry H, Gendron L, Moron JA. Eur J Neurosci. 2015 Jan 9. [Epub ahead of print].
Opioids are well known for their robust analgesic effects. Chronic activation of mu opioid receptors (MOPs) is, however, accompanied by various unwanted effects such as analgesic tolerance. Among other mechanisms, interactions between MOPs and delta opioid receptors (DOPs) are thought to play an important role in morphine-induced behavioral adaptations. Interestingly, certain conditions such as inflammation enhance the function of the DOP through a MOP-dependent mechanism. Here, the authors investigated the role of DOPs during the development of morphine tolerance in an animal model of chronic inflammatory pain. Using behavioral approaches, they first established that repeated systemic morphine treatment induced morphine analgesic tolerance in rats coping with chronic inflammatory pain. They then observed that blockade of DOPs with subcutaneous naltrindole (NTI), a selective DOP antagonist, significantly attenuated the development of morphine tolerance in a dose-dependent manner. They confirmed that this effect was DOP mediated by showing that an acute injection of NTI had no effect on morphine-induced analgesia in naive animals. Previous pharmacological characterizations revealed the existence of DOP subtype 1 and DOP subtype 2. As opposed to NTI, 7-benzylidenenaltrexone and naltriben were reported to be selective DOP subtype 1 and DOP subtype 2 antagonists, respectively. Interestingly, naltriben but not 7-benzylidenenaltrexone was able to attenuate the development of morphine analgesic tolerance in inflamed rats. Altogether, these results suggest that targeting of DOP subtype 2 with antagonists provides a valuable strategy to attenuate the analgesic tolerance that develops after repeated morphine administration in the setting of chronic inflammatory pain.

Affective and Cognitive Mechanisms Of Risky Decision Making Shimp KG, Mitchell MR, Beas BS, Bizon JL, Setlow B. Neurobiol Learn Mem 2015; 117: 60-70.
The ability to make advantageous decisions under circumstances in which there is a risk of adverse consequences is an important component of adaptive behavior; however, extremes in risk taking (either high or low) can be maladaptive and are characteristic of a number of neuropsychiatric disorders. To better understand the contributions of various affective and cognitive factors to risky decision making, cohorts of male Long-Evans rats were trained in a "Risky Decision making Task" (RDT), in which they made discrete trial choices between a small, "safe" food reward and a large, "risky" food reward accompanied by varying probabilities of footshock. Experiment 1 evaluated the relative contributions of the affective stimuli (i.e., punishment vs. reward) to RDT performance by parametrically varying the magnitudes of the footshock and large reward. Varying the shock magnitude had a significant impact on choice of the large, "risky" reward, such that greater magnitudes were associated with reduced choice of the large reward. In contrast, varying the large, "risky" reward magnitude had minimal influence on reward choice. Experiment 2 compared individual variability in RDT performance with performance in an attentional set shifting task (assessing cognitive flexibility), a delayed response task (assessing working memory), and a delay discounting task (assessing impulsive choice). Rats characterized as risk averse in the RDT made more perseverative errors on the set shifting task than did their risk taking counterparts, whereas RDT performance was not related to working memory abilities or impulsive choice. In addition, rats that showed greater delay discounting (greater impulsive choice) showed corresponding poorer performance in the working memory task. Together, these results suggest that reward-related decision making under risk of punishment is more strongly influenced by the punishment than by

the reward, and that risky and impulsive decision making are associated with distinct components of executive function.

Cocaine Increases Dopaminergic Neuron and Motor Activity via Midbrain α1 Adrenergic Signaling Goertz RB, Wanat MJ, Gomez JA, Brown ZJ, Phillips PE, Paladini CA. Neuropsychopharmacology 2015; 40: 1151-1162.
Cocaine reinforcement is mediated by increased extracellular dopamine levels in the forebrain. This neurochemical effect was thought to require inhibition of dopamine reuptake, but cocaine is still reinforcing even in the absence of the dopamine transporter. Here, the authors demonstrate that the rapid elevation in dopamine levels and motor activity elicited by cocaine involves α1 receptor activation within the ventral midbrain. Activation of α1 receptors increases dopaminergic neuron burst firing by decreasing the calcium-activated potassium channel current (SK), as well as elevates dopaminergic neuron pacemaker firing through modulation of both SK and the hyperpolarization-activated cation currents (Ih). Furthermore, the authors found that cocaine increases both the pacemaker and burst-firing frequency of rat ventral-midbrain dopaminergic neurons through an α1 adrenergic receptor-dependent mechanism within the ventral tegmental area and substantia nigra pars compacta. These results demonstrate the mechanism underlying the critical role of α1 adrenergic receptors in the regulation of dopamine neurotransmission and behavior by cocaine.

Cis-Expression Quantitative Trait Loci Mapping Reveals Replicable Associations with Heroin Addiction in OPRM1 Hancock DB, Levy JL, Gaddis NC, Glasheen C, Saccone NL, Page GP, Hulse GK, Wildenauer D, Kelty EA, Schwab SG, Degenhardt L, Martin NG, Montgomery GW, Attia J, Holliday EG, McEvoy M, Scott RJ, Bierut LJ, Nelson EC, Kral AH, Johnson EO. Biol Psychiatry. 2015 Jan 29. [Epub ahead of print].
No opioid receptor, mu 1 (OPRM1) gene polymorphisms, including the functional single nucleotide polymorphism (SNP) rs1799971, have been conclusively associated with heroin/other opioid addiction, despite their biological plausibility. The authors used evidence of polymorphisms altering OPRM1 expression in normal human brain tissue to nominate and then test associations with heroin addiction. They tested 103 OPRM1 SNPs for association with OPRM1 messenger RNA expression in prefrontal cortex from 224 European Americans and African Americans of the BrainCloud cohort. They then tested the 16 putative cis-expression quantitative trait loci (cis-eQTL) SNPs for association with heroin addiction in the Urban Health Study and two replication cohorts, totaling 16,729 European Americans, African Americans, and Australians of European ancestry. Four putative cis-eQTL SNPs were significantly associated with heroin addiction in the Urban Health Study (smallest p = 8.9 × 10-5): rs9478495, rs3778150, rs9384169, and rs562859. Rs3778150, located in OPRM1 intron 1, was significantly replicated (p = 6.3 × 10-5). Meta-analysis across all case-control cohorts resulted in p = 4.3 × 10-8: the rs3778150-C allele (frequency = 16%-19%) being associated with increased heroin addiction risk. Importantly, the functional SNP allele rs1799971-A was associated with heroin addiction only in the presence of rs3778150-C (p = 1.48 × 10-6 for rs1799971-A/rs3778150-C and p = .79 for rs1799971-A/rs3778150-T haplotypes). Lastly, replication was observed for six other intron 1 SNPs that had prior suggestive associations with heroin addiction (smallest p = 2.7 × 10-8 for rs3823010). These findings show that common OPRM1 intron 1 SNPs have replicable associations with heroin addiction. The haplotype structure of rs3778150 and nearby SNPs may underlie the inconsistent associations between rs1799971 and heroin addiction.

Change In Functional Selectivity Of Morphine With the Development Of Antinociceptive Tolerance Macey TA, Bobeck EN, Suchland KL, Morgan MM, Ingram SL. Br J Pharmacol. 2015 Jan; 172(2): 549-561.
Opioids, such as morphine, are the most effective treatment for pain but their efficacy is diminished with the development of tolerance following repeated administration. Recently, the authors found that morphine activated ERK in opioid-tolerant but not in naïve rats, suggesting that morphine activation of μ-opioid receptors is altered following repeated morphine administration. Here, they have tested the hypothesis that μ-opioid receptor activation of ERK in the ventrolateral periaqueductal gray (vlPAG) is dependent on dynamin, a protein implicated in receptor endocytosis. Rats were made tolerant to repeated microinjections of morphine into the vlPAG. The effects of dynamin on ERK activation and antinociception were assessed by microinjecting myristoylated dominant-negative dynamin peptide (Dyn-DN) or a scrambled control peptide into the vlPAG. Microinjection of a fluorescent dermorphin analogue (DERM-A594) into the vlPAG was used to monitor μ-opioid receptor internalization. Morphine did not activate ERK and Dyn-DN administration had no effect on morphine-induced antinociception in saline-pretreated rats. In contrast, morphine-induced ERK activation in morphine-pretreated rats that was blocked by Dyn-DN administration. Dyn-DN also inhibited morphine antinociception. Finally, morphine reduced DERM-A594 internalization only in morphine-tolerant rats indicating that μ-opioid receptors were internalized and unavailable to bind DERM-A594. Repeated morphine administration increased μ-opioid receptor activation of ERK signalling via a dynamin-dependent mechanism. These results demonstrate that the balance of agonist signalling to G-protein and dynamin-dependent pathways is altered, effectively changing the functional selectivity of the agonist-receptor complex.

Eating High Fat Chow, But Not Drinking Sucrose Or Saccharin, Enhances the Development Of Sensitization To the Locomotor Effects Of Cocaine In Adolescent Female Rats Serafine KM, Bentley TA, Koek W, France CP. Behav Pharmacol 2015; 26(3): 321-325.
Eating high fat chow accelerates the development of sensitization to cocaine-induced locomotion in female rats. It is not known whether consumption of sucrose or saccharin also increases sensitivity to the behavioral effects of cocaine or whether continuous (or intermittent) access to these feeding conditions is necessary to change sensitivity. Adolescent female Sprague-Dawley rats were assigned to one of seven feeding conditions from postnatal day 25 through to postnatal day 60. The rats either ate high fat (60% kcal from fat) chow and drank water or ate standard (17% kcal from fat) chow and drank either water, a 10% sucrose solution, or a 0.1% saccharin solution. The rats either had continuous access to high fat chow, sucrose, or saccharin, or had intermittent access (i.e., 2 days/week) to these substances, with access to water and standard chow on other days. As compared with standard chow, continuous (but not intermittent) access to high fat chow enhanced the development of sensitization to cocaine-induced (1-17.8 mg/kg) locomotion; drinking sucrose or saccharin (continuous or intermittent access) did not alter the development of sensitization to cocaine-induced locomotion. The impact of feeding condition on the behavioral effects of cocaine varies between sexes and across dietary composition.

Genome-Wide Association Study of Copy Number Variations (CNVs) with Opioid Dependence Li D, Zhao H, Kranzler HR, Li MD, Jensen KP, Zayats T, Farrer LA, Gelernter J. Neuropsychopharmacology 2015; 40(4): 1016-1026.
Single-nucleotide polymorphisms that have been associated with opioid dependence (OD) altogether account for only a small proportion of the known heritability. Most of the genetic risk

factors are unknown. Some of the 'missing heritability' might be explained by copy number variations (CNVs) in the human genome. The authors used Illumina HumanOmni1 arrays to genotype 5152 African-American and European-American OD cases and screened controls and implemented combined CNV calling methods. After quality control measures were applied, a genome-wide association study (GWAS) of CNVs with OD was performed. For common CNVs, two deletions and one duplication were significantly associated with OD genome-wide (eg, P=2 × 10(-8) and OR (95% CI)=0.64 (0.54-0.74) for a chromosome 18q12.3 deletion). Several rare or unique CNVs showed suggestive or marginal significance with large effect sizes. This study is the first GWAS of OD using CNVs. Some identified CNVs harbor genes newly identified here to be of biological importance in addiction, whereas others affect genes previously known to contribute to substance dependence risk. These findings augment our specific knowledge of the importance of genomic variation in addictive disorders, and provide an addiction CNV pool for further research. These findings require replication.

Inhibitory Learning Is Modulated By Nicotinic Acetylcholine Receptors Meyer HC, Putney RB, Bucci DJ. Neuropharmacology 2015; 89: 360-367.
Prior research has established that stimulating nicotinic acetylcholine receptors can facilitate learning and memory. However, most studies have focused on learning to emit a particular behavior, while little is known about the effects of nicotine on learning to withhold a behavioral response. The present study consisted of a dose response analysis of the effects of nicotine on negative occasion setting, a form of learned inhibition. In this paradigm, rats received one type of training trial in which presentation of a tone by itself was followed immediately by food reward. During the other type of trials, the tone was preceded by presentation of a light and no food was delivered after the tone. Rats gradually learned to approach the cup in anticipation of receiving food reward during presentations of the tone alone, but withheld that behavior when the tone was preceded by the light. Nicotine (0.35 mg/kg) facilitated negative occasion setting by reducing the number of sessions needed to learn the discrimination between trial types and by reducing the rate of responding on non-reinforced trials. Nicotine also increased the orienting response to the light, suggesting that nicotine may have affected the ability to withhold food cup behavior on non-reinforced trials by increasing attention to the light. In contrast to the effects of nicotine, rats treated with mecamylamine (0.125, 0.5, or 2 mg/kg) needed more training sessions to discriminate between reinforced and non-reinforced trials compared to saline-treated rats. The findings indicate that nicotinic acetylcholine receptors may be active during negative occasion setting and that nicotine can potentiate learned inhibition.

Toll-Like Receptor 3 Signaling Inhibits Simian Immunodeficiency Virus Replication In Macrophages From Rhesus Macaques Sang M, Liu JB, Dai M, Wu JG, Ho WZ. Antiviral Res. 2014 Dec; 112: 103-112.
Toll-like receptor 3 (TLR3) recognizes double-stranded RNA and induces multiple intracellular events responsible for innate antiviral immunity against viral infections. Here the authors demonstrate that TLR3 signaling of monocyte-derived macrophages (MDM) from rhesus monkeys by poly I:C inhibited simian immunodeficiency virus (SIV) infection and replication. Investigation of the mechanisms showed that TLR3 activation resulted in the induction of type I and type III interferons (IFNs) and IFN-inducible antiviral factors, including APOBEC3G (A3G), tetherin and SAMHD1. In addition, poly I:C-treated macaque macrophages expressed increased levels of CC chemokines including CCL3, CCL4 and CCL5, the ligands for HIV or SIV coreceptor CCR5.

Furthermore, TLR3 signaling of macaque macrophages induced the expression of cellular microRNAs (miR-29a, -29b, -146a and -9), the newly identified intracellular SIV restriction factors. TLR3 activation-mediated anti-SIV effect could be compromised by the knockdown of IRF3 and IRF7. These findings indicate that TLR3-mediated induction of multiple viral restriction factors contribute to the inhibition of SIV infection in macaque macrophages, which support future preclinical studies using rhesus macaques to determine whether in vivo TLR3 activation is safe and beneficial for treating people infected with HIV.

Differential Roles of α6β2* and α4β2* Neuronal Nicotinic Receptors in Nicotine- and Cocaine-Conditioned Reward in Mice Sanjakdar SS, Maldoon PP, Marks MJ, Brunzell DH, Maskos U, McIntosh JM, Bowers MS, Damaj MI. Neuropsychopharmacology 2015; 40(2): 350-360.
Mesolimbic α6* nicotinic acetylcholine receptors (nAChRs) are thought to have an important role in nicotine behavioral effects. However, little is known about the role of the various α6*-nAChRs subtypes in the rewarding effects of nicotine. In this report, the authors investigated and compared the role of α6*-nAChRs subtypes and their neuro-anatomical locus in nicotine and cocaine reward-like effects in the conditioned place preference (CPP) paradigm, using pharmacological antagonism of α6β2* nAChRs and genetic deletion of the α6 or α4 subunits in mice. They found that α6 KO mice exhibited a rightward shift in the nicotine dose-response curve compared with WT littermates but that α4 KO failed to show nicotine preference, suggesting that α6α4β2*-nAChRs are involved. Furthermore, α6β2* nAChRs in nucleus accumbens were found to have an important role in nicotine-conditioned reward as the intra-accumbal injection of the selective α6β2* α-conotoxin MII [H9A; L15A], blocked nicotine CPP. In contrast to nicotine, α6 KO failed to condition to cocaine, but cocaine CPP in the α4 KO was preserved. Intriguingly, α-conotoxin MII [H9A; L15A], blocked cocaine conditioning in α4 KO mice, implicating α6β2* nAChRs in cocaine reward. Importantly, these effects did not generalize as α6 KO showed both a conditioned place aversion to lithium chloride as well as CPP to palatable food. Finally, dopamine uptake was not different between the α6 KO or WT mice. These data illustrate that the subjective rewarding effects of both nicotine and cocaine may be mediated by mesolimbic α6β2* nAChRs and that antagonists of these receptor subtypes may exhibit therapeutic potential.

The Contribution Of Rare and Common Variants In 30 Genes To Risk Nicotine Dependence Yang J, Wang S, Yang Z, Hodgkinson CA, Iarikova P, Ma JZ, Payne TJ, Goldman D, Li MD. Mol Psychiatry 2014. [Epub ahead of print].
Genetic and functional studies have revealed that both common and rare variants of several nicotinic acetylcholine receptor subunits are associated with nicotine dependence (ND). In this study, the authors identified variants in 30 candidate genes including nicotinic receptors in 200 sib pairs selected from the Mid-South Tobacco Family population with equal numbers of African Americans (AAs) and European Americans (EAs). They selected 135 of the rare and common variants and genotyped them in the Mid-South Tobacco Case-Control (MSTCC) population, which consists of 3088 AAs and 1430 EAs. None of the genotyped common variants showed significant association with smoking status (smokers vs non-smokers), Fagerström Test for ND scores or indexed cigarettes per day after Bonferroni correction. Rare variants in NRXN1, CHRNA9, CHRNA2, NTRK2, GABBR2, GRIN3A, DNM1, NRXN2, NRXN3 and ARRB2 were significantly associated with smoking status in the MSTCC AA sample, with weighted sum statistic (WSS) P-values ranging from 2.42 × 10-3 to 1.31 × 10-4 after 106 phenotype rearrangements. The authors also observed a significant excess of rare nonsynonymous variants exclusive to EA smokers in

NRXN1, CHRNA9, TAS2R38, GRIN3A, DBH, ANKK1/DRD2, NRXN3 and CDH13 with WSS P-values between 3.5 × 10-5 and 1 × 10-6. Variants rs142807401 (A432T) and rs139982841 (A452V) in CHRNA9 and variants V132L, V389L, rs34755188 (R480H) and rs75981117 (N549S) in GRIN3A are of particular interest because they are found in both the AA and EA samples. A significant aggregate contribution of rare and common coding variants in CHRNA9 to the risk for ND (SKAT-C: P=0.0012) was detected by applying the combined sum test in MSTCC EAs. Together, these results indicate that rare variants alone or combined with common variants in a subset of 30 biological candidate genes contribute substantially to the risk of ND.

Potentiated Gene Regulation By Methylphenidate Plus Fluoxetine Treatment: Long-Term Gene Blunting (Zif268, Homer1a) and Behavioral Correlates Beverley JA, Piekarski C, Van Waes V, Steiner H. Basal Ganglia 2014; 4(3-4): 109-116.
Use of psychostimulants such as methylphenidate (Ritalin) in medical treatments and as cognitive enhancers in the healthy is increasing. Methylphenidate produces some addiction-related gene regulation in animal models. Recent findings show that combining selective serotonin reuptake inhibitor (SSRI) antidepressants such as fluoxetine with methylphenidate potentiates methylphenidate-induced gene regulation. The authors investigated the endurance of such abnormal gene regulation by assessing an established marker for altered gene regulation after drug treatments - blunting (repression) of immediate-early gene (IEG) inducibility - 14 days after repeated methylphenidate+fluoxetine treatment in adolescent rats. Thus, they measured the effects of a 6-day repeated treatment with methylphenidate (5 mg/kg), fluoxetine (5 mg/kg) or their combination on the inducibility (by cocaine) of neuroplasticity-related IEGs (Zif268, Homer1a) in the striatum, by in situ hybridization histochemistry. Repeated methylphenidate treatment alone produced modest gene blunting, while fluoxetine alone had no effect. In contrast, fluoxetine given in conjunction with methylphenidate produced pronounced potentiation of methylphenidate-induced blunting for both genes. This potentiation was seen in many functional domains of the striatum, but was most robust in the lateral, sensorimotor striatum. These enduring molecular changes were associated with potentiated induction of behavioral stereotypies in an open-field test. For illicit psychostimulants, blunting of gene expression is considered part of the molecular basis of addiction. These results thus suggest that SSRIs such as fluoxetine may increase the addiction liability of methylphenidate.

HIV-1/Cocaine Induced Oxidative Stress Disrupts Tight Junction Protein-1 In Human Pulmonary Microvascular Endothelial Cells: Role Of Ras/ERK1/2 Pathway Dalvi P, Wang K, Mermis J, Zeng R, Sanderson M, Johnson S, Dai Y, Sharma G, Ladner AO, Dhillon NK. PLoS One. 2014 Jan 7;9(1):e85246.
Intravenous drug use (IVDU) is the major risk factor in the development of HIV-related pulmonary arterial hypertension (HRPAH); however, the pathogenesis of HRPAH in association with IVDU has yet to be characterized. Endothelial injury is considered to be an initiating factor for pulmonary vascular remodeling in animal models of PAH. The authors' previous study shows that simultaneous exposure to HIV-Trans-activator of transcription (Tat) and cocaine exacerbates both disruption of tight junction proteins and permeability of human pulmonary artery endothelial cells compared with either treatment alone. They here now demonstrate that this HIV-Tat and cocaine mediated endothelial dysfunction accompanies with increase in hydrogen peroxide and superoxide radicals generation and involves redox sensitive signaling pathway. Pretreatment with antioxidant cocktail attenuated the cocaine and Tat mediated disassembly of Zonula Occludens (ZO)-1 and enhancement of endothelial monolayer permeability. Furthermore, inhibition of NADPH oxidase by

apocynin or siRNA-mediated knockdown of gp-91(phox) abolished the Tat/cocaine-induced reactive oxygen species (ROS) production, suggesting the NADPH oxidase mediated generation of oxidative radicals. In addition, ROS dependent activation of Ras and ERK1/2 Kinase was observed to be mediating the TJP-1 disassembly, and endothelial dysfunction in response to cocaine and Tat exposure. In conclusion, these findings demonstrate that Tat/cocaine -mediated production of ROS activate Ras/Raf/ERK1/2 pathway that contributes to disruption of tight junction protein leading to pulmonary endothelial dysfunction associated with pulmonary vascular remodeling.

Individual Differences In Anhedonic and Accumbal Dopamine Responses To Chronic Social Stress and Their Link To Cocaine Self-Administration In Female Rats Shimamoto A, Holly EN, Boyson CO, DeBold JF, Miczek KA. Psychopharmacology (Berl) 2015; 232(4): 825-834.
Women are twice as likely as men to develop major depressive disorder. Exposure to chronic stress can induce depression in some vulnerable individuals, while others are resistant to depressive-like symptoms after equivalent levels of chronic stress. In female rats, individual differences in saccharin intake during chronic social defeat stress may predict subsequent cocaine self-administration, and may be attributed to alterations in mesolimbic dopamine activity. Female rats were exposed to 21 days of chronic social defeat stress, during which they were evaluated for their anhedonia-like responses in the form of saccharin intake. After chronic social defeat stress, the rats were tested for behavioral cross-sensitization to cocaine and escalated cocaine self-administration in a 24-h "binge." A separate group of animals underwent in vivo microdialysis of the nucleus accumbens (NAc) shell to assess dopamine (DA) in response to acute cocaine challenge. Cluster analysis revealed two phenotypes among the stressed female rats based on their saccharin intake while being exposed to stress, termed stress-resistant (SR, 28 %) and stress-sensitive (SS, 72 %). The amount of cocaine self-administered during the 24-h "binge" was positively correlated with preceding saccharin intake. The NAc DA response to a cocaine challenge was significantly lower in SR rats than in the SS and non-stressed control rats. No other significant differences were observed in behavioral cross-sensitization or cocaine self-administration prior to the "binge." The authors conclude that female rats showed individual differences in their anhedonic-like response to chronic social defeat stress, and these differences were reliably associated with subsequent cocaine-taking behavior.

Change In Functional Selectivity Of Morphine With the Development Of Antinociceptive Tolerance Macey TA, Bobeck EN, Suchland KL, Morgan MM, Ingram SL. Br J Pharmacol 2015; 172(2): 549-561.
Opioids, such as morphine, are the most effective treatment for pain but their efficacy is diminished with the development of tolerance following repeated administration. Recently, the authors found that morphine activated ERK in opioid-tolerant but not in naïve rats, suggesting that morphine activation of μ-opioid receptors is altered following repeated morphine administration. Here, they have tested the hypothesis that μ-opioid receptor activation of ERK in the ventrolateral periaqueductal gray (vlPAG) is dependent on dynamin, a protein implicated in receptor endocytosis. Rats were made tolerant to repeated microinjections of morphine into the vlPAG. The effects of dynamin on ERK activation and antinociception were assessed by microinjecting myristoylated dominant-negative dynamin peptide (Dyn-DN) or a scrambled control peptide into the vlPAG. Microinjection of a fluorescent dermorphin analogue (DERM-A594) into the vlPAG was used to monitor μ-opioid receptor internalization. Morphine did not activate ERK and Dyn-DN administration had no effect on morphine-induced antinociception in saline-pretreated rats. In

contrast, morphine-induced ERK activation in morphine-pretreated rats that was blocked by Dyn-DN administration. Dyn-DN also inhibited morphine antinociception. Finally, morphine reduced DERM-A594 internalization only in morphine-tolerant rats indicating that μ-opioid receptors were internalized and unavailable to bind DERM-A594. Repeated morphine administration increased μ-opioid receptor activation of ERK signalling via a dynamin-dependent mechanism. These results demonstrate that the balance of agonist signalling to G-protein and dynamin-dependent pathways is altered, effectively changing the functional selectivity of the agonist-receptor complex.

Transport Domain Unlocking Sets the Uptake Rate Of An Aspartate Transporter Akyuz N, Georgieva ER, Zhou Z, Stolzenberg S, Cuendet MA, Khelashvili G, Altman RB, Terry DS, Freed JH, Weinstein H, Boudker O, Blanchard SC. Nature 2015; 518(7537): 68-73.
Glutamate transporters terminate neurotransmission by clearing synaptically released glutamate from the extracellular space, allowing repeated rounds of signalling and preventing glutamate-mediated excitotoxicity. Crystallographic studies of a glutamate transporter homologue from the archaeon Pyrococcus horikoshii, GltPh, showed that distinct transport domains translocate substrates into the cytoplasm by moving across the membrane within a central trimerization scaffold. Here the authors report direct observations of these 'elevator-like' transport domain motions in the context of reconstituted proteoliposomes and physiological ion gradients using single-molecule fluorescence resonance energy transfer (smFRET) imaging. The authors show that GltPh bearing two mutations introduced to impart characteristics of the human transporter exhibits markedly increased transport domain dynamics, which parallels an increased rate of substrate transport, thereby establishing a direct temporal relationship between transport domain motion and substrate uptake. Crystallographic and computational investigations corroborated these findings by revealing that the 'humanizing' mutations favour structurally 'unlocked' intermediate states in the transport cycle exhibiting increased solvent occupancy at the interface between the transport domain and the trimeric scaffold.

From Circuits To Behaviour In the Amygdala Janak PH, Tye KM. Nature 2015; 517(7534): 284-292.
The amygdala has long been associated with emotion and motivation, playing an essential part in processing both fearful and rewarding environmental stimuli. How can a single structure be crucial for such different functions? With recent technological advances that allow for causal investigations of specific neural circuit elements, we can now begin to map the complex anatomical connections of the amygdala onto behavioural function. Understanding how the amygdala contributes to a wide array of behaviours requires the study of distinct amygdala circuits.

Sirtuin 4 Is A Lipoamidase Regulating Pyruvate Dehydrogenase Complex Activity Mathias RA, Greco TM, Oberstein A, Budayeva HG, Chakrabarti R, Rowland EA, Kang Y, Shenk T, Cristea IM. Cell 2014; 159(7): 1615-1625.
Sirtuins (SIRTs) are critical enzymes that govern genome regulation, metabolism, and aging. Despite conserved deacetylase domains, mitochondrial SIRT4 and SIRT5 have little to no deacetylase activity, and a robust catalytic activity for SIRT4 has been elusive. Here, the authors establish SIRT4 as a cellular lipoamidase that regulates the pyruvate dehydrogenase complex (PDH). Importantly, SIRT4 catalytic efficiency for lipoyl- and biotinyl-lysine modifications is superior to its deacetylation activity. PDH, which converts pyruvate to acetyl-CoA, has been known to be primarily regulated by phosphorylation of its E1 component. The authors determine that

SIRT4 enzymatically hydrolyzes the lipoamide cofactors from the E2 component dihydrolipoyllysine acetyltransferase (DLAT), diminishing PDH activity. They demonstrate SIRT4-mediated regulation of DLAT lipoyl levels and PDH activity in cells and in vivo, in mouse liver. Furthermore, metabolic flux switching via glutamine stimulation induces SIRT4 lipoamidase activity to inhibit PDH, highlighting SIRT4 as a guardian of cellular metabolism.

Programming Of Neural Cells By (Endo)Cannabinoids: From Physiological Rules To Emerging Therapies Maccarrone M, Guzman M, Mackie K, Doherty P, Harkany T. Nat Rev Neurosci 2014; 15(12): 786-801.
Among the many signalling lipids, endocannabinoids are increasingly recognized for their important roles in neuronal and glial development. Recent experimental evidence suggests that, during neuronal differentiation, endocannabinoid signalling undergoes a fundamental switch from the prenatal determination of cell fate to the homeostatic regulation of synaptic neurotransmission and bioenergetics in the mature nervous system. These studies also offer novel insights into neuropsychiatric disease mechanisms and contribute to the public debate about the benefits and the risks of cannabis use during pregnancy and in adolescence.

Preclinical Studies Of the Potent and Selective Nicotinic A4β2 Receptor Ligand VMY-2-95 Kong H, Song JK, Yenungonda VM, Zhang L, Shuo T, Cheema AK, Kong Y, Du GH, Brown ML. Mol Pharm. 2015 Feb 2; 12(2): 393-402.
The discovery and development of small molecules that antagonize neuronal nicotinic acetylcholine receptors may provide new ligands for evaluation in models of depression or addiction. The authors discovered a small molecule, VMY-2-95, a nAChR ligand with picomolar affinity and high selectivity for α4β2 receptors. In this study, they investigated its preclinical profile in regards to solubility, lipophilicity, metabolic stability, intestinal permeability, bioavailability, and drug delivery to the rat brain. Metabolic stability of VMY-2-95·2HCl was monitored on human liver microsomes, and specific activity of VMY-2-95·2HCl on substrate metabolism by CYP1A2, 2C9, 2C19, 2D6, and 3A4 was tested in a high-throughput manner. The intestinal transport of VMY-2-95·2HCl was studied through Caco-2 cell monolayer permeability. VMY-2-95·2HCl was soluble in water and chemically stable, and the apparent partition coefficient was 0.682. VMY-2-95·2HCl showed significant inhibition of CYP2C9 and 2C19, but weak or no effect on 1A2, 2D6, and 3A4. The Caco-2 cell model studies revealed that VMY-2-95·2HCl was highly permeable with efflux ratio of 1.11. VMY-2-95·2HCl achieved a maximum serum concentration of 0.56 mg/mL at 0.9 h and was orally available with a half-life of ∼9 h. Furthermore, VMY-2-95·2HCl was detected in the rat brain after 3 mg/kg oral administration and achieved a maximal brain tissue concentration of 2.3 μg/g within 60 min. Overall, the results demonstrate that VMY-2-95·2HCl has good drug like properties and can penetrate the blood-brain barrier with oral administration.

Endocannabinoid Signalling and The Deteriorating Brain Di Marzo V, Stella N, Zimmer A. Nat Rev Neurosci 2015; 16(1): 30-42.
Ageing is characterized by the progressive impairment of physiological functions and increased risk of developing debilitating disorders, including chronic inflammation and neurodegenerative diseases. These disorders have common molecular mechanisms that can be targeted therapeutically. In the wake of the approval of the first cannabinoid-based drug for the symptomatic treatment of multiple sclerosis, the authors examine how endocannabinoid (eCB) signalling controls--and is affected by--normal ageing and neuroinflammatory and neurodegenerative disorders. They propose

a conceptual framework linking eCB signalling to the control of the cellular and molecular hallmarks of these processes, and categorize the key components of endocannabinoid signalling that may serve as targets for novel therapeutics.

Cell-Based Reporters Reveal In Vivo Dynamics Of Dopamine and Norepinephrine Release In Murine Cortex Muller A, Joseph V, Slesinger PA, Kleinfeld D. Nat Methods 2014; 11(12): 1245-1252.
The neuronal coding of stimulus-to-action sequences is believed to involve the release of dopamine (DA) and norepinephrine (NE). The electrochemical similarity of these monoamines, however, confounds real-time measurements of their release. Here the authors report cell-based neurotransmitter fluorescent engineered reporters (CNiFERs) that use the specificity of G protein-coupled receptors (GPCRs) to discriminate nanomolar concentrations of DA and NE. CNiFERs were implanted into the frontal cortex of mice to measure the timing of neurotransmitter release during classical conditioning with the use of two-photon microscopy. The onset of DA release correlated with that of licking and shifted from the time of the reward toward that of the cue upon conditioning. In contrast, concurrent release of NE did not correlate with licking or the cue. This generation of CNiFERs provides unique tools to assess the release of monoamines. The molecular design of these CNiFERs may be generalized to realize CNiFERs for any molecule that activates a GPCR.

Serotonin 5-HT2 Receptor Interactions With Dopamine Function: Implications For Therapeutics In Cocaine Use Disorder Howell LL, Cunningham KA. Pharmacol Rev 2015; 67(1): 176-197.
Cocaine exhibits prominent abuse liability, and chronic abuse can result in cocaine use disorder with significant morbidity. Major advances have been made in delineating neurobiological mechanisms of cocaine abuse; however, effective medications to treat cocaine use disorder remain to be discovered. The present review will focus on the role of serotonin (5-HT; 5-hydroxytryptamine) neurotransmission in the neuropharmacology of cocaine and related abused stimulants. Extensive research suggests that the primary contribution of 5-HT to cocaine addiction is a consequence of interactions with dopamine (DA) neurotransmission. The literature on the neurobiological and behavioral effects of cocaine is well developed, so the focus of the review will be on cocaine with inferences made about other monoamine uptake inhibitors and releasers based on mechanistic considerations. 5-HT receptors are widely expressed throughout the brain, and several different 5-HT receptor subtypes have been implicated in mediating the effects of endogenous 5-HT on DA. However, the 5-HT2A and 5-HT2C receptors in particular have been implicated as likely candidates for mediating the influence of 5-HT in cocaine abuse as well as to traits (e.g., impulsivity) that contribute to the development of cocaine use disorder and relapse in humans. Lastly, new approaches are proposed to guide targeted development of serotonergic ligands for the treatment of cocaine use disorder.

What Can Crystal Structures Of Aminergic Receptors Tell Us About Designing Subtype-Selective Ligands? Michino M, Beuming T, Donthamsetti P, Newman AH, Javitch JA, Shi L. Pharmacol Rev 2015; 67(1): 198-213.
G protein-coupled receptors (GPCRs) are integral membrane proteins that represent an important class of drug targets. In particular, aminergic GPCRs interact with a significant portion of drugs currently on the market. However, most drugs that target these receptors are associated with

undesirable side effects, which are due in part to promiscuous interactions with close homologs of the intended target receptors. Here, based on a systematic analysis of all 37 of the currently available high-resolution crystal structures of aminergic GPCRs, the authors review structural elements that contribute to and can be exploited for designing subtype-selective compounds. They describe the roles of secondary binding pockets (SBPs), as well as differences in ligand entry pathways to the orthosteric binding site, in determining selectivity. In addition, using the available crystal structures, the authors have identified conformational changes in the SBPs that are associated with receptor activation and explore the implications of these changes for the rational development of selective ligands with tailored efficacy.

Considerations When Using Cre-Driver Rodent Lines For Studying Ventral Tegmental Area Circuitry Stuber GD, Stamatakis AM, Kantak PA. Neuron 2015; 85(2): 439-445.
The use of Cre-driver rodent lines for targeting ventral tegmental area (VTA) cell types has generated important and novel insights into how precise neurocircuits regulate physiology and behavior. While this approach generally results in enhanced cellular specificity, an important issue has recently emerged related to the selectivity and penetrance of viral targeting of VTA neurons using several Cre-driver transgenic mouse lines. Here, the authors highlight several considerations when utilizing these tools to study the function of genetically defined neurocircuits. While VTA dopaminergic neurons have previously been targeted and defined by the expression of single genes important for aspects of dopamine neurotransmission, many VTA and neighboring cells display dynamic gene expression phenotypes that are partially consistent with both classically described dopaminergic and non-dopaminergic neurons. Thus, in addition to varying degrees of selectivity and penetrance, distinct Cre lines likely permit targeting of partially overlapping, but not identical VTA cell populations. This Matters Arising Response paper addresses the Lammel et al. (2015) Matters Arising paper, published concurrently in Neuron.

Diversity Of Transgenic Mouse Models For Selective Targeting Of Midbrain Dopamine Neurons Lammel S, Steinberg EE, Foldy C, Wall NR, Beier K, Luo L, Malenka RC. Neuron 2015; 85(2): 429-438.
Ventral tegmental area (VTA) dopamine (DA) neurons have been implicated in reward, aversion, salience, cognition, and several neuropsychiatric disorders. Optogenetic approaches involving transgenic Cre-driver mouse lines provide powerful tools for dissecting DA-specific functions. However, the emerging complexity of VTA circuits requires Cre-driver mouse lines that restrict transgene expression to a precisely defined cell population. Because of recent work reporting that VTA DA neurons projecting to the lateral habenula release GABA, but not DA, the authors performed an extensive anatomical, molecular, and functional characterization of prominent DA transgenic mouse driver lines. They find that transgenes under control of the tyrosine hydroxylase, but not the dopamine transporter, promoter exhibit dramatic non-DA cell-specific expression patterns within and around VTA nuclei. These results demonstrate how Cre expression in unintentionally targeted cells in transgenic mouse lines can confound the interpretation of supposedly cell-type-specific experiments. This Matters Arising paper is in response to Stamatakis et al. (2013), published in Neuron. See also the Matters Arising Response paper by Stuber et al. (2015), published concurrently with this Matters Arising in Neuron.

Transgenic Mice For Intersectional Targeting Of Neural Sensors and Effectors With High Specificity and Performance Madisen L, Garner AR, Shimaoka D, Chuong AS, Klapoetke NC, Li L, van der Bourg A, Niino Y, Egolf L, Monetti C, Gu H, Mills M, Cheng A, Tasic B, Nguyen TN, Sunkin SM, Benucci A, Nagy A, Miyawaki A, Helmchen F, Empson RM, Knopfel T, Boyden ES, Reid RC, Carandini M, Zeng H. Neuron 2015; 85(5): 942-958.
An increasingly powerful approach for studying brain circuits relies on targeting genetically encoded sensors and effectors to specific cell types. However, current approaches for this are still limited in functionality and specificity. Here the authors utilize several intersectional strategies to generate multiple transgenic mouse lines expressing high levels of novel genetic tools with high specificity. They developed driver and double reporter mouse lines and viral vectors using the Cre/Flp and Cre/Dre double recombinase systems and established a new, retargetable genomic locus, TIGRE, which allowed the generation of a large set of Cre/tTA-dependent reporter lines expressing fluorescent proteins, genetically encoded calcium, voltage, or glutamate indicators, and optogenetic effectors, all at substantially higher levels than before. High functionality was shown in example mouse lines for GCaMP6, YCX2.60, VSFP Butterfly 1.2, and Jaws. These novel transgenic lines greatly expand the ability to monitor and manipulate neuronal activities with increased specificity.

Orbitofrontal Cortex Uses Distinct Codes For Different Choice Attributes In Decisions Motivated By Curiosity Blanchard TC, Hayden BY, Bromberg-Martin ES. Neuron 2015; 85(3): 602-614.
Decision makers are curious and consequently value advance information about future events. The authors made use of this fact to test competing theories of value representation in area 13 of orbitofrontal cortex (OFC). In a new task, the authors found that monkeys reliably sacrificed primary reward (water) to view advance information about gamble outcomes. While monkeys integrated information value with primary reward value to make their decisions, OFC neurons had no systematic tendency to integrate these variables, instead encoding them in orthogonal manners. These results suggest that the predominant role of the OFC is to encode variables relevant for learning, attention, and decision making, rather than integrating them into a single scale of value. They also suggest that OFC may be placed at a relatively early stage in the hierarchy of information-seeking decisions, before evaluation is complete. Thus, these results delineate a circuit for information-seeking decisions and suggest a neural basis for curiosity.

Understanding HIV Latency: The Road to an HIV Cure Dahabieh MS, Battivelli E, Verdin E. Annu Rev Med 2015; 66: 407-421.
Treatment with antiretroviral therapy dramatically increases the survival of HIV-infected individuals. However, treatment has to be continued for life because it does not lead to the full eradication of infection. HIV persists in resting CD4(+) T cells, and possibly other cell types, and can reemerge from these cells when therapy is interrupted. Here, the authors review molecular mechanisms that have been proposed to contribute to HIV latency, as well as the relative roles of cis- and trans-acting mechanisms. They also discuss existing and future therapeutic opportunities regarding HIV latency that might lead to a future cure for HIV infection.

Synaptic Plasticity Mediating Cocaine Relapse Requires Matrix Metalloproteinases Smith ACW, Kupchik YM, Scofield MD, Gipson CD, Wiggins A, Thomas CA, Kalivas PW. Nat Neurosci 2014; 17(12): 1655-1657.
Relapse to cocaine use necessitates remodeling excitatory synapses in the nucleus accumbens and synaptic reorganization requires matrix metalloproteinase (MMP) degradation of the extracellular matrix proteins. The authors found enduring increases in MMP-2 activity in rats after withdrawal from self-administered cocaine and transient increases in MMP-9 during cue-induced cocaine relapse. Cue-induced heroin and nicotine relapse increased MMP activity, and increased MMP activity was required for both cocaine relapse and relapse-associated synaptic plasticity.

Selective Conversion Of Fibroblasts Into Peripheral Sensory Neurons Blanchard W, Eade KT, Szucs A, Lo Sardo V, Tsunemoto RK, Williams D, Sanna PP, Baldwin KK. Nat Neurosci 2015; 18(1): 25-35.
Humans and mice detect pain, itch, temperature, pressure, stretch and limb position via signaling from peripheral sensory neurons. These neurons are divided into three functional classes (nociceptors/pruritoceptors, mechanoreceptors and proprioceptors) that are distinguished by their selective expression of TrkA, TrkB or TrkC receptors, respectively. The authors found that transiently coexpressing Brn3a with either Ngn1 or Ngn2 selectively reprogrammed human and mouse fibroblasts to acquire key properties of these three classes of sensory neurons. These induced sensory neurons (iSNs) were electrically active, exhibited distinct sensory neuron morphologies and matched the characteristic gene expression patterns of endogenous sensory neurons, including selective expression of Trk receptors. In addition, the authors found that calcium-imaging assays could identify subsets of iSNs that selectively responded to diverse ligands known to activate itch- and pain-sensing neurons. These results offer a simple and rapid means for producing genetically diverse human sensory neurons suitable for drug screening and mechanistic studies.

A Hierarchy Of Intrinsic Timescales Across Primate Cortex Murray JD, Bernacchia A, Freedman DJ, Romo R, Wallis JD, Cai X, Padoa-Schioppa C, Pasternak T, Seo H, Lee D, Wang X-J. Nat Neurosci 2014; 17(12): 1661-1663.
Specialization and hierarchy are organizing principles for primate cortex, yet there is little direct evidence for how cortical areas are specialized in the temporal domain. The authors measured timescales of intrinsic fluctuations in spiking activity across areas and found a hierarchical ordering, with sensory and prefrontal areas exhibiting shorter and longer timescales, respectively. On the basis of these findings, the authors suggest that intrinsic timescales reflect areal specialization for task-relevant computations over multiple temporal ranges.

Anxiety, Depression, and Cigarette Smoking: A Transdiagnostic Vulnerability Framework To Understanding Emotion-Smoking Comorbidity Leventhal AM, Zvolensky MJ. Psychol Bull 2015; 141(1): 176-212.
Research into the comorbidity between emotional psychopathology and cigarette smoking has often focused upon anxiety and depression's manifest symptoms and syndromes, with limited theoretical and clinical advancement. This article presents a novel framework to understanding emotion-smoking comorbidity. The authors propose that transdiagnostic emotional vulnerabilities-core biobehavioral traits reflecting maladaptive responses to emotional states that underpin multiple types of emotional psychopathology-link various anxiety and depressive psychopathologies to smoking. This framework is applied in a review and synthesis of the empirical literature on 3

transdiagnostic emotional vulnerabilities implicated in smoking: (a) anhedonia (Anh; diminished pleasure/interest in response to rewards), (b) anxiety sensitivity (AS; fear of anxiety-related sensations), and (c) distress tolerance (DT; ability to withstand distressing states). The authors conclude that Anh, AS, and DT collectively (a) underpin multiple emotional psychopathologies, (b) amplify smoking's anticipated and actual affect-enhancing properties and other mechanisms underlying smoking, (c) promote progression across the smoking trajectory (i.e., initiation, escalation/progression, maintenance, cessation/relapse), and (d) are promising targets for smoking intervention. After existing gaps are identified, an integrative model of transdiagnostic processes linking emotional psychopathology to smoking is proposed. The model's key premise is that Anh amplifies smoking's anticipated and actual pleasure-enhancing effects, AS amplifies smoking's anxiolytic effects, and poor DT amplifies smoking's distress terminating effects. Collectively, these processes augment the reinforcing properties of smoking for individuals with emotional psychopathology to heighten risk of smoking initiation, progression, maintenance, cessation avoidance, and relapse. The authors conclude by drawing clinical and scientific implications from this framework that may generalize to other comorbidities.

Phenotypic Differences In hiPSC NPCs Derived From Patients With Schizophrenia Brennand K, Savas JN, Kim Y, Tran N, Simone A, Hashimoto-Torii K, Beaumont KG, Kim HJ, Topol A, Ladran I, Abdelrahim M, Matikainen-Ankney B, Chao S-H, Mrksich M, Rakic P, Fang G, Zhang B, Yates 3rd JR, Gage FH. Mol Psychiatry 2015; 20(3): 361-368.
Consistent with recent reports indicating that neurons differentiated in vitro from human-induced pluripotent stem cells (hiPSCs) are immature relative to those in the human brain, gene expression comparisons of our hiPSC-derived neurons to the Allen BrainSpan Atlas indicate that they most resemble fetal brain tissue. This finding suggests that, rather than modeling the late features of schizophrenia (SZ), hiPSC-based models may be better suited for the study of disease predisposition. The authors now report that a significant fraction of the gene signature of SZ hiPSC-derived neurons is conserved in SZ hiPSC neural progenitor cells (NPCs). They used two independent discovery-based approaches-microarray gene expression and stable isotope labeling by amino acids in cell culture (SILAC) quantitative proteomic mass spectrometry analyses-to identify cellular phenotypes in SZ hiPSC NPCs from four SZ patients. From the authors' findings that SZ hiPSC NPCs show abnormal gene expression and protein levels related to cytoskeletal remodeling and oxidative stress, they predicted, and subsequently observed, aberrant migration and increased oxidative stress in SZ hiPSC NPCs. These reproducible NPC phenotypes were identified through scalable assays that can be applied to expanded cohorts of SZ patients, making them a potentially valuable tool with which to study the developmental mechanisms contributing to SZ.

Daytime Spikes In Dopaminergic Activity Drive Rapid Mood-Cycling In Mice Sidor MM, Spencer SM, Dzirasa K, Parekh PK, Tye KM, Warden MR, Arey RN, Enwright 3rd JF, Jacobsen JPR, Kumar S, Remillard EM, Caron MG, Deisseroth K, McClung CA. Mol Psychiatry 2015; 5. [Epub ahead of print].
Disruptions in circadian rhythms and dopaminergic activity are involved in the pathophysiology of bipolar disorder, though their interaction remains unclear. Moreover, a lack of animal models that display spontaneous cycling between mood states has hindered our mechanistic understanding of mood switching. Here, the authors find that mice with a mutation in the circadian Clock gene (ClockΔ19) exhibit rapid mood-cycling, with a profound manic-like phenotype emerging during the day following a period of euthymia at night. Mood-cycling coincides with abnormal daytime spikes

in ventral tegmental area (VTA) dopaminergic activity, tyrosine hydroxylase (TH) levels and dopamine synthesis. To determine the significance of daytime increases in VTA dopamine activity to manic behaviors, the authors developed a novel optogenetic stimulation paradigm that produces a sustained increase in dopamine neuronal activity and find that this induces a manic-like behavioral state. Time-dependent dampening of TH activity during the day reverses manic-related behaviors in ClockΔ19 mice. Finally, the authors show that CLOCK acts as a negative regulator of TH transcription, revealing a novel molecular mechanism underlying cyclic changes in mood-related behavior. Taken together, these studies have identified a mechanistic connection between circadian gene disruption and the precipitation of manic episodes in bipolar disorder.

Spatial Encoding Of Cyclic AMP Signaling Specificity By GPCR Endocytosis Tsvetanova NG, von Zastrow M. Nat Chem Biol 2014; 10(12): 1061-1065.
G protein-coupled receptors (GPCRs) are well known to signal via cyclic AMP (cAMP) production at the plasma membrane, but it is now clear that various GPCRs also signal after internalization. Apart from its temporal impact through prolonging the cellular response, the authors wondered whether the endosome-initiated signal encodes any discrete spatial information. Using the β2-adrenoceptor (β2-AR) as a model, they show that endocytosis is required for the full repertoire of downstream cAMP-dependent transcriptional control. Next, they describe an orthogonal optogenetic approach to definitively establish that the location of cAMP production is indeed the critical variable determining the transcriptional response. Finally, their results suggest that this spatial encoding scheme helps cells functionally discriminate chemically distinct β2-AR ligands according to differences in their ability to promote receptor endocytosis. These findings reveal a discrete principle for achieving cellular signaling specificity based on endosome-mediated spatial encoding of intracellular second messenger production and 'location-aware' downstream transcriptional control.

Immunomodulatory Lysophosphatidylserines Are Regulated By ABHD16A and ABHD12 Interplay Kamat SS, Camara K, Parsons WH, Chen D-H, Dix MM, Bird TD, Howell AR, Cravatt BF. Nat Chem Biol 2015; 11(2): 164-171.
Lysophosphatidylserines (lyso-PSs) are a class of signaling lipids that regulate immunological and neurological processes. The metabolism of lyso-PSs remains poorly understood in vivo. Recently, the authors determined that ABHD12 is a major brain lyso-PS lipase, implicating lyso-PSs in the neurological disease polyneuropathy, hearing loss, ataxia, retinitis pigmentosa and cataract (PHARC), which is caused by null mutations in the ABHD12 gene. Here, the authors couple activity-based profiling with pharmacological and genetic methods to annotate the poorly characterized enzyme ABHD16A as a phosphatidylserine (PS) lipase that generates lyso-PS in mammalian systems. They describe a small-molecule inhibitor of ABHD16A that depletes lyso-PSs from cells, including lymphoblasts derived from subjects with PHARC. In mouse macrophages, disruption of ABHD12 and ABHD16A respectively increases and decreases both lyso-PSs and lipopolysaccharide-induced cytokine production. Finally, Abhd16a(-/-) mice have decreased brain lyso-PSs, which runs counter to the elevation in lyso-PS in Abhd12(-/-) mice. These findings illuminate an ABHD16A-ABHD12 axis that dynamically regulates lyso-PS metabolism in vivo, designating these enzymes as potential targets for treating neuroimmunological disorders.

Understanding Opioid Reward Fields HL, Margolis EB. Trends Neurosci 2015. [Epub ahead of print].
Opioids are the most potent analgesics in clinical use; however, their powerful rewarding properties can lead to addiction. The scientific challenge is to retain analgesic potency while limiting the development of tolerance, dependence, and addiction. Both rewarding and analgesic actions of opioids depend upon actions at the mu opioid (MOP) receptor. Systemic opioid reward requires MOP receptor function in the midbrain ventral tegmental area (VTA) which contains dopaminergic neurons. VTA dopaminergic neurons are implicated in various aspects of reward including reward prediction error, working memory, and incentive salience. It is now clear that subsets of VTA neurons have different pharmacological properties and participate in separate circuits. The degree to which MOP receptor agonists act on different VTA circuits depends upon the behavioral state of the animal, which can be altered by manipulations such as food deprivation or prior exposure to MOP receptor agonists.

Epigenetic Mechanisms In Fear Conditioning: Implications For Treating Post-Traumatic Stress Disorder Kwapis JL, Wood MA. Trends Neurosci 2014; 37(12): 706-720.
Post-traumatic stress disorder (PTSD) and other anxiety disorders stemming from dysregulated fear memory are problematic and costly. Understanding the molecular mechanisms that contribute to the formation and maintenance of these persistent fear associations is crucial to developing treatments for PTSD. Epigenetic mechanisms, which control gene expression to produce long-lasting changes in cellular function, may support the formation of fear memory underlying PTSD. The authors address here the role of epigenetic mechanisms in the formation, storage, updating, and extinction of fear memories. They also discuss methods of targeting these epigenetic mechanisms to reduce the initial formation of fear memory or to enhance its extinction. Epigenetic mechanisms may provide a novel target for pharmaceutical and other treatments to reduce aversive memory contributing to PTSD.

Millisecond-Scale Motor Encoding In A Cortical Vocal Area Tang C, Chehayeb D, Srivastava K, Nemenman I, Sober SJ. PLoS Biol 2014; 12(12): e1002018.
Studies of motor control have almost universally examined firing rates to investigate how the brain shapes behavior. In principle, however, neurons could encode information through the precise temporal patterning of their spike trains as well as (or instead of) through their firing rates. Although the importance of spike timing has been demonstrated in sensory systems, it is largely unknown whether timing differences in motor areas could affect behavior. The authors tested the hypothesis that significant information about trial-by-trial variations in behavior is represented by spike timing in the songbird vocal motor system. They found that neurons in motor cortex convey information via spike timing far more often than via spike rate and that the amount of information conveyed at the millisecond timescale greatly exceeds the information available from spike counts. These results demonstrate that information can be represented by spike timing in motor circuits and suggest that timing variations evoke differences in behavior.

Mechanism of Inactivation of γ-Aminobutyric Acid Aminotransferase by (1S,3S)-3-Amino-4-difluoromethylene-1-cyclopentanoic Acid (CPP-115) Lee H, Doud EH, Wu R, Sanishvili R, Juncosa JI, Liu D, Kelleher NL, Silverman RB. J Am Chem Soc 2015; 137(7): 2628-2640.
γ-Aminobutyric acid aminotransferase (GABA-AT) is a pyridoxal 5'-phosphate (PLP)-dependent enzyme that degrades GABA, the principal inhibitory neurotransmitter in mammalian cells. When

the concentration of GABA falls below a threshold level, convulsions can occur. Inhibition of GABA-AT raises GABA levels in the brain, which can terminate seizures as well as have potential therapeutic applications in treating other neurological disorders, including drug addiction. Among the analogues that the authors previously developed, (1S,3S)-3-amino-4-difluoromethylene-1-cyclopentanoic acid (CPP-115) showed 187 times greater potency than that of vigabatrin, a known inactivator of GABA-AT and approved drug (Sabril) for the treatment of infantile spasms and refractory adult epilepsy. Recently, CPP-115 was shown to have no adverse effects in a Phase I clinical trial. Here the authors report a novel inactivation mechanism for CPP-115, a mechanism-based inactivator that undergoes GABA-AT-catalyzed hydrolysis of the difluoromethylene group to a carboxylic acid with concomitant loss of two fluoride ions and coenzyme conversion to pyridoxamine 5'-phosphate (PMP). The partition ratio for CPP-115 with GABA-AT is about 2000, releasing cyclopentanone-2,4-dicarboxylate (22) and two other precursors of this compound (20 and 21). Time-dependent inactivation occurs by a conformational change induced by the formation of the aldimine of 4-aminocyclopentane-1,3-dicarboxylic acid and PMP (20), which disrupts an electrostatic interaction between Glu270 and Arg445 to form an electrostatic interaction between Arg445 and the newly formed carboxylate produced by hydrolysis of the difluoromethylene group in CPP-115, resulting in a noncovalent, tightly bound complex. This represents a novel mechanism for inactivation of GABA-AT and a new approach for the design of mechanism-based inactivators in general.

DAT Isn't All That: Cocaine Reward and Reinforcement Require Toll-Like Receptor 4 Signaling Northcutt AL, Hutchinson MR, Wang X, Baratta MV, Hiranita T, Cochran TA, Pomrenze MB, Galer EL, Kopajtic TA, Li CM, Amat J, Larson G, Cooper DC, Huang Y, O'Neill CE, Yin H, Zahniser NR, Katz JL, Rice KC, Maier SF, Bachtell RK, Watkins LR. Mol Psychiatry 2015. [Epub ahead of print].
The initial reinforcing properties of drugs of abuse, such as cocaine, are largely attributed to their ability to activate the mesolimbic dopamine system. Resulting increases in extracellular dopamine in the nucleus accumbens (NAc) are traditionally thought to result from cocaine's ability to block dopamine transporters (DATs). Here the authors demonstrate that cocaine also interacts with the immunosurveillance receptor complex, Toll-like receptor 4 (TLR4), on microglial cells to initiate central innate immune signaling. Disruption of cocaine signaling at TLR4 suppresses cocaine-induced extracellular dopamine in the NAc, as well as cocaine conditioned place preference and cocaine self-administration. These results provide a novel understanding of the neurobiological mechanisms underlying cocaine reward/reinforcement that includes a critical role for central immune signaling, and offer a new target for medication development for cocaine abuse treatment.

Endogenous Adenosine A3 Receptor Activation Selectively Alleviates Persistent Pain States Little JW, Ford A, Symons-Liguori AM, Chen Z, Janes K, Doyle T, Xie J, Luongo L, Tosh DK, Maione S, Bannister K, Dickenson AH, Vanderah TW, Porreca F, Jacobson KA, Salvemini D. Brain 2015; 138(Pt 1): 28-35.
Chronic pain is a global burden that promotes disability and unnecessary suffering. To date, efficacious treatment of chronic pain has not been achieved. Thus, new therapeutic targets are needed. Here, the authors demonstrate that increasing endogenous adenosine levels through selective adenosine kinase inhibition produces powerful analgesic effects in rodent models of experimental neuropathic pain through the A3 adenosine receptor (A3AR, now known as ADORA3) signalling pathway. Similar results were obtained by the administration of a novel and

highly selective A3AR agonist. These effects were prevented by blockade of spinal and supraspinal A3AR, lost in A3AR knock-out mice, and independent of opioid and endocannabinoid mechanisms. A3AR activation also relieved non-evoked spontaneous pain behaviours without promoting analgesic tolerance or inherent reward. Further examination revealed that A3AR activation reduced spinal cord pain processing by decreasing the excitability of spinal wide dynamic range neurons and producing supraspinal inhibition of spinal nociception through activation of serotonergic and noradrenergic bulbospinal circuits. Critically, engaging the A3AR mechanism did not alter nociceptive thresholds in non-neuropathy animals and therefore produced selective alleviation of persistent neuropathic pain states. These studies reveal A3AR activation by adenosine as an endogenous anti-nociceptive pathway and support the development of A3AR agonists as novel therapeutics to treat chronic pain.

Stabilization Of Morphine Tolerance With Long-Term Dosing: Association With Selective Upregulation Of Mu-Opioid Receptor Splice Variant mRNAs Xu J, Faskowitz AJ, Rossi GC, Xu M, Lu Z, Pan Y-X, Pasternak GW. Proc Natl Acad Sci U S A 2015; 112(1): 279-284.
Chronic morphine administration is associated with the development of tolerance, both clinically and in animal models. Many assume that tolerance is a continually progressive response to chronic opioid dosing. However, clinicians have long appreciated the ability to manage cancer pain in patients for months on stable opioid doses, implying that extended dosing may eventually result in a steady state in which the degree of tolerance remains constant despite the continued administration of a fixed morphine dose. Preclinical animal studies have used short-term paradigms, typically a week or less, whereas the clinical experience is based upon months of treatment. Chronic administration of different fixed morphine doses produced a progressive increase in the ED50 that peaked at 3 wk in mice, consistent with prior results at shorter times. Continued morphine dosing beyond 3 wk revealed stabilization of the level of tolerance for up to 6 wk with no further increase in the ED50. The degree of tolerance at all time points was dependent upon the dose of morphine. The mRNA levels for the various mu opioid receptor splice variants were assessed to determine whether stabilization of morphine tolerance was associated with changes in their levels. After 6 wk of treatment, mRNA levels of the variants increased as much as 300-fold for selected variants in specific brain regions. These findings reconcile preclinical and clinical observations regarding the development of morphine tolerance.

A Peripheral Endocannabinoid Mechanism Contributes To Glucocorticoid-Mediated Metabolic Syndrome vBowles NP, Karatsoreos IN, Li X, Vemuri VK, Wood J-A, Li Z, Tamashiro KLK, Schwartz GJ, Makriyannis AM, Kunos G, Hillard CJ, McEwen BS, Hill MN. Proc Natl Acad Sci USA 2015; 112(1): 285-290.
Glucocorticoids are known to promote the development of metabolic syndrome through the modulation of both feeding pathways and metabolic processes; however, the precise mechanisms of these effects are not well-understood. Recent evidence shows that glucocorticoids possess the ability to increase endocannabinoid signaling, which is known to regulate appetite, energy balance, and metabolic processes through both central and peripheral pathways. The aim of this study was to determine the role of endocannabinoid signaling in glucocorticoid-mediated obesity and metabolic syndrome. Using a mouse model of excess corticosterone exposure, the authors found that the ability of glucocorticoids to increase adiposity, weight gain, hormonal dysregulation, hepatic steatosis, and dyslipidemia was reduced or reversed in mice lacking the cannabinoid CB1 receptor as well as mice treated with the global CB1 receptor antagonist AM251. Similarly, a neutral,

peripherally restricted CB1 receptor antagonist (AM6545) was able to attenuate the metabolic phenotype caused by chronic corticosterone, suggesting a peripheral mechanism for these effects. Biochemical analyses showed that chronic excess glucocorticoid exposure produced a significant increase in hepatic and circulating levels of the endocannabinoid anandamide, whereas no effect was observed in the hypothalamus. To test the role of the liver, specific and exclusive deletion of hepatic CB1 receptor resulted in a rescue of the dyslipidemic effects of glucocorticoid exposure, while not affecting the obesity phenotype or the elevations in insulin and leptin. Together, these data indicate that glucocorticoids recruit peripheral endocannabinoid signaling to promote metabolic dysregulation, with hepatic endocannabinoid signaling being especially important for changes in lipid metabolism.

Disruption Of the Na+ Ion Binding Site As A Mechanism For Positive Allosteric Modulation Of the Mu-Opioid Receptor Livingston KE, Traynor JR. Proc Natl Acad Sci USA 2014; 111(51): 18369-18374.
Positive allosteric modulation of the mu-opioid receptor (MOPr), the site of action of all clinically used opioids, represents a potential approach for the management of pain. The authors recently reported on positive allosteric modulators of MOPr (mu-PAMs), a class A G protein coupled receptor (GPCR). This study was designed to examine the mechanism of allostery by comparing the degree to which opioid ligand structure governs modulation. To do this the authors examined the interaction of the mu-PAM, BMS-986122, with a chemically diverse range of MOPr orthosteric ligands. Generally, for full agonists BMS-986122 enhanced the binding affinity and potency to activate G protein with no alteration in the maximal effect. In contrast, lower efficacy agonists including morphine were insensitive to alterations in binding affinity and showed little to no change in potency to stimulate G protein. Instead, there was an increase in maximal G protein stimulation. Antagonists were unresponsive to the modulatory effects of BMS-986122. Sodium is a known endogenous allosteric modulator of MOPr and alters orthosteric agonist affinity and efficacy. The sensitivity of an orthosteric ligand to BMS-986122 was strongly correlated with its sensitivity to NaCl. In addition, BMS-986122 decreased the ability of NaCl to modulate agonist binding in an allosteric fashion. Overall, BMS-986122 displayed marked probe dependence that was based upon the efficacy of the orthosteric ligand and can be explained using the Monod-Wyman-Changeux two-state model of allostery. Furthermore, disruption of the Na(+) ion binding site may represent a common mechanism for allosteric modulation of class A GPCRs.

Inoculation Stress Hypothesis Of Environmental Enrichment Crofton EJ, Zhang Y, Green TA. Neurosci Biobehav Rev 2015; 49: 19-31.
One hallmark of psychiatric conditions is the vast continuum of individual differences in susceptibility vs. resilience resulting from the interaction of genetic and environmental factors. The environmental enrichment paradigm is an animal model that is useful for studying a range of psychiatric conditions, including protective phenotypes in addiction and depression models. The major question is how environmental enrichment, a non-drug and non-surgical manipulation, can produce such robust individual differences in such a wide range of behaviors. This paper draws from a variety of published sources to outline a coherent hypothesis of inoculation stress as a factor producing the protective enrichment phenotypes. The basic tenet suggests that chronic mild stress from living in a complex environment and interacting non-aggressively with conspecifics can inoculate enriched rats against subsequent stressors and/or drugs of abuse. This paper reviews the enrichment phenotypes, mulls the fundamental nature of environmental enrichment vs. isolation,

discusses the most appropriate control for environmental enrichment, and challenges the idea that cortisol/corticosterone equals stress. The intent of the inoculation stress hypothesis of environmental enrichment is to provide a scaffold with which to build testable hypotheses for the elucidation of the molecular mechanisms underlying these protective phenotypes and thus provide new therapeutic targets to treat psychiatric/neurological conditions.

Kinetically Selective Inhibitors of Histone Deacetylase 2 (HDAC2) as Cognition Enhancers
Wagner FF, Zhang Y-L, Fass DM, Joseph N, Gale JP, Weiwer M, McCarren P, Fisher SL, Kaya T, Zhao W-N, Reis SA, Hennig KM, Thomas M, Lemercier BC, Lewis MC, Guan JS, Moyer MP, Scolnick E, Haggarty SJ, Tsai L-H, Holson EB. Chem Sci 2015; 6(1): 804-815.
Aiming towards the development of novel nootropic therapeutics to address the cognitive impairment common to a range of brain disorders, the authors set out to develop highly selective small molecule inhibitors of HDAC2, a chromatin modifying histone deacetylase implicated in memory formation and synaptic plasticity. Novel ortho-aminoanilide inhibitors were designed and evaluated for their ability to selectively inhibit HDAC2 versus the other Class I HDACs. Kinetic and thermodynamic binding properties were essential elements of our design strategy and two novel classes of ortho-aminoanilides, that exhibit kinetic selectivity (biased residence time) for HDAC2 versus the highly homologous isoform HDAC1, were identified. These kinetically selective HDAC2 inhibitors (BRD6688 and BRD4884) increased H4K12 and H3K9 histone acetylation in primary mouse neuronal cell culture assays, in the hippocampus of CK-p25 mice, a model of neurodegenerative disease, and rescued the associated memory deficits of these mice in a cognition behavioural model. These studies demonstrate for the first time that selective pharmacological inhibition of HDAC2 is feasible and that inhibition of the catalytic activity of this enzyme may serve as a therapeutic approach towards enhancing the learning and memory processes that are affected in many neurological and psychiatric disorders.

Genomic Mosaicism With Increased Amyloid Precursor Protein (APP) Gene Copy Number In Single Neurons From Sporadic Alzheimer's Disease Brains Bushman DM, Kaeser GE, Siddoway B, Westra JW, Rivera RR, Rehen SK, Yung YC, Chun J. Elife 2015; 4.
Previous reports have shown that individual neurons of the brain can display somatic genomic mosaicism of unknown function. In this study, the authors report altered genomic mosaicism in single, sporadic Alzheimer's disease (AD) neurons characterized by increases in DNA content and amyloid precursor protein (APP) gene copy number. AD cortical nuclei displayed large variability with average DNA content increases of ~8% over non-diseased controls that were unrelated to trisomy 21. Two independent single-cell copy number analyses identified amplifications at the APP locus. The use of single-cell qPCR identified up to 12 copies of APP in sampled neurons. Peptide nucleic acid (PNA) probes targeting APP, combined with super-resolution microscopy detected primarily single fluorescent signals of variable intensity that paralleled single-cell qPCR analyses. These data identify somatic genomic changes in single neurons, affecting known and unknown loci, which are increased in sporadic AD, and further indicate functionality for genomic mosaicism in the CNS.

Neural Substrates Of Inhibitory Control Deficits In 22q11.2 Deletion Syndrome† Montojo CA, Jalbrzikowski M, Congdon E, Domicoli S, Chow C, Dawson C, Karlsgodt KH, Bilder RM, Bearden CE. Cereb Cortex 2015; 25(4): 1069-1079.
22q11.2 deletion syndrome (22q11DS) is associated with elevated levels of impulsivity, inattention, and distractibility, which may be related to underlying neurobiological dysfunction due to haploinsufficiency for genes involved in dopaminergic neurotransmission (i.e. catechol-O-methyltransferase). The Stop-signal task has been employed to probe the neural circuitry involved in response inhibition (RI); findings in healthy individuals indicate that a fronto-basal ganglia network underlies successful inhibition of a prepotent motor response. However, little is known about the neurobiological substrates of RI difficulties in 22q11DS. Here, the authors investigated this using functional magnetic resonance imaging while 45 adult participants (15 22q11DS patients, 30 matched controls) performed the Stop-signal task. Healthy controls showed significantly greater activation than 22q11DS patients within frontal cortical and basal ganglia regions during successful RI, whereas 22q11DS patients did not show increased neural activity relative to controls in any regions. Using the Barratt Impulsivity Scale, the authors also investigated whether neural dysfunction during RI was associated with cognitive impulsivity in 22q11DS patients. RI-related activity within left middle frontal gyrus and basal ganglia was associated with severity of self-reported cognitive impulsivity. These results suggest reduced engagement of RI-related brain regions in 22q11DS patients, which may be relevant to characteristic behavioral manifestations of the disorder.

Pyramidal Cell Selective Ablation Of N-Methyl-D-Aspartate Receptor 1 Causes Increase In Cellular and Network Excitability Tatard-Leitman VM, Jutzeler CR, Suh J, Saunders JA, Billingslea EN, Morita S, White R, Featherstone RE, Ray R, Ortinski PI, Banerjee A, Gandal MJ, Lin R, Alexandrescu A, Liang Y, Gur RE, Borgmann-Winter KE, Carlson GC, Hahn C-G, Siegel SJ. Biol Psychiatry 2015; 77(6): 556-568.
Neuronal activity at gamma frequency is impaired in schizophrenia (SZ) and is considered critical for cognitive performance. Such impairments are thought to be due to reduced N-methyl-D-aspartate receptor (NMDAR)-mediated inhibition from parvalbumin interneurons, rather than a direct role of impaired NMDAR signaling on pyramidal neurons. However, recent studies suggest a direct role of pyramidal neurons in regulating gamma oscillations. In particular, a computational model has been proposed in which phasic currents from pyramidal cells could drive synchronized feedback inhibition from interneurons. As such, impairments in pyramidal neuron activity could lead to abnormal gamma oscillations. However, this computational model has not been tested experimentally and the molecular mechanisms underlying pyramidal neuron dysfunction in SZ remain unclear. In the present study, the authors tested the hypothesis that SZ-related phenotypes could arise from reduced NMDAR signaling in pyramidal neurons using forebrain pyramidal neuron specific NMDA receptor 1 knockout mice. The mice displayed increased baseline gamma power, as well as sociocognitive impairments. These phenotypes were associated with increased pyramidal cell excitability due to changes in inherent membrane properties. Interestingly, mutant mice showed decreased expression of GIRK2 channels, which has been linked to increased neuronal excitability. These data demonstrate for the first time that NMDAR hypofunction in pyramidal cells is sufficient to cause electrophysiological, molecular, neuropathological, and behavioral changes related to SZ.

Chronic Cannabinoid Receptor 2 Activation Reverses Paclitaxel Neuropathy Without Tolerance Or Cannabinoid Receptor 1-Dependent Withdrawal Deng L, Guindon J, Cornett BL, Makriyannis A, Mackie K, Hohmann AG. Biol Psychiatry 2015; 77(5): 475-487.
Mixed cannabinoid receptor 1 and 2 (CB1 and CB2) agonists such as Δ(9)-tetrahydrocannabinol (Δ(9)-THC) can produce tolerance, physical withdrawal, and unwanted CB1-mediated central nervous system side effects. Whether repeated systemic administration of a CB2-preferring agonist engages CB1 receptors or produces CB1-mediated side effects is unknown. The authors evaluated antiallodynic efficacy, possible tolerance, and cannabimimetic side effects of repeated dosing with a CB2-preferring agonist AM1710 in a model of chemotherapy-induced neuropathy produced by paclitaxel using CB1 knockout (CB1KO), CB2 knockout (CB2KO), and wild-type (WT) mice. Comparisons were made with the prototypic classic cannabinoid Δ(9)-THC. The authors also explored the site and possible mechanism of action of AM1710. Paclitaxel-induced mechanical and cold allodynia developed to an equivalent degree in CB1KO, CB2KO, and WT mice. Both AM1710 and Δ(9)-THC suppressed established paclitaxel-induced allodynia in WT mice. In contrast to Δ(9)-THC, chronic administration of AM1710 did not engage CB1 activity or produce antinociceptive tolerance, CB1-mediated cannabinoid withdrawal, hypothermia, or motor dysfunction. Antiallodynic efficacy of systemic administration of AM1710 was absent in CB2KO mice and WT mice receiving the CB2 antagonist AM630, administered either systemically or intrathecally. Intrathecal administration of AM1710 also attenuated paclitaxel-induced allodynia in WT mice, but not CB2KO mice, implicating a possible role for spinal CB2 receptors in AM1710 antiallodynic efficacy. Finally, both acute and chronic administration of AM1710 decreased messenger RNA levels of tumor necrosis factor-α and monocyte chemoattractant protein 1 in lumbar spinal cord of paclitaxel-treated WT mice. These results highlight the potential of prolonged use of CB2 agonists for managing chemotherapy-induced allodynia with a favorable therapeutic ratio marked by sustained efficacy and absence of tolerance, physical withdrawal, or CB1-mediated side effects.

Methylphenidate Exerts Dose-Dependent Effects On Glutamate Receptors and Behaviors Cheng J, Xiong Z, Duffney LJ, Wei J, Liu A, Liu S, Chen G-J, Yan Z. Biol Psychiatry 2014; 76(12): 953-962.
Methylphenidate (MPH), a psychostimulant drug used to treat attention-deficit/hyperactivity disorder, produces the effects of increasing alertness and improving attention. However, misuse of MPH has been associated with an increased risk of aggression and psychosis. The authors sought to determine the molecular mechanism underlying the complex actions of MPH. Adolescent (4-week-old) rats were given one injection of MPH at different doses. The impact of MPH on glutamatergic signaling in pyramidal neurons of prefrontal cortex was measured. Behavioral changes induced by MPH were also examined in parallel. Administration of low-dose (.5 mg/kg) MPH selectively potentiated N-methyl-D-aspartate receptor (NMDAR)-mediated excitatory postsynaptic currents (EPSCs) via adrenergic receptor activation, whereas high-dose (10 mg/kg) MPH suppressed both NMDAR-mediated and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor-mediated EPSCs. The dual effects of MPH on EPSCs were associated with bidirectional changes in the surface level of glutamate receptor subunits. Behavioral tests also indicated that low-dose MPH facilitated prefrontal cortex-mediated temporal order recognition memory and attention. Animals injected with high-dose MPH exhibited significantly elevated locomotive activity. Inhibiting the function of synaptosomal-associated protein 25, a key SNARE protein involved in NMDAR exocytosis, blocked the increase of NMDAR-mediated EPSCs by low-dose MPH. In animals exposed to repeated stress, administration of low-dose MPH effectively restored NMDAR function

and temporal order recognition memory via a mechanism dependent on synaptosomal-associated protein 25. These results provide a potential mechanism underlying the cognitive-enhancing effects of low-dose MPH as well as the psychosis-inducing effects of high-dose MPH.

Direct Regulation of Diurnal Drd3 Expression and Cocaine Reward by NPAS2 Ozburn AR, Falcon E, Twaddle A, Nugent AL, Gillman AG, Spencer SM, Arey RN, Mukherjee S, Lyons-Weiler J, Self DW, McClung CA. Biol Psychiatry 2015; 77(5): 425-433.
Circadian gene disruptions are associated with the development of psychiatric disorders, including addiction. However, the mechanisms by which circadian genes regulate reward remain poorly understood. The authors used mice with a mutation in Npas2 and adeno-associated virus-short hairpin RNA mediated knockdown of Npas2 and Clock in the nucleus accumbens (NAc). They performed conditioned place preference assays. They utilized cell sorting quantitative real-time polymerase chain reaction, and chromatin immunoprecipitation followed by deep sequencing. Npas2 mutants exhibit decreased sensitivity to cocaine reward, which is recapitulated with a knockdown of neuronal PAS domain protein 2 (NPAS2) specifically in the NAc, demonstrating the importance of NPAS2 in this region. Interestingly, reducing circadian locomotor output cycles kaput (CLOCK) (a homologue of NPAS2) in the NAc had no effect, suggesting an important distinction in NPAS2 and CLOCK function. Furthermore, the authors found that NPAS2 expression is restricted to Drd1 expressing neurons while CLOCK is ubiquitous. Moreover, NPAS2 and CLOCK have distinct temporal patterns of DNA binding, and we identified novel and unique binding sites for each protein. The authors identified the Drd3 dopamine receptor as a direct transcriptional target of NPAS2 and found that NPAS2 knockdown in the NAc disrupts its diurnal rhythm in expression. Chronic cocaine treatment likewise disrupts the normal rhythm in Npas2 and Drd3 expression in the NAc, which may underlie behavioral plasticity in response to cocaine. Together, these findings identify an important role for the circadian protein, NPAS2, in the NAc in the regulation of dopamine receptor expression and drug reward.

Genome-Wide Association Study Of Nicotine Dependence In American Populations: Identification Of Novel Risk Loci In Both African-Americans and European-Americans
Gelernter J, Kranzler HR, Sherva R, Almasy L, Herman AI, Koesterer R, Zhao H, Farrer LA. Biol Psychiatry 2015; 77(5): 493-503.
The authors report a genome-wide association study (GWAS) of nicotine dependence defined on the basis of scores on the Fagerström Test for Nicotine Dependence in European-American (EA) and African-American (AA) populations. The authors' sample, from the one used in their previous GWAS, included only subjects who had smoked >100 cigarettes lifetime (2114 EA and 2602 AA subjects) and an additional 927 AA and 2003 EA subjects from the Study of Addiction: Genetics and Environment project [via the database of Genotypes and Phenotypes (dbGAP)]. GWAS analysis considered Fagerström Test for Nicotine Dependence score as an ordinal trait, separately in each population and sample and by combining the results in meta-analysis. The authors also conducted analyses that were adjusted for other substance use disorder criteria in a single nucleotide polymorphism (SNP) subset. In EAs, one chromosome 7 intergenic region was genome-wide significant (GWS): rs13225753, $p = 3.48 \times 10(-8)$ (adjusted). In AAs, GWS associations were observed at numerous SNPs mapped to a region on chromosome 14 of >305,000 base pairs (minimal $p = 4.74 \times 10(-10)$). Two chromosome 8 regions were associated: $p = 4.45 \times 10(-8)$ at DLC1 SNP rs289519 (unadjusted) and $p = 1.10 \times 10(-9)$ at rs6996964 (adjusted for other substances), located between CSGALNACT1 and INTS10. No GWS associations were observed at

the chromosome 15 nicotinic receptor gene cluster (CHRNA5-CHRNA3-CHRNB4) previously associated with nicotine dependence and smoking quantity traits. TSNAX-DISC1 SNP rs821722 (p = 1.46 × 10(-7)) was the most significant result with substantial contributions from both populations; the authors previously identified DISC1 associations with opioid dependence. Pathway analysis identified association with nitric oxide synthase and adenosine monophosphate-activated protein kinase pathways in EAs. The key risk loci identified, which require replication, offer novel insights into nicotine dependence biology.

A Novel Anxiogenic Role For the Delta Opioid Receptor Expressed In GABAergic Forebrain Neurons Chu Sin Chung P, Keyworth HL, Martin-Garcia E, Charbogne P, Darcq E, Bailey A, Filliol D, Matifas A, Scherrer G, Ouagazzal A-M, Gaveriaux-Ruff C, Befort K, Maldonado R, Kitchen I, Kieffer BL. Biol Psychiatry 2015; 77(4): 404-415.
The delta opioid receptor (DOR) is broadly expressed throughout the nervous system; it regulates chronic pain, emotional responses, motivation, and memory. Neural circuits underlying DOR activities have been poorly explored by genetic approaches. The authors used conditional mouse mutagenesis to elucidate receptor function in GABAergic neurons of the forebrain. They characterized DOR distribution in the brain of Dlx5/6-CreXOprd1(fl/fl) (Dlx-DOR) mice and tested main central DOR functions through behavioral testing. The DOR proteins were strongly deleted in olfactory bulb and striatum and remained intact in cortex and basolateral amygdala. Olfactory perception, circadian activity, and despair-like behaviors were unchanged. In contrast, locomotor stimulant effects of SNC80 (DOR agonist) and SKF81297 (D1 agonist) were abolished and increased, respectively. The Dlx-DOR mice showed lower levels of anxiety in the elevated plus maze, opposing the known high anxiety in constitutive DOR knockout animals. Also, Dlx-DOR mice reached the food more rapidly in a novelty suppressed feeding task, despite their lower motivation for food reward observed in an operant paradigm. Finally, c-fos protein staining after novelty suppressed feeding was strongly reduced in amygdala, concordant with the low anxiety phenotype of Dlx-DOR mice. The authors demonstrate that DORs expressed in the forebrain mediate the described locomotor effect of SNC80 and inhibit D1-stimulated hyperactivity. These data also reveal an unanticipated anxiogenic role for this particular DOR subpopulation, with a potential novel adaptive role. In emotional responses, DORs exert dual anxiolytic and anxiogenic roles, both of which may have implications in the area of anxiety disorders.

Genetics Of Complex Traits In Psychiatry Gelernter J. Biol Psychiatry 2015; 77(1): 36-42.
Virtually all psychiatric traits are genetically complex. This article discusses the genetics of complex traits in psychiatry. The complexity is accounted for by numerous factors, including multiple risk alleles, epistasis, and epigenetic effects such as methylation. Risk alleles can individually be common or rare, and can include, for example, single nucleotide polymorphisms and copy number variants that are transmitted or are new mutations, and other kinds of variation. Many different kinds of variation can be important for trait risk, either together in various proportions or as different factors in different subjects. Until more recently, approaches to complex traits were limited, and consequently only a few variants, usually of individually minor effect, were identified. At the present time, a much richer armamentarium exists that includes the routine application of genome-wide association studies and next-generation high-throughput sequencing and the combination of this information with other biologically relevant information, such as expression data. We have also seen the emergence of large meta-analysis and mega-analysis consortia. These developments are extremely important for psychiatric genetics, have advanced the

field substantially, and promise formidable gains in the years to come as they are applied more widely.

Interneurons Are Necessary For Coordinated Activity During Reversal Learning In Orbitofrontal Cortex Bissonette GB, Schoenbaum G, Roesch MR, Powell EM. Biol Psychiatry 2015; 77(5): 454-464.
Cerebral cortical gamma-aminobutyric acidergic interneuron dysfunction is hypothesized to lead to cognitive deficits comorbid with human neuropsychiatric disorders, including schizophrenia, autism, and epilepsy. The authors have previously shown that mice that harbor mutations in the Plaur gene, which is associated with schizophrenia, have deficits in frontal cortical parvalbumin-expressing interneurons. Plaur mice have impaired reversal learning, similar to deficits observed in patients with schizophrenia. The authors examined the role of parvalbumin interneurons in orbitofrontal cortex during reversal learning by recording single unit activity from 180 control and 224 Plaur mouse neurons during a serial reversal task. Neural activity was analyzed during correct and incorrect decision choices and reward receipt. Neurons in control mice exhibited strong phasic responses both during discrimination and reversal learning to decisions and rewards, and the strength of the response was correlated with behavioral performance. Although baseline firing was significantly enhanced in Plaur mice, neural selectivity for correct or erroneous decisions was diminished and not correlated with behavior, and reward encoding was downscaled. In addition, Plaur mice showed a significant reduction in the number of neurons that encoded expected outcomes across task phases during the decision period. These data indicate that parvalbumin interneurons are necessary for the representation of outcomes in orbitofrontal cortex. Deficits in inhibition blunt selective neural firing during key decisions, contributing to behavioral inflexibility. These data provide a potential explanation for disorders of cognitive control that accompany the loss of these gamma-aminobutyric acidergic interneurons in human neuropsychiatric disorders, such as autism, epilepsy, and schizophrenia.

Effects Of Adolescent Caffeine Consumption On Cocaine Sensitivity O'Neill CE, Levis SC, Schreiner DC, Amat J, Maier SF, Bachtell RK. Neuropsychopharmacology 2015; 40(4): 813-821.
Caffeine is the most commonly used psychoactive substance, and consumption by adolescents has risen markedly in recent years. The authors identified the effects of adolescent caffeine consumption on cocaine sensitivity and determined neurobiological changes within the nucleus accumbens (NAc) that may underlie caffeine-induced hypersensitivity to cocaine. Male Sprague-Dawley rats consumed caffeine (0.3 g/l) or water for 28 days during adolescence (postnatal day 28-55; P28-P55) or adulthood (P67-P94). Testing occurred in the absence of caffeine during adulthood (P62-82 or P101-121). Cocaine-induced and quinpirole (D2 receptor agonist)-induced locomotion was enhanced in rats that consumed caffeine during adolescence. Adolescent consumption of caffeine also enhanced the development of a conditioned place preference at a sub-threshold dose of cocaine (7.5 mg/kg, i.p.). These behavioral changes were not observed in adults consuming caffeine for an equivalent period of time. Sucrose preferences were not altered in rats that consumed caffeine during adolescence, suggesting there are no differences in natural reward. Caffeine consumption during adolescence reduced basal dopamine levels and augmented dopamine release in the NAc in response to cocaine (5 mg/kg, i.p.). Caffeine consumption during adolescence also increased the expression of the dopamine D2 receptor, dopamine transporter, and adenosine A1 receptor and decreased adenosine A2A receptor expression in the NAc. Consumption of caffeine during adulthood increased adenosine A1 receptor expression in the NAc, but no other protein expression

changes were observed. Together these findings suggest that caffeine consumption during adolescence produced changes in the NAc that are evident in adulthood and may contribute to increases in cocaine-mediated behaviors.

Repeated Social Stress Increases Reward Salience and Impairs Encoding Of Prediction By Rat Locus Coeruleus Neurons Chaijale NN, Snyder K, Arner J, Curtis AL, Valentino RJ. Neuropsychopharmacology 2015; 40(2): 513-523.
Stress is implicated in psychopathology characterized by cognitive dysfunction. Cognitive responses to stress are regulated by the locus coeruleus-norepinephrine (LC-NE) system. As social stress is a prevalent human stressor, this study determined the impact of repeated social stress on the relationship between LC neuronal activity and behavior during the performance of cognitive tasks. Social stress-exposed rats performed better at intradimensional set shifting (IDS) and made fewer perseverative errors during reversal learning (REV). LC neurons of control rats were task responsive, being activated after the choice and before reward. Social stress shifted LC neuronal activity from being task responsive to being reward responsive during IDS and REV. LC neurons of stressed rats were activated by reward and tonically inhibited by reward omission with incorrect choices. In contrast, LC neurons of stress-naive rats were only tonically inhibited by reward omission. Reward-related LC activation in stressed rats was unrelated to predictability because it did not habituate as learning progressed. The findings suggest that social stress history increases reward salience and impairs processes that compute predictability for LC neurons. These effects of social stress on LC neuronal activity could facilitate learning as indicated by improved performance in stressed rats. However, the ability of social stress history to enhance responses to behavioral outcomes may have a role in the association between stress and addictive behaviors. In addition, magnified fluctuations in LC activity in response to opposing behavioral consequences may underlie volatile changes in emotional arousal that characterize post-traumatic stress disorder.

Brief Intermittent Cocaine Self-Administration and Abstinence Sensitizes Cocaine Effects On the Dopamine Transporter and Increases Drug Seeking Calipari ES, Siciliano CA, Zimmer BA, Jones SR. Neuropsychopharmacology 2015; 40(3): 728-735.
Although traditional sensitization paradigms, which result in an augmentation of cocaine-induced locomotor behavior and dopamine (DA) overflow following repeated experimenter-delivered cocaine injections, are often used as a model to study drug addiction, similar effects have been difficult to demonstrate following cocaine self-administration. The authors have recently shown that intermittent access (IntA) to cocaine can result in increased cocaine potency at the DA transporter (DAT); however, traditional sensitization paradigms often show enhanced effects following withdrawal/abstinence periods. Therefore, the authors determined a time course of IntA-induced sensitization by examining the effects of 1 or 3 days of IntA, as well as a 7-day abstinence period on DA function, cocaine potency, and reinforcement. Here they show that cocaine potency is increased following as little as 3 days of IntA and further augmented following an abstinence period. In addition, IntA plus abstinence produced greater evoked DA release in the presence of cocaine as compared with all other groups, demonstrating that following abstinence, both cocaine's ability to increase DA release and inhibit uptake at the DAT, two separate mechanisms for increasing DA levels, are enhanced. Finally, the authors found that IntA-induced sensitization of the DA system resulted in an increased reinforcing efficacy of cocaine, an effect that was augmented after the 7-day abstinence period. These results suggest that sensitization of the DA system may have an important role in the early stages of drug abuse and may drive the increased drug seeking and taking

that characterize the transition to uncontrolled drug use. Human data suggest that intermittency, sensitization, and periods of abstinence have an integral role in the process of addiction, highlighting the importance of utilizing pre-clinical models that integrate these phenomena, and suggesting that IntA paradigms may serve as novel models of human addiction.

The Rostromedial Tegmental Nucleus Modulates Behavioral Inhibition Following Cocaine Self-Administration In Rats Huff ML, LaLumiere RT. Neuropsychopharmacology 2015; 40(4): 861-873.
Recent findings suggest that the mesolimbic dopamine neurons, known to promote cocaine-seeking behavior, are strongly inhibited by a newly characterized region of the midbrain known as the rostromedial tegmental nucleus (RMTg). The RMTg appears to be involved in generating reward-prediction error signals and inhibition of motivated behaviors, suggesting its potential involvement in the extinction of cocaine seeking as well. Therefore, to address this question, male Sprague-Dawley rats underwent surgeries for implantation of catheters and cannulas targeted at the RMTg. After cocaine self-administration, rats underwent modified extinction training. Pre- or post-training intra-RMTg microinjections of the allosteric AMPA receptor potentiator PEPA during the first 5 days of extinction training appeared to enhance the retention of the extinction learning. Following the extinction training, rats underwent cue-induced reinstatement or an 'inactivation-alone' extinction tests. RMTg inactivation before a cue-induced reinstatement session or inactivation alone before a standard extinction session increased overall lever pressing. To determine whether these effects generalized to other motivated behaviors, additional experiments examining food-seeking behavior were also conducted. The results from the food-seeking experiments indicate that PEPA microinjections into the RMTg did not influence the extinction of food seeking and that, at least in rats that had not been given PEPA during the extinction learning experiments, RMTg inactivation had no effect on lever pressing during the cue-induced reinstatement or inactivation-alone tests. These findings suggest that the RMTg provides general behavioral inhibition and is potentially involved in learning to extinguish cocaine-seeking behavior in rats.

The Role of Brain Interleukin-1 in Stress-Enhanced Fear Learning Jones ME, Lebonville CL, Barrus D, Lysle DT. Neuropsychopharmacology 2015; 40: 1289-1296.
Posttraumatic stress disorder (PTSD) has been shown to be associated with pro-inflammatory markers, including elevated plasma levels of interleukin-1β (IL-1β). However, the precise role of neuroinflammation and central immune signaling on the development of this debilitating psychological disorder is not known. Here, the authors used stress-enhanced fear learning (SEFL), an animal model of the disorder, to examine the role of central IL-1β in PTSD. The results show that the severe stressor in SEFL induces a time-dependent increase in IL-1β immunoreactivity and mRNA expression within the dentate gyrus of the dorsal hippocampus (DH). There was no increase in IL-1β in the basolateral amygdala or the perirhinal cortex. Moreover, blocking the action of IL-1β following the severe stressor with IL-1 receptor antagonist (10 μg, intracerebroventricular (i.c.v.), 24 and 48 h after the stressor) prevented the development of SEFL. To provide further support for the role of IL-1β in the development of SEFL, we show that systemic morphine, a treatment which is known to reduce both PTSD and SEFL, also reduces IL-1β expression in the DH induced by the severe stressor. These studies provide the first evidence that IL-1 is involved SEFL and suggest that IL-1 signaling in the brain may have a critical role in the development of PTSD.

Expression of the 5-HT1A Serotonin Receptor in the Hippocampus Is Required for Social Stress Resilience and the Antidepressant-Like Effects Induced by the Nicotinic Partial Agonist Cytisine Mineur YS, Einstein EB, Bentham MP, Wigestrand MB, Blakeman S, Newbold SA, Picciotto MR. Neuropsychopharmacology 2015; 40(4): 938-946.
Nicotinic acetylcholine receptor (nAChR) blockers potentiate the effects of selective serotonin reuptake inhibitors (SSRIs) in some treatment-resistant patients; however, it is not known whether these effects are independent, or whether the two neurotransmitter systems act synergistically. The authors first determined that the SSRI fluoxetine and the nicotinic partial agonist cytisine have synergistic effects in a mouse model of antidepressant efficacy, whereas serotonin depletion blocked the effects of cytisine. Using a pharmacological approach, the authors found that the 5-HT1A agonist 8-OH-DPAT also potentiated the antidepressant-like effects of cytisine, suggesting that this subtype might mediate the interaction between the serotonergic and cholinergic systems. The 5-HT1A receptors are located both presynaptically and postsynaptically. They therefore knocked down 5-HT1A receptors in either the dorsal raphe (presynaptic autoreceptors) or the hippocampus (a brain area with high expression of 5-HT1A heteroreceptors sensitive to cholinergic effects on affective behaviors). Knockdown of 5-HT1A receptors in hippocampus, but not dorsal raphe, significantly decreased the antidepressant-like effect of cytisine. This study suggests that serotonin signaling through postsynaptic 5-HT1A receptors in the hippocampus is critical for the antidepressant-like effects of a cholinergic drug and begins to elucidate the molecular mechanisms underlying interactions between the serotonergic and cholinergic systems related to mood disorders.

Individual Differences in Impulsive Action Reflect Variation in the Cortical Serotonin 5-HT2A Receptor System Fink LH, Anastasio NC, Fox RG, Rice KC, Moeller FG, Cunningham KA. Neuropsychopharmacology 2015. [Epub ahead of print].
Impulsivity is an important feature of multiple neuropsychiatric disorders, and individual variation in the degree of inherent impulsivity could play a role in the generation or exacerbation of problematic behaviors. Serotonin (5-HT) actions at the 5-HT2AR receptor (5-HT2AR) promote and 5-HT2AR antagonists suppress impulsive action (the inability to withhold premature responses; motor impulsivity) upon systemic administration or microinfusion directly into the medial prefrontal cortex (mPFC), a node in the corticostriatal circuit that is thought to play a role in the regulation of impulsive action. The authors hypothesized that the functional capacity of the 5-HT2AR, which is governed by its expression, localization, and protein/protein interactions (eg, postsynaptic density 95 (PSD95)), may drive the predisposition to inherent impulsive action. Stable high-impulsive (HI) and low-impulsive (LI) phenotypes were identified from an outbred rodent population with the 1-choice serial reaction time (1-CSRT) task. HI rats exhibited a greater head-twitch response following administration of the preferential 5-HT2AR agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) and were more sensitive to the effects of the selective 5-HT2AR antagonist M100907 to suppress impulsive action relative to LI rats. A positive correlation was observed between levels of premature responses and 5-HT2AR binding density in frontal cortex ([3H]-ketanserin radioligand binding). Elevated mPFC 5-HT2AR protein expression concomitant with augmented association of the 5-HT2AR with PSD95 differentiated HI from LI rats. The observed differential sensitivity of HI and LI rats to 5-HT2AR ligands and associated distinct 5-HT2AR protein profiles provide evidence that spontaneously occurring individual differences in impulsive action reflect variation in the cortical 5-HT2AR system

Trace Amine-Associated Receptor 1 Regulation of Methamphetamine Intake and Related Traits Harkness JH, Shi X, Janowsky A, Phillips TJ. Neuropsychopharmacology 2015. [Epub ahead of print].
Continued methamphetamine (MA) use is dependent on a positive MA experience and is likely attenuated by sensitivity to the aversive effects of MA. Bidirectional selective breeding of mice for high (MAHDR) or low (MALDR) voluntary consumption of MA demonstrates a genetic influence on MA intake. Quantitative trait locus (QTL) mapping identified a QTL on mouse chromosome 10 that accounts for greater than 50% of the genetically-determined differences in MA intake in the MAHDR and MALDR lines. The trace amine-associated receptor 1 gene (Taar1) is within the confidence interval of the QTL and encodes a receptor (TAAR1) that modulates monoamine neurotransmission and at which MA serves as an agonist. The authors demonstrate the existence of a non-functional allele of Taar1 in the DBA/2J mouse strain, one of the founder strains of the selected lines, and show that this non-functional allele co-segregates with high MA drinking and with reduced sensitivity to MA-induced conditioned taste aversion (CTA) and hypothermia. The functional Taar1 allele, derived from the other founder strain, C57BL/6J, segregates with low MA drinking and heightened sensitivity to MA-induced CTA and hypothermia. A role for TAAR1 in these phenotypes is corroborated in Taar1 transgenic mice: Taar1 knockout mice consume more MA and exhibit insensitivity to MA-induced CTA and hypothermia, compared to Taar1 wildtype mice. These are the first data to show that voluntary MA consumption is, in part, regulated by TAAR1 function. Behavioral and physiological studies indicate that TAAR1 increases sensitivity to aversive effects of MA, and may thereby protect against MA use.

Hypocretin Receptor 2 Antagonism Dose-Dependently Reduces Escalated Heroin Self-Administration in Rat. Schmeichel BE, Barbier E, Misra KK, Contet C, Schlosburg JE, Grigoriadis D, Williams JP, Karlsson C, Pitcairn C, Heilig M, Koob GF, Vendruscolo LF. Neuropsychopharmacology 2015; 40: 1123-1129.
The hypocretin/orexin (HCRT) system has been associated with both positive and negative drug reinforcement, implicating HCRT receptor 1 (HCRT-R1) signaling in drug-related behaviors for all major drug classes, including opioids. However, to date there are limited studies investigating the role of HCRT receptor 2 (HCRT-R2) signaling in compulsive-like drug seeking. Escalation of drug intake with extended access has been suggested to model the transition from controlled drug use to compulsive-like drug seeking/taking. The current study examined the effects of a HCRT-R2 antagonist, NBI-80713, on heroin self-administration in rats allowed short- (1 h; ShA) or long- (12 h; LgA) access to intravenous heroin self-administration. Results indicate that systemically administered NBI-80713 dose-dependently decreased heroin self-administration in LgA, but not in ShA, animals. Quantitative PCR analyses showed an increase in Hcrtr2 mRNA levels in the central amygdala, a stress-related brain region, of LgA rats. These observations suggest a functional role for HCRT-R2 signaling in compulsive-like heroin self-administration associated with extended access and indicate HCRT-R2 antagonism as a potential pharmacological target for the treatment of heroin dependence.

Mouse Model of the OPRM1 (A118G) Polymorphism: Differential Heroin Self-Administration Behavior Compared with Wild-Type Mice Zhang Y, Picetti R, Butelman ER, Ho A, Blendy JA, Kreek MJ. Neuropsychopharmacology 2015; 40: 1091-1100.
Mu-opioid receptors (MOPRs) are the target of heroin and other prescription opioids, which are currently responsible for massive addiction morbidity in the US. The gene coding for the human

MOPR (OPRM1) has an important functional single nucleotide polymorphism (SNP), A118G. The OPRM1 A118G genotype results in substantially increased risk of heroin addiction in humans; however, the neurobiological mechanism for this increased risk is not fully understood. This study examined heroin self-administration (SA) behavior in A112G (G/G) mice, harboring a functionally equivalent SNP in Oprm1 with a similar amino acid substitution, in extended (4 h) SA sessions. Adult male and female G/G mice and 'wild-type' litter mates (A/A) were allowed to self-administer heroin (0.25 mg/kg/unit dose, FR1 with a nose poke response) for 4 h/day, for 10 consecutive days. Half of the mice then continued in a heroin dose-response study, while extinction from heroin SA was studied in the other half. In vivo microdialysis was used to measure acute heroin-induced increases of striatal dopamine in the GG vs AA genotypes. Male and female G/G mice responded for heroin significantly more (and thus had greater intake) than A/A mice, in the initial 10 days of heroin SA, and in the subsequent dose-response study. There were no significant differences in extinction of SA between the A/A and G/G mice. Heroin-induced increases in striatal dopamine levels are higher in the GG mice than in the AA mice. Both male and female G/G mice self-administered more heroin than did A/A mice over a 10-day period, possibly because of the greater increases of heroin-induced striatal dopamine in the GG mice. Furthermore, G/G male mice escalated the amount of heroin self-administration across 10 extended-access sessions more than A/A male mice did. These are the first studies to examine the acquisition of heroin SA in this mouse model. These studies may lead to a better understanding of the neurobiological and behavioral mechanisms that underlie greater risk of heroin addiction in carriers of the A118G SNP.

Effects of Oral and Intravenous Administration of Buspirone on Food-Cocaine Choice in Socially Housed Male Cynomolgus Monkeys Czoty PW, Nader MA. Neuropsychopharmacology 2015; 40: 1072-1083.

Drugs acting at D3 dopamine receptors have been suggested as medications for cocaine dependence. These experiments examined the effects of intravenously and orally administered buspirone, a D2-like receptor antagonist with high affinity for D3 and D4 receptors, on the relative reinforcing strength of cocaine in group-housed male cynomolgus monkeys. Use of socially housed monkeys permitted the assessment of whether social status, known to influence D2-like receptor availability, modulates the behavioral effects of buspirone. Buspirone was administered acutely to monkeys self-administering cocaine under a food-drug choice procedure in which a cocaine self-administration dose-effect curve was determined daily. When administered by either route, buspirone significantly decreased cocaine choice in dominant-ranked monkeys. In subordinate monkeys, however, i.v. buspirone was ineffective on average, and oral buspirone increased choice of lower cocaine doses. The effects of buspirone only differed according to route of administration in subordinate monkeys. Moreover, it is noteworthy that the effects of buspirone were similar to those of the D3 receptor-selective antagonist PG01037 and qualitatively different than those of less selective drugs that act at D2-like or serotonin (5-HT)1A receptors, suggesting a D3 and possibly D4 receptor mechanism of action for buspirone. Taken together, the data support the utility of drugs targeting D3/D4 receptors as potential treatments for cocaine addiction, particularly in combination with enriching environmental manipulations.

The Uncompetitive N-methyl-D-Aspartate Antagonist Memantine Reduces Binge-Like Eating, Food-Seeking Behavior, and Compulsive Eating: Role of the Nucleus Accumbens Shell Smith KL, Rao RR, Velazquez-Sanchez C, Valenza M, Giuliano C, Everitt BJ, Sabino V, Cottone P. Neuropsychopharmacology 2015; 40: 1163-1171.
Binge-eating disorder is characterized by excessive, uncontrollable consumption of palatable food within brief periods of time. The role of the glutamatergic N-methyl-D-aspartate (NMDA) receptor system in hedonic feeding is poorly understood. The aim of this study was to characterize the effects of the uncompetitive NMDA receptor antagonist memantine on palatable food-induced behavioral adaptations using a rat model, which mimics the characteristic symptomatology observed in binge-eating disorder. For this purpose, the authors allowed male Wistar rats to respond to obtain a highly palatable, sugary diet (Palatable group) or a regular chow diet (Chow control group), for 1 h a day, under a fixed-ratio 1 (FR1) schedule of reinforcement. Upon stabilization of food responding, we tested the effects of memantine on the Chow and Palatable food groups' intake. Then, the authors tested the effects of memantine on food-seeking behavior, under a second-order schedule of reinforcement. Furthermore, they investigated the effects of memantine on the intake of food when it was offered in an aversive, bright compartment of a light/dark conflict test. Finally, they evaluated the effects of memantine on FR1 responding for food, when microinfused into the nucleus accumbens (NAcc) shell or core. Memantine dose-dependently decreased binge-like eating and fully blocked food-seeking behavior and compulsive eating, selectively in the Palatable food group. The drug treatment did not affect performance of the control Chow food group. Finally, intra-NAcc shell, but not core, microinfusion of memantine decreased binge-like eating. Together, these findings substantiate a role of memantine as a potential pharmacological treatment for binge-eating disorder.

Astrocytic Dysfunction and Addiction: Consequences Of Impaired Glutamate Homeostasis Scofield MD, Kalivas PW. Neuroscientist 2014; 20(6): 610-622.
Addiction is characterized as a chronic relapsing disorder whereby addicted individuals persistently engage in drug seeking and use despite profound negative consequences. The results of studies using animal models of addiction and relapse indicate that drug seeking is mediated by alterations in cortico-accumbal plasticity induced by chronic drug exposure. Among the maladaptive responses to drug exposure are long-lasting alterations in the expression of proteins localized to accumbal astrocytes, which are responsible for maintaining glutamate homeostasis. These alterations engender an aberrant potentiation of glutamate transmission in the cortico-accumbens circuit that is linked to the reinstatement of drug seeking. Accordingly, pharmacological restoration of glutamate homeostasis functions as an efficient method of reversing drug-induced plasticity and inhibiting drug seeking in both rodents and humans.

Pharmacodynamics Of Long-Acting Folic Acid-Receptor Targeted Ritonavir-Boosted Atazanavir Nanoformulations Puligujja P, Balkundi SS, Kendrick LM, Baldridge HM, Hilaire JR, Bade AN, Dash PK, Zhang G, Poluektova LY, Gorantla S, Liu X-M, Ying T, Feng Y, Wang Y, Dimitrov DS, McMillan JM, Gendelman HE. Biomaterials 2015; 41: 141-150.
Long-acting nanoformulated antiretroviral therapy (nanoART) that targets monocyte-macrophages could improve the drug's half-life and protein-binding capacities while facilitating cell and tissue depots. To this end, ART nanoparticles that target the folic acid (FA) receptor and permit cell-based drug depots were examined using pharmacokinetic and pharmacodynamic (PD) tests. FA receptor-targeted poloxamer 407 nanocrystals, containing ritonavir-boosted atazanavir (ATV/r), significantly

increased drug bioavailability and PD by five and 100 times, respectively. Drug particles administered to human peripheral blood lymphocyte reconstituted NOD.Cg-Prkdc(scid)Il2rg (tm1Wjl)/SzJ mice and infected with HIV-1ADA led to ATV/r drug concentrations that paralleled FA receptor beta staining in both the macrophage-rich parafollicular areas of spleen and lymph nodes. Drug levels were higher in these tissues than what could be achieved by either native drug or untargeted nanoART particles. The data also mirrored potent reductions in viral loads, tissue viral RNA and numbers of HIV-1p24+ cells in infected and treated animals. The authors conclude that FA-P407 coating of ART nanoparticles readily facilitates drug carriage and antiretroviral responses.

Medial Amygdalar Aromatase Neurons Regulate Aggression In Both Sexes Unger EK, Burke Jr KJ, Yang CF, Bender KJ, Fuller PM, Shah NM. Cell Rep 2015; 10(4): 453-462.
Aromatase-expressing neuroendocrine neurons in the vertebrate male brain synthesize estradiol from circulating testosterone. This locally produced estradiol controls neural circuits underlying courtship vocalization, mating, aggression, and territory marking in male mice. How aromatase-expressing neuronal populations control these diverse estrogen-dependent male behaviors is poorly understood, and the function, if any, of aromatase-expressing neurons in females is unclear. Using targeted genetic approaches, the authors show that aromatase-expressing neurons within the male posterodorsal medial amygdala (MeApd) regulate components of aggression, but not other estrogen-dependent male-typical behaviors. Remarkably, aromatase-expressing MeApd neurons in females are specifically required for components of maternal aggression, which the authors show is distinct from intermale aggression in pattern and execution. Thus, aromatase-expressing MeApd neurons control distinct forms of aggression in the two sexes. Moreover, these findings indicate that complex social behaviors are separable in a modular manner at the level of genetically identified neuronal populations.

Genetic Disruption Of 2-Arachidonoylglycerol Synthesis Reveals A Key Role For Endocannabinoid Signaling In Anxiety Modulation Shonesy BC, Bluett RJ, Ramikie TS, Baldi R, Hermanson DJ, Kingsley PJ, Marnett LJ, Winder DG, Colbran RJ, Patel S. Cell Rep 2014; 9(5): 1644-1653.
Endocannabinoid (eCB) signaling has been heavily implicated in the modulation of anxiety and depressive behaviors and emotional learning. However, the role of the most-abundant endocannabinoid 2-arachidonoylglycerol (2-AG) in the physiological regulation of affective behaviors is not well understood. Here, the authors show that genetic deletion of the 2-AG synthetic enzyme diacylglycerol lipase α (DAGLα) in mice reduces brain, but not circulating, 2-AG levels. DAGLα deletion also results in anxiety-like and sex-specific anhedonic phenotypes associated with impaired activity-dependent eCB retrograde signaling at amygdala glutamatergic synapses. Importantly, acute pharmacological normalization of 2-AG levels reverses both phenotypes of DAGLα-deficient mice. These data suggest 2-AG deficiency could contribute to the pathogenesis of affective disorders and that pharmacological normalization of 2-AG signaling could represent an approach for the treatment of mood and anxiety disorders.

Rheb Inhibits Protein Synthesis by Activating the PERK-eIF2α Signaling Cascade Tyagi R, Shahani N, Gorgen L, Ferretti M, Pryor W, Chen PY, Swarnkar S, Worley PF, Karbstein K, Snyder SH, Subramaniam S. Cell Rep 2015. [Epub ahead of print].
Rheb, a ubiquitous small GTPase, is well known to bind and activate mTOR, which augments protein synthesis. Inhibition of protein synthesis is also physiologically regulated. Thus, with cell

stress, the unfolded protein response system leads to phosphorylation of the initiation factor eIF2α and arrest of protein synthesis. The authors now demonstrate a major role for Rheb in inhibiting protein synthesis by enhancing the phosphorylation of eIF2α by protein kinase-like ER kinase (PERK). Interplay between the stimulatory and inhibitory roles of Rheb may enable cells to modulate protein synthesis in response to varying environmental stresses.

Diversity Of Cortical Interneurons In Primates: The Role Of the Dorsal Proliferative Niche Radonjic NV, Ayoub AE, Memi F, Yu X, Maroof A, Jakovcevski I, Anderson SA, Rakic P, Zecevic N. Cell Rep 2014; 9(6): 2139-2151.
Evolutionary elaboration of tissues starts with changes in the genome and location of the stem cells. For example, GABAergic interneurons of the mammalian neocortex are generated in the ventral telencephalon and migrate tangentially to the neocortex, in contrast to the projection neurons originating in the ventricular/subventricular zone (VZ/SVZ) of the dorsal telencephalon. In human and nonhuman primates, evidence suggests that an additional subset of neocortical GABAergic interneurons is generated in the cortical VZ and a proliferative niche, the outer SVZ. The origin, magnitude, and significance of this species-specific difference are not known. The authors use a battery of assays applicable to the human, monkey, and mouse organotypic cultures and supravital tissue to identify neuronal progenitors in the cortical VZ/SVZ niche that produce a subset of GABAergic interneurons. The findings suggest that these progenitors constitute an evolutionary novelty contributing to the elaboration of higher cognitive functions in primates.

Input-and Cell-Type-Specific Endocannabinoid-Dependent LTD In the Striatum Wu Y-W, Kim J-I, Tawfik VL, Lalchandani RR, Scherrer G, Ding JB. Cell Rep 2015; 10(1): 75-87.
Changes in basal ganglia plasticity at the corticostriatal and thalamostriatal levels are required for motor learning. Endocannabinoid-dependent long-term depression (eCB-LTD) is known to be a dominant form of synaptic plasticity expressed at these glutamatergic inputs; however, whether eCB-LTD can be induced at all inputs on all striatal neurons is still debatable. Using region-specific Cre mouse lines combined with optogenetic techniques, the authors directly investigated and distinguished between corticostriatal and thalamostriatal projections. They found that eCB-LTD was successfully induced at corticostriatal synapses, independent of postsynaptic striatal spiny projection neuron (SPN) subtype. Conversely, eCB-LTD was only nominally present at thalamostriatal synapses. This dichotomy was attributable to the minimal expression of cannabinoid type 1 (CB1) receptors on thalamostriatal terminals. Furthermore, coactivation of dopamine receptors on SPNs during LTD induction re-established SPN-subtype-dependent eCB-LTD. Altogether, these findings lay the groundwork for understanding corticostriatal and thalamostriatal synaptic plasticity and for striatal eCB-LTD in motor learning

BEHAVIORAL AND BRAIN DEVELOPMENT RESEARCH

Predisposition to and Effects of Methamphetamine Use on the Adolescent Brain Lyoo IK, Yoon S, Kim TS, Lim SM, Choi Y, Kim JE, Hwang J, Jeong HS, Cho HB, Chung YA, Renshaw PF. Mol Psychiatry. 2015 Feb 10. doi: 10.1038/mp.2014.191. [Epub ahead of print].
Adolescence is a period of heightened vulnerability both to addictive behaviors and drug-induced brain damage. Yet, only limited information exists on the brain mechanisms underlying these adolescent-specific characteristics. Moreover, distinctions in brain correlates between predisposition to drug use and effects of drugs in adolescents are unclear. Using cortical thickness and diffusion tensor image analyses, the authors found greater and more widespread gray and white matter alterations, particularly affecting the frontostriatal system, in adolescent methamphetamine (MA) users compared with adult users. Among adolescent-specific gray matter alterations related to MA use, smaller cortical thickness in the orbitofrontal cortex was associated with family history of drug use. These findings highlight that the adolescent brain, which undergoes active myelination and maturation, is more vulnerable to MA-related alterations than the adult brain. Furthermore, MA-use-related executive dysfunction was greater in adolescent MA users than in adult users. These findings may provide explanation for the severe behavioral complications and relapses that are common in adolescent-onset drug addiction. Additionally, these results may provide insights into distinguishing the neural mechanisms that underlie the predisposition to drug addiction from effects of drugs in adolescents.

Executive Function and Cortical Thickness in Youths Prenatally Exposed to Cocaine, Alcohol and Tobacco Gautam P, Warner TD, Kan EC, Sowell ER. Dev Cogn Neurosci. 2015 Feb 2. pii: S1878-9293(15)00024-9.
Small and detrimental, albeit inconsistent, effects of prenatal cocaine exposure (PCE) during early childhood have been reported. The teratogenic effects of prenatal alcohol (PAE) and tobacco exposure (PTE) on neurobehavior are more firmly established than PCE. The authors tested if co-exposure to all three drugs could be related to greater differences in brain structure than exposure to cocaine alone. Participants (n=42, PCE=27; age range=14-16 years) received an executive function battery prior to a T1-weighted 3T structural MRI scan. Cortical thickness was measured using FreeSurfer (v5.1). Fetal drug exposure was quantified through maternal self-reports usage during pregnancy. Using general linear modeling, the authors found no main effects of PCE on cortical thickness, but significant main effects of PAE and PTE in superior and medial frontal regions, after co-varying for the effects of age, sex, and each drug of exposure. Significant alcohol-by-tobacco interactions and significant cocaine-by-alcohol interactions on cortical thickness in medial parietal and temporal regions were also observed. Poly-drug exposure and cognitive function also showed significant interactions with cortical thickness: lower cortical thickness was associated with better performance in PCE-exposed adolescents. Results suggest that although children with PCE have subtle brain cortical differences, these differences persist until mid-to-late adolescence.

Prenatal Tobacco Exposure and Infant Stress Reactivity: Role of Child Sex and Maternal Behavior Eiden RD, Molnar DS, Granger DA, Colder CR, Schuetze P, Huestis MA. Dev Psychobiol. 2015 Mar; 57(2): 212-225.
This study examined the association between prenatal tobacco exposure (PTE) and infant cortisol reactivity at 9 months of infant age. Child sex and maternal parenting behavior were hypothesized

moderators. The sample included 217 (148 tobacco-exposed, 69 non-exposed) mother-child dyads. Data used were obtained from pregnancy assessments, mother-infant feeding interactions at 2 months, and salivary cortisol at four time points in response to frustration at 9 months. Results indicated a significant association between PTE and infant cortisol that was moderated by infant sex and maternal intrusiveness. That is, PTE boys had lower cortisol than control boys, but there was no association between PTE and cortisol among girls. There was a significant association between PTE and cortisol among infants of intrusive mothers, but not among infants with non-intrusive mothers. Thus, PTE was associated with cortisol hypo-reactivity such that boys and non-exposed infants experiencing high maternal intrusiveness were at greater risk.

Prenatal Drug Exposure to Illicit Drugs Alters Working Memory-related Brain Activity and Underlying Network Properties in Adolescence Schweitzer JB, Riggins T, Liang X, Gallen C, Kurup PK, Ross TJ, Black MM, Nair P, Salmeron BJ. Neurotoxicol Teratol. 2015 Feb 12;48C:69-77.
The persistence of effects of prenatal drug exposure (PDE) on brain functioning during adolescence is poorly understood. The authors explored neural activation to a visuospatial working memory (VSWM) versus a control task using functional magnetic resonance imaging (fMRI) in adolescents with PDE and a community comparison group (CC) of non-exposed adolescents. They applied graph theory metrics to resting state data using a network of nodes derived from the VSWM task activation map to further explore connectivity underlying WM functioning. Participants (ages 12-15years) included 47 adolescents (27 PDE and 20 CC). All analyses controlled for potentially confounding differences in birth characteristics and postnatal environment. Significant group by task differences in brain activation emerged in the left middle frontal gyrus (BA 6) with the CC group, but not the PDE group, activating this region during VSWM. The PDE group deactivated the culmen, whereas the CC group activated it during the VSWM task. The CC group demonstrated a significant relation between reaction time and culmen activation, not present in the PDE group. The network analysis underlying VSWM performance showed that PDE group had lower global efficiency than the CC group and a trend level reduction in local efficiency. The network node corresponding to the BA 6 group by task interaction showed reduced nodal efficiency and fewer direct connections to other nodes in the network. These results suggest that adolescence reveals altered neural functioning related to response planning that may reflect less efficient network functioning in youth with PDE.

Structural Connectivity of Neural Reward Networks in Youth at Risk for Substance Use Disorders Squeglia LM, Sorg SF, Jacobus J, Brumback T, Taylor CT, Tapert SF. Psychopharmacology (Berl). 2015 Jan 7. [Epub ahead of print].
Having a positive family history of alcohol use disorders (FHP), as well as aberrant reward circuitry, has been implicated in the initiation of substance use during adolescence. This study explored the relationship between FHP status and reward circuitry in substance naïve youth to better understand future risky behaviors. Participants were 49 FHP and 45 demographically matched family history negative (FHN) substance-naïve 12-14 year-olds (54 % female). Subjects underwent structural magnetic resonance imaging, including diffusion tensor imaging. Nucleus accumbens and orbitofrontal cortex volumes were derived using FreeSurfer, and FSL probabilistic tractography probed structural connectivity and differences in white matter diffusivity estimates (e.g. fractional anisotropy, and mean, radial, and axial diffusivity) between fiber tracts connecting these regions. FHP and FHN youth did not differ on nucleus accumbens or orbitofrontal cortex volumes, white

matter tract volumes, or percentages of streamlines (a proxy for fiber tract count) connecting these regions. However, within white matter tracts connecting the nucleus accumbens to the orbitofrontal cortex, FHP youth had significantly lower mean and radial and radial diffusivity (ps < 0.03) than FHN youth. While white matter macrostructure between salience and reward regions did not differ between FHP and FHN youth, FHP youth showed greater white matter coherence within these tracts than FHN youth. Aberrant connectivity between reward regions in FHP youth could be linked to an increased risk for substance use initiation.

Prenatal Marijuana Exposure Predicts Marijuana Use in Young Adulthood Sonon KE, Richardson GA, Cornelius JR, Kim KH, Day NL. Neurotoxicol Teratol. 2015 Jan-Feb; 47: 10-15.
Studies have reported effects of prenatal marijuana exposure (PME) on cognitive and behavioral outcomes. An earlier publication from this study found that PME predicted early onset of marijuana use and frequency of marijuana use at age 14. No study has reported the effects of PME on marijuana use in young adulthood. This is a developmental period when substance use peaks, and by which, initiation of substance use has largely occurred. Subjects were from a longitudinal cohort. Women were interviewed initially in their fourth prenatal month and women and their offspring were followed through 22 years. Significant covariates of offspring marijuana use at 22 years were identified and controlled for using ordinal logistic regression. PME predicted marijuana use in the offspring at 22 years after controlling for significant covariates. Prenatal alcohol exposure, offspring race, gender, and age were also significant predictors, but family history of substance abuse or disorder, and sociodemographic and psychological characteristics of the mother and offspring were not. This association was not moderated by gender or race. PME is associated with subsequent marijuana use in young adulthood after considering the effects of other significant factors. These findings have important implications for public health given the recent trend toward legitimization of marijuana use.

Maternal-fetal Attachment Differentiates Patterns of Prenatal Smoking and Exposure Massey SH, Bublitz MH, Magee SR, Salisbury A, Niaura RS, Wakschlag LS, Stroud LR. Addict Behav. 2015 Jan 20; 45C:51-56**.**
Smoking cessation during pregnancy may reflect altruistic motives on behalf of the unborn baby. The authors test the hypothesis that pregnancy quitters have higher maternal-fetal attachment than persistent smokers, and secondarily explore how maternal-fetal attachment differs among non-smokers, pregnancy quitters, and persistent smokers. Participants were 156 women in the Behavior and Mood in Babies and Mothers study who provided report of smoking throughout pregnancy via timeline follow back interviews, with salivary cotinine confirmation of reported cessation at 30 and 35week gestation, and postpartum day one. Maternal Fetal Attachment Scale total and subscale scores (role-taking, differentiation of self from fetus, interaction with fetus, attributing characteristics to fetus, giving of self) were examined among non-smokers, pregnancy quitters, and persistent smokers. At 30weeks, pregnancy quitters scored higher on the 'giving of self' subscale compared to persistent smokers (21.6±2.4 versus 19.9±2.9; p=.004). Maternal 'giving of self' also differentiated pregnancies exposed to cigarette smoking from those without exposure from 30weeks through delivery (19.9±2.9 versus 21.2±2.2; p=.002). Controlling for age, income, unemployment, gravida, and father's smoking status, 'giving of self' differentiated pregnancy quitters from persistent smokers [OR=5.144; 95% C.I. 1.509 - 17.538; B (SE) =1.638 (.626); p=.009]. Women who reported a greater desire to maintain their personal health for the health of their fetus were more

likely to quit smoking during pregnancy. Implications of findings for interventions and understanding mechanisms of risk are discussed.

Parental Knowledge of Adolescent Activities: Links with Parental Attachment Style and Adolescent Substance Use Jones JD, Ehrlich KB, Lejuez CW, Cassidy J. J Fam Psychol. 2015 Mar 2. [Epub ahead of print].
Parents' knowledge of their adolescents' whereabouts and activities is a robust predictor of adolescent risk behavior, including the use of drugs and alcohol. Surprisingly few studies have attempted to identify parental characteristics that are associated with the degree of parental knowledge. The present study is the first to examine how parental attachment style relates to mother, father, and adolescent reports of parental knowledge. Further, the authors used structural equation modeling to test the associations among parents' attachment styles, reports of parental knowledge, and adolescents' alcohol and marijuana use. Participants included 203 adolescents (M age = 14.02, SD = .91) living in 2-parent households and their parent(s). As predicted, mothers' and fathers' insecure attachment styles were negatively associated with self-reported and adolescent-reported parental knowledge and all 3 reports of parental knowledge were negatively related to adolescent substance use. Mothers' and fathers' attachment styles were unrelated to adolescent substance use. However, evidence emerged for indirect effects of parental attachment style on adolescent substance use through reports of parental knowledge. Implications for prevention efforts and the importance of multiple reporters within the family are discussed.

A Comparison of Delay Discounting in Adolescents and Adults in Treatment for Cannabis Use Disorders Lee DC, Stanger C, Budney AJ. Exp Clin Psychopharmacol. 2015 Feb 2. [Epub ahead of print]**.**
Delay discounting is associated with problematic substance use and poorer treatment outcomes in adolescents and adults with substance use disorders. Although some research has addressed delay discounting among individuals with cannabis use disorders (CUDs), results have been equivocal, and no study has examined whether discounting rates differ between adolescent and adult cannabis users. The aim of this study was to compare discounting rates between adolescents and adults in treatment for CUD to determine whether discounting at intake or changes in discounting across treatment differed between age groups. Participants were 165 adolescents and 104 adults enrolled in treatment for CUD. Participants completed a delay discounting task at intake and end of treatment for 2 commodities (money and cannabis) at 2 different magnitudes ($100 and $1,000). Repeated measures mixed models examined differences in discounting rates by commodity and magnitude across age groups at intake and changes in discounting across treatment. At intake, adolescents discounted money more than adults whereas adults showed greater discounting at $100 magnitude than $1,000. In addition, adults had greater decreases in discounting of cannabis over the course of treatment. Overall, adolescents appeared less sensitive to changes in magnitude of rewards, discounted money at higher rates, and showed less improvement in discounting over the course of treatment compared to adults. Comparing delay discounting in adolescents and adults with CUD can contribute to a better understanding of how development influences the effect of discounting on substance use to better inform treatment for substance use disorders.

Parental Cultural Socialization of Mexican-American Adolescents' Family Obligation Values and Behaviors Tsai KM, Telzer EH, Gonzales NA, Fuligni AJ. Child Dev. 2015 Mar 2. doi: 10.1111/cdev.12358. [Epub ahead of print]**.**
The current study examined how parents' cultural socialization efforts contribute to adolescents' family obligation values and behaviors and how these processes may depend upon the relational climate at home. Utilizing survey and daily diary methodologies, 428 Mexican-American adolescents (50% males; M_{age} = 15 years) and their parents (83% mothers; M_{age} = 42 years) participated in the study. Adolescents reported on their family obligation values and engagement in family assistance tasks across 14 days. Parents reported on their cultural socialization practices. Results indicated that parental cultural socialization was associated with adolescents' family obligation values and behaviors when parent-child relationships were low in conflict and high in support. Findings suggest that the transmission of cultural values and practices is best facilitated through positive parent-child relationships.

Tobacco May Mask Poorer Episodic Memory among Young Adult Cannabis Users Schuster RM, Crane NA, Mermelstein R, Gonzalez R. Neuropsychology. 2015 Jan 5. [Epub ahead of print]**.**
Co-occurring cannabis and tobacco use has become increasingly prevalent among young adults, but it is not clear how tobacco use may alter the neurocognitive profile typically observed among cannabis users. Although there is substantial evidence citing cannabis and tobacco's individual effect on episodic memory and related brain structures, few studies have examined the effect of combined cannabis and tobacco use on memory. This investigation examined relationships between amount of past year cannabis and tobacco use on 4 different indices of episodic memory among a sample of young adults who identified cannabis as their drug of choice. Results indicated that more cannabis use was linked with poorer initial acquisition, total learning, and delayed recall on the Hopkins Verbal Learning Test-Revised, but only among cannabis users who sporadically smoked cigarettes in the past year. Conversely, the amount of past year cannabis use was not associated with episodic memory performance among individuals who more consistently smoked cigarettes in the past year. These differences could not be explained by several relevant potential confounds. These findings provide important insight into a potential mechanism (i.e., attenuation of cognitive decrements) that might reinforce use of both substances and hamper cessation attempts among cannabis users who also smoke cigarettes. Ongoing and future research will help to better understand how co-use of cannabis and tobacco affects memory during acute intoxication and abstinence and the stability of these associations over time.

If All Your Friends Jumped off a Bridge: The Effect of Others' Actions on Engagement in and Recommendation of Risky Behaviors Helfinstein SM, Mumford JA, Poldrack RA. J Exp Psychol Gen. 2015 Feb; 144(1): 12-17.
There is a large gap between the types of risky behavior we recommend to others and those we engage in ourselves. In this study, the authors hypothesized that a source of this gap is greater reliance on information about others' behavior when deciding whether to take a risk oneself than when deciding whether to recommend it to others. To test this hypothesis, they asked participants either to report their willingness to engage in a series of risky behaviors themselves; their willingness to recommend those behaviors to a loved one; or, how good of an idea it would be for either them or a loved one to engage in the behaviors. The authors then asked them to evaluate those behaviors on criteria related to the expected utility of the risk (benefits, costs, and likelihood of costs), and on engagement in the activity by people they knew. They found that, after accounting for

effects of perceived benefit, cost, and likelihood of cost, perceptions of others' behavior had a dramatically larger impact on participants' willingness to engage in a risk than on their willingness to recommend the risk or their prescriptive evaluation of the risk. These findings indicate that the influence of others' choices on risk-taking behavior is large, direct, cannot be explained by an economic utility model of risky decision-making, and goes against one's own better judgment.

Association of Fatty Acid Ethyl Esters in Meconium and Cognitive Development during Childhood and Adolescence Min MO, Singer LT, Minnes S, Wu M, Bearer CF. J Pediatr. 2015 Jan 13. pii: S0022-3476(14)01157-3.
The purpose of this study was to examine associations between amounts of fatty acid ethyl esters (FAEEs) in meconium and cognitive development in school-aged children exposed to alcohol and drugs in utero. A secondary analysis of a prospective cohort of children, primarily African American and of low socioeconomic status that was recruited at birth was conducted. FAEEs were quantified with gas chromatography via a flame ionization detector. Meconium was analyzed for FAEEs in 216 newborns; 191 of these infants were assessed for IQ at ages 9, 11, and 15 years with the Wechsler Intelligence Scales for Children-Fourth Edition. Longitudinal mixed model analyses indicated that, after the authors controlled for maternal and child covariates, greater concentrations of FAEEs (ethyl myristate, ethyl oleate, ethyl linoleate, and ethyl linolenate) were associated with lower Wechsler Intelligence Scales for Children-Fourth Edition Verbal Comprehension Index, Working Memory Index, and Full-Scale IQ scores. Associations of FAEEs with Verbal Comprehension Index, Working Memory Index, and Full-Scale IQ did not vary over time. No associations of FAEEs with Perceptual Reasoning and Processing Speed Indices were found. Elevated levels of FAEEs in meconium are potential markers for identifying newborns at risk for poor cognitive development related to prenatal alcohol exposure.

Physiological Reactivity during Object Manipulation among Cigarette-exposed Infants at 9 Months of Age Schuetze P, Lessard J, Colder CR, Maiorana N, Shisler S, Eiden RD, Huestis MA, Henrie J. Neurotoxicol Teratol. 2015 Feb 12; 48C: 64-68.
The purpose of this study was to examine the association between prenatal exposure to cigarettes and heart rate during an object manipulation task at 9 months of age. Second-by-second heart rate was recorded for 181 infants who were prenatally exposed to cigarettes and 77 nonexposed infants during the manipulation of four standardized toys. A series of longitudinal multilevel models were run to examine the association of prenatal smoking on the intercept and slope of heart rate during four 90-second object manipulation tasks. After controlling for maternal age, prenatal marijuana and alcohol use, duration of focused attention and activity level, results indicated that the heart rates of exposed infants significantly increased during the object manipulation task. These findings suggest casual rather than focused attention and a possible increase in physiological arousal during object manipulation.

Predictors of Changes in Smoking from 3rd Trimester to 9 Months Postpartum Shisler S, Homish GG, Molnar DS, Schuetze P, Colder CR, Eiden RD. Nicotine Tob Res. 2015 Mar 5. pii: ntv057. [Epub ahead of print].
While much has been written about postpartum smoking relapse prevention, few have examined changes in smoking behavior from pregnancy (3rd trimester) through 9 months postpartum among pregnant smokers, particularly for the large number of women who decrease tobacco consumption during pregnancy but do not quit altogether. Data were obtained from 168 women who smoked

during their pregnancy. Women were followed longitudinally from their first prenatal appointment through 9 months postpartum. Maternal substance use was assessed using the Timeline Followback and verified by maternal salivary analyses. Breastfeeding, other substance use, and partner smoking were assessed through maternal interviews at each time point and were considered as potential predictors of change in smoking. Women returned to more than half of their levels of preconception tobacco consumption by 9 months postpartum. There was one significant predictor of changes in smoking patterns pregnancy to postpartum. Women who breastfed their infants for at least 90 days smoked far less postpartum than women who breastfed for a short time or did not breastfeed at all. As noted in previous research of pregnant quitters, postpartum relapse prevention or harm reduction interventions should ideally be timed early in the postpartum period. Additionally, promoting breastfeeding among pregnant smokers and supporting women through at least 3 months of breastfeeding may be beneficial to such interventions.

The Superior Longitudinal Fasciculus in Typically Developing Children and Adolescents: Diffusion Tensor Imaging and Neuropsychological Correlates Urger SE, De Bellis MD, Hooper SR, Woolley DP, Chen SD, Provenzale J. Child Neurol. 2015 Jan; 30(1): 9-20.
The relationship between superior longitudinal fasciculus microstructural integrity and neuropsychological functions were examined in 49 healthy children (range: 5-17 years) using diffusion tensor imaging. Seven major cognitive domains (intelligence, fine-motor, attention, language, visual-spatial, memory, executive function) were assessed. Data analyses used correlational methods. After adjusting for age and gender, fractional anisotropy and axial diffusivity values in the superior longitudinal fasciculus were positively correlated with executive functions of set shifting, whereas left superior longitudinal fasciculus fractional anisotropy values correlated with attention and language. Apparent diffusion coefficient values in the left superior longitudinal fasciculus negatively correlated with inhibitory control. In the left arcuate fasciculus, fractional anisotropy correlated with IQ and attention, whereas radial diffusivity values negatively correlated with IQ, fine-motor skills, and expressive language. Findings from this study provide an examination of the relationship between superior longitudinal fasciculus integrity and children's neuropsychological abilities that can be useful in monitoring pediatric neurologic diseases.

Methamphetamine and Cannabis Abuse in Adolescence: A Quasi-experimental Study on Specific and Long-term Neurocognitive Effects Cuzen NL, Koopowitz SM, Ferrett HL, Stein DJ, Yurgelun-Todd D. BMJ Open. 2015 Jan 30; 5(1):e005833.
Methamphetamine abuse affects brain structure and function. Although methamphetamine and cannabis are commonly abused together, few studies have investigated the differential neurocognitive consequences of methamphetamine abuse with or without cannabis. Furthermore, the effects of drug use on the developing adolescent brain remain poorly understood. The authors compared neurocognitive function between adolescents with 'pure' methamphetamine abuse, those with comorbid methamphetamine and cannabis abuse, and healthy controls at baseline and follow-up. Individuals residing in the greater Cape Town region, between the ages of 13 and 18 years, were recruited into either Methamphetamine only group (Meth-only; n=10), Methamphetamine and cannabis group (Meth-cann; n=10) or healthy control (n=20) groups using a quasi-experimental design. All participants underwent a comprehensive neurocognitive assessment. Substance-use variables and psychiatric symptom counts were also recorded. A portion of the Meth-only and control participants completed 12-month follow-up assessments. While the Meth-cann group demonstrated widespread neurocognitive deficits at baseline, these deficits were restricted to the

self-monitoring domain in the Meth-only group at baseline and at follow-up. Methamphetamine abuse with cannabis abuse is associated with significantly more neurocognitive impairment than methamphetamine abuse alone, and such deficits may be enduring.

Impulsivity and Cigarette Craving among Adolescent Daily and Occasional Smokers Mathew AR, Burris JL, Froeliger B, Saladin ME, Carpenter MJ. Addict Behav. 2015 Jan 30; 45C:134-138.
Impulsivity is a multi-dimensional construct that is robustly related to cigarette smoking. While underlying factors that account for this relation are not well understood, craving has been proposed as a central mechanism linking impulsivity to smoking. In order to further refine our understanding of associations between impulsivity and cigarette craving, the current study examined the association between impulsivity and tonic and cue-elicited craving among a sample of adolescent smokers. We expected trait impulsivity would be positively associated with both tonic and cue-elicited craving, and that this relationship would be stronger among daily vs. occasional smokers. One-hundred and six smokers (ages 16-20) completed the questionnaires and reported their cigarette craving prior to and immediately following presentation of each of three counterbalanced cue types: (a) in vivo smoking, (b) alcohol, and (c) neutral cue. Impulsivity was positively associated with tonic craving for daily smokers (β=.38; p=.005), but not occasional smokers (β=.01; p=.95), with a significant impulsivity x smoker group interaction (β=1.31; p=.03). Impulsivity was unrelated to craving following smoking or alcohol cue, regardless of smoker group (all p's>.16). Results suggest a moderated effect in which impulsivity is positively associated with tonic craving for daily smokers, but not occasional smokers. Tonic craving may serve as a mechanism linking impulsivity, smoking persistence, and nicotine dependence among daily smokers.

A Multimodal Approach for Determining Brain Networks by Jointly Modeling Functional and Structural Connectivity Xue W, Bowman FD, Pileggi AV, Mayer AR. Front Comput Neurosci. 2015 Feb 20; 9: 22.
Recent innovations in neuroimaging technology have provided opportunities for researchers to investigate connectivity in the human brain by examining the anatomical circuitry as well as functional relationships between brain regions. Existing statistical approaches for connectivity generally examine resting-state or task-related functional connectivity (FC) between brain regions or separately examine structural linkages. As a means to determine brain networks, the authors present a unified Bayesian framework for analyzing FC utilizing the knowledge of associated structural connections, which extends an approach by Patel et al. (2006a) that considers only functional data. They introduce an FC measure that rests upon assessments of functional coherence between regional brain activity identified from functional magnetic resonance imaging (fMRI) data. The authors' structural connectivity (SC) information is drawn from diffusion tensor imaging (DTI) data, which is used to quantify probabilities of SC between brain regions. They formulate a prior distribution for FC that depends upon the probability of SC between brain regions, with this dependence adhering to structural-functional links revealed by our fMRI and DTI data. They further characterize the functional hierarchy of functionally connected brain regions by defining an ascendancy measure that compares the marginal probabilities of elevated activity between regions. In addition, they describe topological properties of the network, which is composed of connected region pairs, by performing graph theoretic analyses. They demonstrate the use of our Bayesian model using fMRI and DTI data from a study of auditory processing. They further illustrate the advantages of our method by comparisons to methods that only incorporate functional information.

Genome-Wide Association Study of Behavioral Disinhibition in a Selected Adolescent Sample Derringer J, Corley RP, Haberstick BC, Young SE, Demmitt BA, Howrigan DP, Kirkpatrick RM, Iacono WG, McGue M, Keller MC, Brown S, Tapert S, Hopfer CJ, Stallings MC, Crowley TJ, Rhee SH, Krauter K, Hewitt JK, McQueen MB. Behav Genet. 2015 Jan 31. [Epub ahead of print].
Behavioral disinhibition (BD) is a quantitative measure designed to capture the heritable variation encompassing risky and impulsive behaviors. As a result, BD represents an ideal target for discovering genetic loci that predispose individuals to a wide range of antisocial behaviors and substance misuse that together represent a large cost to society as a whole. Published genome-wide association studies (GWAS) have examined specific phenotypes that fall under the umbrella of BD (e.g. alcohol dependence, conduct disorder); however no GWAS has specifically examined the overall BD construct. The authors conducted a GWAS of BD using a sample of 1,901 adolescents over-selected for characteristics that define high BD, such as substance and antisocial behavior problems, finding no individual locus that surpassed genome-wide significance. Although no single SNP was significantly associated with BD, restricted maximum likelihood analysis estimated that 49.3 % of the variance in BD within the Caucasian sub-sample was accounted for by the genotyped SNPs ($p = 0.06$). Gene-based tests identified seven genes associated with BD ($p \leq 2.0 \times 10^{-6}$). Although the current study was unable to identify specific SNPs or pathways with replicable effects on BD, the substantial sample variance that could be explained by all genotyped SNPs suggests that larger studies could successfully identify common variants associated with BD.

Genetic Relationship between the Addiction Diagnosis in Adults and Their Childhood Measure of Addiction Liability Vanyukov M, Kim K, Irons D, Kirisci L, Neale M, Ridenour T, Hicks B, Tarter R, Reynolds M, Kirillova G, McGue M, Iacono W. Behav Genet. 2015 Jan;45(1):1-11.
Transmissible liability index (TLI), developed employing a high-risk design and item response theory, enables quantification of the latent trait of liability to drug use disorders (DUD) in children. TLI has been shown to have high heritability and predict DUD in young adulthood. This study extends prior research and determines the genetic contribution of DUD liability measured by TLI to adult liability as indexed by DUD diagnosis. The study utilizes data from a twin sample tracked from age 11 to age 25. In addition to confirming TLI's high heritability and predictive validity, it shows that the genetic component of variance in TLI assessed in childhood accounts for over half of the genetic variance in DUD diagnosis and the entire phenotypic relationship between the two liability measures. This validates TLI as an early measure of DUD liability and supports its utility in early-age genetic and other mechanistic studies of DUD.

Long-Term Consequences of Adolescent Parenthood among African-American Urban Youth: A Propensity Score Matching Approach Assini-Meytin LC, Green KM. J Adolesc Health. 2015 Mar 10. pii: S1054-139X(15)00024-5.
The aim of this study was to improve understanding of long-term socioeconomic consequences of teen parenting for men and women. Analysis is based on the Woodlawn Study, a longitudinal study of an African-American cohort from a socially disadvantaged community in Chicago; data were collected at childhood (N = 1,242), adolescence (N = 705), young adulthood (age 32 years, N = 952), and midlife (age 42 years, N = 833). This analysis focused on the 1,050 individuals with data on teen parenting. The authors used propensity score matching to account for differences in background characteristics between teenage parents and their peers and used multiple imputations to account for differential attrition. The regression models after propensity score matching showed

that at the age of 32 years, in comparison to nonteen mothers, teenage mothers were more likely to be unemployed, live in poverty, depend on welfare, and have earned a GED or completed high school compared to finishing college. At the age of 32 years, teen fathers were more likely to be without a job than nonteen fathers. At the age of 42 years, the effect of teen parenting for women remained statistically significant for education and income. There were no significant associations between teen parenting and outcomes for men at the age of 42 years. Socioeconomic consequences of teenage parenting among African-Americans from disadvantaged background seem to be primarily concentrated in women and persist throughout adulthood. In addition to promoting the delay of parenting after the teenage years, it is critical to provide programs at early stages in the life course to mitigate the negative socioeconomic consequences of teenage motherhood as effects for women are broad.

Epigenetic Basis of Opiate Suppression of BDNF Gene Expression in the Ventral Tegmental Area Koo JW, Mazei-Robison MS, LaPlant Q, Egervari G, Braunscheidel KM, Adank DN, Ferguson D, Feng J, Sun H, Scobie KN, Damez-Werno DM, Ribeiro E, Peña CJ, Walker D, Bagot RC, Cahill ME, Anderson SA, Labonté B, Hodes GE, Browne H, Chadwick B, Robison AJ, Vialou VF, Dias C, Lorsch Z, Mouzon E, Lobo MK, Dietz DM, Russo SJ, Neve RL, Hurd YL, Nestler EJ. Nat Neurosci. 2015 Mar; 18(3): 415-422.
Brain-derived neurotrophic factor (BDNF) has a crucial role in modulating neural and behavioral plasticity to drugs of abuse. The authors found a persistent downregulation of exon-specific BDNF expression in the ventral tegmental area (VTA) in response to chronic opiate exposure, which was mediated by specific epigenetic modifications at the corresponding BDNF gene promoters. Exposure to chronic morphine increased stalling of RNA polymerase II at these BDNF promoters in VTA and altered permissive and repressive histone modifications and occupancy of their regulatory proteins at the specific promoters. Furthermore, they found that morphine suppressed binding of phospho-CREB (cAMP response element binding protein) to Bdnf promoters in VTA, which resulted from enrichment of trimethylated H3K27 at the promoters, and that decreased NURR1 (nuclear receptor related-1) expression also contributed to BDNF repression and associated behavioral plasticity to morphine. These findings suggest previously unknown epigenetic mechanisms of morphine-induced molecular and behavioral neuroadaptations.

Functional Activation and Effective Connectivity Differences in Adolescent Marijuana Users Performing a Simulated Gambling Task Acheson A, Ray KL, Hines CS, Li K, Dawes MA, Mathias CW, Dougherty DM, Laird AR. J Addict. 2015; 2015:783106.
Adolescent marijuana use is associated with structural and functional differences in forebrain regions while performing memory and attention tasks. In the present study, the authors investigated neural processing in adolescent marijuana users experiencing rewards and losses. Fourteen adolescents with frequent marijuana use (>5 uses per week) and 14 nonuser controls performed a computer task where they were required to guess the outcome of a simulated coin flip while undergoing magnetic resonance imaging. Across all participants, "Wins" and "Losses" were associated with activations including cingulate, middle frontal, superior frontal, and inferior frontal gyri and declive activations. Relative to controls, users had greater activity in the middle and inferior frontal gyri, caudate, and claustrum during "Wins" and greater activity in the anterior and posterior cingulate, middle frontal gyrus, insula, claustrum, and declive during "Losses." Effective connectivity analyses revealed similar overall network interactions among these regions for users and controls during both "Wins" and "Losses." However, users and controls had significantly

different causal interactions for 10 out of 28 individual paths during the "Losses" condition. Collectively, these results indicate adolescent marijuana users have enhanced neural responses to simulated monetary rewards and losses and relatively subtle differences in effective connectivity.

Methadone and Buprenorphine for Opioid Dependence during Pregnancy: A Retrospective Cohort Study Meyer MC, Johnston AM, Crocker AM, Heil SH. J Addict Med. 2015 Jan 22. [Epub ahead of print]**.**
The objective of this study was to compare maternal characteristics, prenatal care, and newborn outcomes in a cohort of opioid-dependent pregnant women treated with methadone versus buprenorphine. In a retrospective cohort study, 609 pregnant, opioid-dependent women were treated with methadone (n = 248) or buprenorphine (n = 361) between 2000 and 2012 at a single institution. Mothers treated with buprenorphine were more likely to start medication before or earlier in pregnancy, had longer gestation, and gave birth to larger infants. Newborns of buprenorphine- versus methadone-maintained mothers required treatment for neonatal abstinence significantly less often and for a shorter duration. These data suggest pregnancy outcomes with buprenorphine to treat opioid dependence during pregnancy in clinical practice are as good and often better than outcomes with methadone. These results are consistent with efficacy data from randomized clinical trials and further support the use of buprenorphine for the treatment of opioid dependence during pregnancy.

Sexual Discounting among High-risk Youth Ages 18-24: Implications for Sexual and Substance Use Risk Behaviors. Dariotis JK, Johnson MW. Exp Clin Psychopharmacol. 2015 Feb; 23(1):49-58.
Youth under 25 show substantial sexual and substance use risk behaviors. One factor associated with risk behaviors is delay discounting, the devaluation of delayed outcomes. This study determined if delay discounting for sexual outcomes is related to sexual risk and substance use among 18-24 year olds. Females (70) and males (56) completed the Sexual Discounting Task, which assessed their likelihood of having unprotected immediate sex versus waiting for sex with a condom, at various delays, with 4 hypothetical sexual partners selected from photographs: the person they most wanted to have sex with, least wanted to have sex with, judged most likely to have a sexually transmitted infection (STI), and judged least likely to have an STI. They also completed instruments assessing HIV knowledge, sexual behaviors, substance use, risk attitudes, inhibition, impulsivity, and sensation-seeking. Condom use likelihood generally decreased with increasing delay. Preference for immediate, unprotected sex was greater for partners whom participants most (vs. least) wanted to have sex with and judged least (vs. most) likely to have an STI. Preference for immediate, unprotected sex in the "most want to have sex with" and "least likely to have an STI" conditions was related to greater lifetime risky sexual partners, lifetime number of unique substances used, disregard of social approval/danger, disinhibition, and sensation/excitement-seeking. Males showed greater likelihood of unprotected sex than females when condom use was undelayed, but delay similarly affected condom use between sexes. Delay discounting should be considered in strategies to minimize youth risk behavior.

NCAM1-TTC12-ANKK1-DRD2 Variants and Smoking Motives as Intermediate Phenotypes for Nicotine Dependence Bidwell LC, McGeary JE, Gray JC, Palmer RH, Knopik VS, MacKillop J. Psychopharmacology (Berl). 2015 Apr; 232(7): 1177-1186.
Nicotine dependence (ND) is a heterogeneous phenotype with complex genetic influences. The use of intermediate ND phenotypes may clarify genetic influences and reveal specific etiological

pathways. Prior work has found that the four Primary Dependence Motives (PDM) subscales (Automaticity, Craving, Loss of Control, and Tolerance) of the Wisconsin Inventory of Smoking Motives (WISDM) represent heavy, pervasive smoking, which is a core feature of nicotine dependence, making these motives strong candidates as intermediate phenotypes. This study examines the WISDM PDM as a novel intermediate phenotype of nicotine dependence. The study used data from 734 European Americans who smoked at least 5 cigs/day [M = 16.2 (SD = 9.5) cigs/day], completed a phenotypic assessment, and provided a sample of DNA. Based on prior evidence of the role of genetic variation in the NCAM1-TTC12-ANKK1-DRD2 region on chromosome 11q23 in smoking behavior, associations among 12 region loci with nicotine dependence and PDM phenotypes were examined using haplotype and individual loci approaches. In addition, mediational analysis tested the indirect pathway from genetic variation to smoking motives to nicotine dependence. NCAM1-TTC12-ANKK1-DRD2 region loci and haplotypes were significantly associated with the motive of Automaticity and, further, Automaticity significantly mediated associations among NCAM1-TTC12-ANKK1-DRD2 cluster variants and nicotine dependence. These results suggest that motives related to automaticity are a viable intermediate phenotype for understanding genetic contributions to nicotine dependence. Further, NCAM1-TTC12-ANKK1-DRD2 variants may increase the likelihood that a person will become dependent via a highly automatic smoking ritual that can be elicited with little awareness.

Characterizing and Differentiating Task-based and Resting State fMRI Signals via Two-stage Sparse representations Zhang S, Li X, Lv J, Jiang X, Guo L, Liu T. Brain Imaging Behav. 2015 Mar 3. [Epub ahead of print].
A relatively underexplored question in fMRI is whether there are intrinsic differences in terms of signal composition patterns that can effectively characterize and differentiate task-based or resting state fMRI (tfMRI or rsfMRI) signals. In this paper, the authors propose a novel two-stage sparse representation framework to examine the fundamental difference between tfMRI and rsfMRI signals. Specifically, in the first stage, the whole-brain tfMRI or rsfMRI signals of each subject were composed into a big data matrix, which was then factorized into a subject-specific dictionary matrix and a weight coefficient matrix for sparse representation. In the second stage, all of the dictionary matrices from both tfMRI/rsfMRI data across multiple subjects were composed into another big data-matrix, which was further sparsely represented by a cross-subjects common dictionary and a weight matrix. This framework has been applied on the recently publicly released Human Connectome Project (HCP) fMRI data and experimental results revealed that there are distinctive and descriptive atoms in the cross-subjects common dictionary that can effectively characterize and differentiate tfMRI and rsfMRI signals, achieving 100 % classification accuracy. Moreover, our methods and results can be meaningfully interpreted, e.g., the well-known default mode network (DMN) activities can be recovered from the very noisy and heterogeneous aggregated big-data of tfMRI and rsfMRI signals across all subjects in HCP Q1 release.

Increased Pre- and Early-Adolescent Stress in Youth with a Family History of Substance Use Disorder and Early Substance Use Initiation Charles NE, Mathias CW, Acheson A, Bray BC, Ryan SR, Lake SL, Liang Y, Dougherty DM. J Youth Adolesc. 2015 Mar 19. [Epub ahead of print]**.**
Individuals with a family history of substance use disorders (Family History Positive) are more likely to have early-onset substance use (i.e., prior to age 15), which may contribute to their higher rates of substance use disorders. One factor that may differentiate Family History Positive youth who engage in early-onset substance use from other Family History Positive youth is exposure to

stressors. The aim of this study was to quantify how exposure to stressors from age 11-15 varies as a function of family history of substance use disorders and early-onset substance use. Self-reported stressors were prospectively compared in a sample of predominately (78.9 %) Hispanic youth that included 68 Family History Positive youth (50 % female) who initiated substance use by age 15 and demographically matched non-users with (n = 136; 52.9 % female) and without (n = 75; 54.7 % female) family histories of substance use disorders. Stressors were assessed at 6-month intervals for up to 4 years. Both the severity of stressors and the degree to which stressors were caused by an individual's own behavior were evaluated. All three groups differed from one another in overall exposure to stressors and rates of increase in stressors over time, with Family History Positive youth who engaged in early-onset substance use reporting the greatest exposure to stressors. Group differences were more pronounced for stressors caused by the participants' behavior. Family History Positive users had higher cumulative severity of stressors of this type, both overall and across time. These results indicate greater exposure to stressors among Family History Positive youth with early-onset substance use, and suggest that higher rates of behavior-dependent stressors may be particularly related to early-onset use.

CLINICAL NEUROSCIENCE RESEARCH

Neural Substrates of Approach-Avoidance Conflict Decision-Making Aupperle RL, Melrose AJ, Francisco A, Paulus MP, Stein MB. Human Brain Mapping. 2015; 36(2):449–462.
Animal approach-avoidance conflict paradigms have been used extensively to operationalize anxiety, quantify the effects of anxiolytic agents, and probe the neural basis of fear and anxiety. Results from human neuroimaging studies support that a frontal-striatal-amygdala neural circuitry is important for approach-avoidance learning. However, the neural basis of decision-making is much less clear in this context. Thus, the authors combined a recently developed human approach-avoidance paradigm with functional magnetic resonance imaging (fMRI) to identify neural substrates underlying approach-avoidance conflict decision-making. Fifteen healthy adults completed the approach-avoidance conflict (AAC) paradigm during fMRI. Analyses of variance were used to compare conflict to nonconflict (avoid-threat and approach-reward) conditions and to compare level of reward points offered during the decision phase. Trial-by-trial amplitude modulation analyses were used to delineate brain areas underlying decision-making in the context of approach/avoidance behavior. Conflict trials as compared to the nonconflict trials elicited greater activation within bilateral anterior cingulate cortex, anterior insula, and caudate, as well as right dorsolateral prefrontal cortex (PFC). Right caudate and lateral PFC activation was modulated by level of reward offered. Individuals who showed greater caudate activation exhibited less approach behavior. On a trial-by-trial basis, greater right lateral PFC activation related to less approach behavior. Taken together, results suggest that the degree of activation within prefrontal-striatal-insula circuitry determines the degree of approach versus avoidance decision-making. Moreover, the degree of caudate and lateral PFC activation related to individual differences in approach-avoidance decision-making. Therefore, the approach-avoidance conflict paradigm is ideally suited to probe anxiety-related processing differences during approach-avoidance decision-making.

Insula-Dorsal Anterior Cingulate Cortex Coupling is Associated with Enhanced Brain Reactivity to Smoking Cues Janes AC, Farmer S, Peechatka AL, Frederick BB, Lukas SE. Neuropsychopharmacology. 2015 Jan. [Epub ahead of print].
The insula plays a critical role in maintaining nicotine dependence and reactivity to smoking cues. More broadly, the insula and the dorsal anterior cingulate cortex (dACC) are key nodes of the salience network (SN), which integrates internal and extrapersonal information to guide behavior. Thus, insula-dACC interactions may be integral in processing salient information such as smoking cues that facilitate continued nicotine use. The authors evaluated functional magnetic resonance imaging (fMRI) data from nicotine-dependent participants during rest, and again when they viewed smoking-related images. Greater insula-dACC coupling at rest was significantly correlated with enhanced smoking cue-reactivity in brain areas associated with attention and motor preparation, including the visual cortex, right ventral lateral prefrontal cortex, and the dorsal striatum. In an independent cohort, the authors found that insula-dACC connectivity was stable over 1-h delay and was not influenced by changes in subjective craving or expired carbon monoxide, suggesting that connectivity strength between these regions may be a trait associated with heightened cue-reactivity. Finally, they also showed that insula reactivity to smoking cues correlates with a rise in cue-reactivity throughout the entire SN, indicating that the insula's role in smoking cue-reactivity is not functionally independent, and may actually represent the engagement of the entire SN. Collectively, these data provide a more network-level understanding of the insula's role in nicotine

dependence and shows a relationship between inherent brain organization and smoking cue-reactivity.

Distinct Brain Systems Mediate the Effects of Nociceptive Input and Self-regulation on Pain
Woo CW, Roy M, Buhle JT, Wager TD. PLoS Biol. 2015 Jan 6; 13(1): e1002036.
Cognitive self-regulation can strongly modulate pain and emotion. However, it is unclear whether self-regulation primarily influences primary nociceptive and affective processes or evaluative ones. In this study, participants engaged in self-regulation to increase or decrease pain while experiencing multiple levels of painful heat during functional magnetic resonance imaging (fMRI) imaging. Both heat intensity and self-regulation strongly influenced reported pain, but they did so via two distinct brain pathways. The effects of stimulus intensity were mediated by the neurologic pain signature (NPS), an a priori distributed brain network shown to predict physical pain with over 90% sensitivity and specificity across four studies. Self-regulation did not influence NPS responses; instead, its effects were mediated through functional connections between the nucleus accumbens and ventromedial prefrontal cortex. This pathway was unresponsive to noxious input, and has been broadly implicated in valuation, emotional appraisal, and functional outcomes in pain and other types of affective processes. These findings provide evidence that pain reports are associated with two dissociable functional systems: nociceptive/affective aspects mediated by the NPS, and evaluative/functional aspects mediated by a fronto-striatal system.

Effects of Marijuana Use on Impulsivity and Hostility in Daily Life Ansell EB, Laws HB, Roche MJ, Sinha R. Drug and Alcohol Dependence. 2015 March 1; 148: 136–142.
Marijuana use is increasingly prevalent among young adults. While research has found adverse effects associated with marijuana use within experimentally controlled laboratory settings, it is unclear how recreational marijuana use affects day-to-day experiences in users. The present study sought to examine the effects of marijuana use on within-person changes in impulsivity and interpersonal hostility in daily life using smartphone administered assessments. Forty-three participants with no substance dependence reported on their alcohol consumption, tobacco use, recreational marijuana use, impulsivity, and interpersonal hostility over the course of 14 days. Responses were analyzed using multilevel modeling. Marijuana use was associated with increased impulsivity on the same day and the following day relative to days when marijuana was not used, independent of alcohol use. Marijuana was also associated with increased hostile behaviors and perceptions of hostility in others on the same day when compared to days when marijuana was not used. These effects were independent of frequency of marijuana use or alcohol use. There were no significant effects of alcohol consumption on impulsivity or interpersonal hostility. Marijuana use is associated with changes in impulse control and hostility in daily life. This may be one route by which deleterious effects of marijuana are observed for mental health and psychosocial functioning. Given the increasing prevalence of recreational marijuana use and the potential legalization in some states, further research on the potential consequences of marijuana use in young adults' day-to-day life is warranted.

Correlates of Polysomnographic Sleep Changes in Cocaine Dependence: Self-administration and Clinical Outcomes Angarita GA, Canavan SV, Forselius E, Bessette A, Morgan PT. Drug and Alcohol Dependence. 2014 Oct 1; 143: 173–180.
Abstinence from chronic cocaine use is associated with abnormal sleep architecture. As sleep abnormalities are associated with clinical outcome in alcohol dependence, the authors hypothesized

a similar relationship in cocaine dependence. They report data from a cocaine self-administration study (N = 12) and the placebo arm of a randomized clinical trial (N = 20). Self-administration participants underwent three cocaine self-administration sessions during a three-week inpatient stay. Treatment participants underwent two weeks of inpatient followed by six weeks of outpatient treatment including once-weekly cognitive behavioral therapy. Measurements included polysomnography from early and late in abstinence during the inpatient stays. Clinical outcomes included amount of cocaine self-administered, urine tests, and self-reported use and withdrawal symptoms. Change in slow-wave sleep from early to late abstinence (ΔSWS; $p = 0.05$), late abstinence rapid eye movement sleep (REM; $p = 0.002$), and late abstinence total sleep time ($p = 0.02$) were negatively correlated with the amount of cocaine self-administered. Early abstinence REM was positively correlated with withdrawal symptoms ($p = 0.02$). Late abstinence REM was positively correlated with percent negative urines and maximum consecutive number of days abstinent (both $p < 0.001$). ΔSWS was positively correlated with percent negative urines ($p = 0.03$) and participants with increased SWS had greater percent negative urines ($p = 0.008$) and maximum consecutive number of days abstinent ($p = 0.009$). Correlations between sleep deficits and amount of cocaine self-administered, clinical outcomes, and severity of withdrawal symptoms underscore the relevance of sleep in clinical outcomes in the treatment of cocaine dependence.

Hippocampal Volume Mediates the Relationship between Measures of Pre-treatment Cocaine Use and Within-treatment Cocaine Abstinence Xu J, Kober H, Wang X, DeVito EE, Carroll KM, Potenza MN. Drug and Alcohol Dependence. 2014 Oct 1; 143: 74–80.
Data suggest that the amygdala and hippocampus contribute to cocaine seeking and use, particularly following exposure to cocaine-related cues and contexts. Furthermore, indices of pre-treatment cocaine-use severity have been shown to correlate with treatment outcome in cocaine-dependent patients. The aim of this study was to assess the relationships between amygdalar and hippocampal volumes and cocaine use before and during treatment. High-resolution magnetic-resonance brain images were obtained from 23 cocaine-dependent patients prior to treatment and 54 healthy comparison individuals. Automated segmentation of the amygdala and hippocampus images was performed in FreeSurfer. Cocaine-dependent patients subsequently received behavioral therapy alone or combined with contingency management as part of a treatment trial, and cocaine-use indices (self-report, urine toxicology) were collected. Comparison participants and cocaine-dependent patients did not show significant difference in amygdalar and hippocampal volumes at pre-treatment. Within the patient group, greater hippocampal volumes were correlated with more days of cocaine use before treatment and with poorer treatment outcome as indexed by shorter durations of continuous abstinence from cocaine and lower percentages of cocaine-negative urine samples during treatment. Mediation analysis indicated that pre-treatment hippocampal volumes mediated the relationships between pre-treatment cocaine use and treatment outcomes. The finding of a significant correlation between hippocampal volume and pre-treatment cocaine-use severity and treatment response suggests that hippocampal volume should be considered when developing individualized treatments for cocaine dependence.

The Influence of Cannabis Motives on Alcohol, Cannabis, and Tobacco Use among Treatment-seeking Cigarette Smokers Foster DW, Allan NP, Zvolensky MJ, Schmidt NB. Drug Alcohol Depend. 2015 Jan 1;146:81-88.
The present study evaluated the effects of cannabis motives on multi-substance use in an effort to examine the incremental validity of cannabis motives with respect to substance use outcomes.

Participants were 167 treatment-seeking smokers (41.92% female; Mage=28.74; SD=11.88) who reported smoking an average of 10 or more cigarettes daily for at least one year. Structural equation modeling was used to examine the association between cannabis motives and two dependent variables each for alcohol (drinking frequency and alcohol problems), cannabis (cannabis use frequency and cannabis problems), and tobacco (average cigarettes per day and nicotine dependence). Findings indicated that conformity motives were linked with increases in alcohol problems and cannabis problems. Enhancement motives were associated with increased cannabis use and cannabis problems. Coping motives were linked with increased cannabis use and cannabis problems. Contrary to expectations, expansion motives were associated with reductions in the number of cigarettes smoked per day. Also, results supported expectations that the observed effects due to cannabis motives were unique from shared variance with theoretically relevant covariates. The present findings supported predictions that cannabis motives would evince effects on the use of multiple substances over and above theoretically relevant variables. However, results indicate that the relationship between cannabis motives and multi-substance use is complex, and therefore, additional research is warranted to better understand substance use intervention.

Cocaine Dependent Individuals Discount Future Rewards More Than Future Losses for Both Cocaine and Monetary Outcomes Johnson MW, Bruner NR, Johnson PS. Addict Behav. 2015 Jan; 40: 132-136.

Cocaine dependence and other forms of drug dependence are associated with steeper devaluation of future outcomes (delay discounting). Although studies in this domain have typically assessed choices between monetary gains (e.g., receive less money now versus receive more money after a delay), delay discounting is also applicable to decisions involving losses (e.g., small loss now versus larger delayed loss), with gains typically discounted more than losses (the "sign effect"). It is also known that drugs are discounted more than equivalently valued money. In the context of drug dependence, however, relatively little is known about the discounting of delayed monetary and drug losses and the presence of the sign effect. In this within-subject, laboratory study, delay discounting for gains and losses was assessed for cocaine and money outcomes in cocaine-dependent individuals (n=89). Both cocaine and monetary gains were discounted at significantly greater rates than cocaine and monetary losses, respectively (i.e., the sign effect). Cocaine gains were discounted significantly more than monetary gains, but cocaine and monetary losses were discounted similarly. Results suggest that cocaine is discounted by cocaine-dependent individuals in a systematic manner similar to other rewards. Because the sign effect was shown for both cocaine and money, delayed aversive outcomes may generally have greater impact than delayed rewards in shaping present behavior in this population.

A Neural Mechanism for Nonconscious Activation of Conditioned Placebo and Nocebo Responses Jensen KB, Kaptchuk TJ, Chen X, Kirsch I, Ingvar M, Gollub RL, Kong J. Cereb Cortex. 2014 Dec 1. [Epub ahead of print].

Fundamental aspects of human behavior operate outside of conscious awareness. Yet, theories of conditioned responses in humans, such as placebo and nocebo effects on pain, have a strong emphasis on conscious recognition of contextual cues that trigger the response. Here, the authors investigated the neural pathways involved in nonconscious activation of conditioned pain responses, using functional magnetic resonance imaging in healthy participants. Nonconscious compared with conscious activation of conditioned placebo analgesia was associated with increased activation of the orbitofrontal cortex, a structure with direct connections to affective brain regions and basic

reward processing. During nonconscious nocebo, there was increased activation of the thalamus, amygdala, and hippocampus. In contrast to previous assumptions about conditioning in humans, the authors' results show that conditioned pain responses can be elicited independently of conscious awareness and our results suggest a hierarchical activation of neural pathways for nonconscious and conscious conditioned responses. Demonstrating that the human brain has a nonconscious mechanism for responding to conditioned cues has major implications for the role of associative learning in behavioral medicine and psychiatry. These results may also open up for novel approaches to translational animal-to-human research since human consciousness and animal cognition is an inherent paradox in all behavioral science.

Dynamic Interactions between Plasma IL-1 Family Cytokines and Central Endogenous Opioid Neurotransmitter Function in Humans Prossin AR, Zalcman SS, Heitzeg MM, Koch AE, Campbell PL, Phan KL, Stohler CS, Zubieta J-K. Neuropsychopharmacology. 2015 Feb; 40(3): 554-565.
Evidence in animal models suggests IL-1 family cytokines interact with central endogenous opioid neurotransmitter systems, inducing or perpetuating pathological states such as persistent pain syndromes, depression, substance use disorders, and their comorbidity. Understanding these interactions in humans is particularly relevant to understanding pathological states wherein this neurotransmitter system is implicated (i.e., persistent pain, mood disorders, substance use disorders, etc.). Here, the authors examined relationships between IL-1β, IL-1ra, and functional measures of the endogenous opioid system in 34 healthy volunteers, in the absence and presence of a standardized sustained muscular pain challenge, a psychophysical challenge with emotionally and physically stressful components. Mu-opioid receptor availability in vivo was examined with [(11)C]carfentanil positron emission tomography (PET) scanning. Sex and neuroticism impacted IL-1 family cytokines; higher baseline IL-1β and IL-1ra was identified in females with lower neuroticism. Higher baseline IL-1β was also associated with reduced μ-opioid receptor availability (amygdala) and greater pain sensitivity. The pain challenge increased IL-1β in females with high neuroticism. Strong associations between IL-1ra (an anti-nociceptive cytokine) and μ-opioid receptor activation (VP/NAcc) were identified during the pain challenge and the resulting analgesic effect of μ-opioid receptor activation was moderated by changes in IL-1β whereby volunteers with greater pain induced increase in IL-1β experienced less endogenous opioid analgesia. This study demonstrates the presence of relationships between inflammatory factors and a specific central neurotransmitter system and circuitry, of relevance to understanding interindividual variations in regulation of responses to pain and other physical and emotional stressors.

Influence of Dorsolateral Prefrontal Cortex and Ventral Striatum on Risk Avoidance in Addiction: A Mediation Analysis Yamamoto DJ, Woo CW, Wager TD, Regner MF, Tanabe J. Drug Alcohol Depend. 2015 Apr 1; 149: 10-17.
Alterations in frontal and striatal function are hypothesized to underlie risky decision making in drug users, but how these regions interact to affect behavior is incompletely understood. The authors used mediation analysis to investigate how prefrontal cortex and ventral striatum together influence risk avoidance in abstinent drug users. Thirty-seven abstinent substance-dependent individuals (SDI) and 43 controls underwent fMRI while performing a decision-making task involving risk and reward. Analyses of a priori regions-of-interest tested whether activity in dorsolateral prefrontal cortex (DLPFC) and ventral striatum (VST) explained group differences in risk avoidance. Whole-brain analysis was conducted to identify brain regions influencing the

negative VST-risk avoidance relationship. Right DLPFC (RDLPFC) positively mediated the group-risk avoidance relationship ($p<0.05$); RDLPFC activity was higher in SDI and predicted higher risk avoidance across groups, controlling for SDI vs. controls. Conversely, VST activity negatively influenced risk avoidance ($p<0.05$); it was higher in SDI, and predicted lower risk avoidance. Whole-brain analysis revealed that, across group, RDLPFC and left temporal-parietal junction positively ($p\leq0.001$) while right thalamus and left middle frontal gyrus negatively ($p<0.005$) mediated the VST activity-risk avoidance relationship. RDLPFC activity mediated less risky decision making while VST mediated more risky decision making across drug users and controls. These results suggest a dual pathway underlying decision making, which, if imbalanced, may adversely influence choices involving risk. Modeling contributions of multiple brain systems to behavior through mediation analysis could lead to a better understanding of mechanisms of behavior and suggest neuromodulatory treatments for addiction.

Acquisition of Responses to a Methamphetamine-Associated Cue in Healthy Humans: Self-Report, Behavioral, and Psychophysiological Measures Mayo LM, de Wit H. Neuropsychopharmacology. 2015 Jan. [Epub ahead of print].
Drug-associated cues elicit conditioned responses in human drug users, and are thought to facilitate a drug-seeking behavior. Yet, little is known about how these associations are acquired, or about the specificity of the conditioned response modalities. In this study, healthy, nondependent volunteers (N=90) completed a conditioning paradigm in which they received a moderate dose of methamphetamine paired with one stimulus and placebo with another stimulus, each on two separate occasions. Their responses to these cues were measured with a behavioral preference, self-reported 'liking', emotional reactivity, and attentional bias measures, both before and after the conditioning. Following the conditioning procedure, subjects exhibited a behavioral preference, positive emotional reactivity, and attentional bias toward the methamphetamine-associated cue, compared with the placebo stimulus. In addition, subjects who reported greater positive subjective drug effects during the conditioning displayed a more robust conditioning. This work demonstrates that healthy nondependent volunteers readily acquire conditioned responses to neutral stimuli paired with a drug. The procedure has significant value to study individual variation in acquisition of conditioned responses as a possible risk factor for drug taking, and to study the neural basis of conditioned drug responses.

Functional Network Overlap as Revealed by fMRI Using sICA and Its Potential Relationships with Functional Heterogeneity, Balanced Excitation and Inhibition, and Sparseness of Neuron Activity Xu J, Calhoun VD, Worhunsky PD, Xiang H, Li J, Wall JT, Pearlson GD, Potenza MN. PLoS One. 2015 Feb 25; 10(2): e0117029.
Functional magnetic resonance imaging (fMRI) studies traditionally use general linear model-based analysis (GLM-BA) and regularly report task-related activation, deactivation, or no change in activation in separate brain regions. However, several recent fMRI studies using spatial independent component analysis (sICA) find extensive overlap of functional networks (FNs), each exhibiting different task-related modulation (e.g., activation vs. deactivation), different from the dominant findings of GLM-BA. This study used sICA to assess overlap of FNs extracted from four datasets, each related to a different cognitive task. FNs extracted from each dataset overlapped with each other extensively across most or all brain regions and showed task-related concurrent increases, decreases, or no changes in activity. These findings indicate that neural substrates showing task-related concurrent but different modulations in activity intermix with each other and distribute

across most of the brain. Furthermore, spatial correlation analyses found that most FNs were highly consistent in spatial patterns across different datasets. This finding indicates that these FNs probably reflect large-scale patterns of task-related brain activity. The authors hypothesize that FN overlaps as revealed by sICA might relate to functional heterogeneity, balanced excitation and inhibition, and population sparseness of neuron activity, three fundamental properties of the brain. These possibilities deserve further investigation.

Effects of Incentives, Age, and Behavior on Brain Activation during Inhibitory Control: A Longitudinal fMRI Study Paulsen DJ, Hallquist MN, Geier CF, Luna B. Dev Cogn Neurosci. 2015 Feb; 11: 105-115.
The authors investigated changes in brain function supporting inhibitory control under age-controlled incentivized conditions, separating age- and performance-related activation in an accelerated longitudinal design including 10- to 22-year-olds. Better inhibitory control correlated with striatal activation during neutral trials, while Age X Behavior interactions in the striatum indicated that in the absence of extrinsic incentives, younger subjects with greater reward circuitry activation successfully engage in greater inhibitory control. Age was negatively correlated with ventral amygdala activation during Loss trials, suggesting that amygdala function more strongly mediates bottom-up processing earlier in development when controlling the negative aspects of incentives to support inhibitory control. Together, these results indicate that with development, reward-modulated cognitive control may be supported by incentive processing transitions in the amygdala, and from facilitative to obstructive striatal function during inhibitory control.

Smoking Automaticity and Tolerance Moderate Brain Activation during Explore-Exploit Behavior Addicott MA, Pearson JM, Froeliger B, Platt ML, McClernon FJ. Psychiatry Research. 2014; 224(3): 254–261.
The adaptive trade-off between exploration and exploitation is a key component in models of reinforcement learning. Over the past decade, these models have been applied to the study of reward-seeking behavior. Drugs of addiction induce reward-seeking behavior and modify its underlying neurophysiological processes. These neurophysiological changes may underlie a behavioral shift from a flexible, exploratory mode to a focused, exploitative mode, which precedes the development of inflexible, habitual drug use. The goal of this study was to investigate the relationship between explore/exploit behavior and drug addiction by examining the neural correlates of this behavior in cigarette smokers. Participants (n=22) with a range of smoking behaviors completed a smoking dependence motives questionnaire and played a 6-armed bandit task while undergoing functional magnetic resonance imaging (fMRI). Exploratory behavior produced greater activation in the bilateral superior parietal and bilateral frontal cortices than exploitative behavior. Exploitative behavior produced greater activation in the bilateral superior and middle temporal gyri than exploratory behavior. fMRI data and orthogonalized smoking dependence motive scores were entered into multiple linear regression analyses. After controlling for nicotine tolerance, smoking automaticity positively correlated with activation in the same bilateral parietal regions preferentially activated by exploratory choices. These preliminary results link smoking dependence motives to variation in the neural processes that mediate exploratory decision making.

Stimulus Devaluation Induced by Stopping Action Wessel JR, O'Doherty JP, Berkebile MM, Linderman D, Aron AR. Journal of Experimental Psychology. General. 2014; 143(6):2316–2329.
Impulsive behavior in humans partly relates to inappropriate overvaluation of reward-associated stimuli. Hence, it is desirable to develop methods of behavioral modification that can reduce stimulus value. Here, the authors tested whether one kind of behavioral modification--the rapid stopping of actions in the face of reward-associated stimuli--could lead to subsequent devaluation of those stimuli. They developed a novel paradigm with three consecutive phases: implicit reward learning, a stop-signal task, and an auction procedure. In the learning phase, the authors associated abstract shapes with different levels of reward. In the stop-signal phase, they paired half those shapes with occasional stop-signals, requiring the rapid stopping of an initiated motor response, while the other half of shapes was not paired with stop signals. In the auction phase, they assessed the subjective value of each shape via willingness-to-pay. In 2 experiments, the authors found that participants bid less for shapes that were paired with stop-signals compared to shapes that were not. This suggests that the requirement to try to rapidly stop a response decrements stimulus value. Two follow-on control experiments suggested that the result was specifically due to stopping action rather than aversiveness, effort, conflict, or salience associated with stop signals. This study makes a theoretical link between research on inhibitory control and value. It also provides a novel behavioral paradigm with carefully operationalized learning, treatment, and valuation phases. This framework lends itself to both behavioral modification procedures in clinical disorders and research on the neural underpinnings of stimulus devaluation.

Belief about Nicotine Selectively Modulates Value and Reward Prediction Error Signals in Smokers Gu X, Lohrenz T, Salas R, Baldwin PR, Soltani A, Kirk U, Cinciripini PM, Montague PR. Proceedings of the National Academy of Sciences of the United States of America. 2015; 112(8):2539–2544.
Little is known about how prior beliefs impact biophysically described processes in the presence of neuroactive drugs, which presents a profound challenge to the understanding of the mechanisms and treatments of addiction. The authors engineered smokers' prior beliefs about the presence of nicotine in a cigarette smoked before a functional magnetic resonance imaging session where subjects carried out a sequential choice task. Using a model-based approach, they show that smokers' beliefs about nicotine specifically modulated learning signals (value and reward prediction error) defined by a computational model of mesolimbic dopamine systems. Belief of "no nicotine in cigarette" (compared with "nicotine in cigarette") strongly diminished neural responses in the striatum to value and reward prediction errors and reduced the impact of both on smokers' choices. These effects of belief could not be explained by global changes in visual attention and were specific to value and reward prediction errors. Thus, by modulating the expression of computationally explicit signals important for valuation and choice, beliefs can override the physical presence of a potent neuroactive compound like nicotine. These selective effects of belief demonstrate that belief can modulate model-based parameters important for learning. The implications of these findings may be far ranging because belief-dependent effects on learning signals could impact a host of other behaviors in addiction as well as in other mental health problems.

Cannabis-Related Episodic Memory Deficits and Hippocampal Morphological Differences in Healthy Individuals and Schizophrenia Subjects Smith MJ, Cobia DJ, Reilly JL, Gilman JM, Roberts AG, Alpert KI, Wang L, Breiter HC, Csernansky JG. Hippocampus. 2015. [E-pub ahead of print; DOI:10.1002/hipo.22427].
Cannabis use has been associated with episodic memory (EM) impairments and abnormal hippocampus morphology among both healthy individuals and schizophrenia subjects. Considering the hippocampus' role in EM, research is needed to evaluate the relationship between cannabis-related hippocampal morphology and EM among healthy and clinical groups. The authors examined differences in hippocampus morphology between control and schizophrenia subjects with and without a past (not current) cannabis use disorder (CUD). Subjects group-matched on demographics included 44 healthy controls (CON), 10 subjects with a CUD history (CON-CUD), 28 schizophrenia subjects with no history of substance use disorders (SCZ), and 15 schizophrenia subjects with a CUD history (SCZ-CUD). Large-deformation, high-dimensional brain mapping with MRI produced surface-based representations of the hippocampus that were compared across all four groups and correlated with EM and CUD history. Surface maps of the hippocampus were generated to visualize morphological differences. CON-CUD and SCZ-CUD were characterized by distinct cannabis-related hippocampal shape differences and parametric deficits in EM performance. Shape differences observed in CON-CUD were associated with poorer EM performance, while shape differences observed in SCZ-CUD were associated with a longer duration of CUD and shorter duration of CUD remission. A past history of CUD may be associated with notable differences in hippocampal morphology and EM impairments among adults with and without schizophrenia. Although the results may be compatible with a causal hypothesis, the authors must consider that the observed cannabis-related shape differences in the hippocampus could also be explained as biomarkers of a neurobiological susceptibility to poor memory or the effects of cannabis.

MDMA: A Social Drug in a Social Context Kirkpatrick MG, de Wit H. Psychopharmacology. 2015; 232(6):1155–1163.
The drug ±3,4-methylenedioxymethamphetamine (MDMA, "ecstasy," "molly") is thought to produce prosocial effects and enhance social interaction. However, in most laboratory studies to date, the participants have been tested under nonsocial conditions, which may not simulate the effects the drug produces in more naturalistic social settings. Healthy experienced MDMA users participated in three laboratory sessions in which they received MDMA (0.5 or 1.0 mg/kg or placebo, double blind). They were randomly assigned to one of three social conditions, in which they were tested alone (solitary (SOL); N = 10), in the presence of a research assistant (research assistant present (RAP); N = 11) or in the presence of another participant who also received the drug (other participant present (OPP); N = 11). As expected, MDMA increased heart rate and blood pressure and produced positive subjective effects in all the three groups. It also increased ratings of attractiveness of another person and increased social interaction in RAP and OPP. The social context affected certain responses to the drug. The effects of MDMA were greater in the OPP condition, compared to the SOL or RAP conditions, on measures of "feel drug," "dizzy," and on cardiovascular. But responses to the drug on other measures, including social behavior, did not differ across the conditions. These findings provide some support for the idea that drugs produce greater effects when they are used in the presence of other drug users. However, the influence of the social context was modest, and it remains to be determined whether other variables related to social context would substantially alter the effects of MDMA or other drugs.

EPIDEMIOLOGY RESEARCH

Genetic Predisposition To Schizophrenia Associated With Increased Use Of Cannabis
Power RA, Verweij KJH, Zuhair M, Montgomery GW, Henders AK, Heath AC, Madden PAF, Medland SE, Wray NR, Martin NG. Mol Psychiatry. 2014; 19(11): 1201-1204.
Cannabis is the most commonly used illicit drug worldwide. With debate surrounding the legalization and control of use, investigating its health risks has become a pressing area of research. One established association is that between cannabis use and schizophrenia, a debilitating psychiatric disorder affecting ~1% of the population over their lifetime. Although considerable evidence implicates cannabis use as a component cause of schizophrenia, it remains unclear whether this is entirely due to cannabis directly raising risk of psychosis, or whether the same genes that increase psychosis risk may also increase risk of cannabis use. In a sample of 2082 healthy individuals, we show an association between an individual & burden of schizophrenia risk alleles and use of cannabis. This was significant both for comparing those who have ever versus never used cannabis (P=2.6 10(-4)), and for quantity of use within users (P=3.010(-3)). Although directly predicting only a small amount of the variance in cannabis use, these findings suggest that part of the association between schizophrenia and cannabis is due to a shared genetic etiology. This form of gene-environment correlation is an important consideration when calculating the impact of environmental risk factors, including cannabis use.

Subthreshold Posttraumatic Stress Disorder in the World Health Organization World Mental Health Surveys McLaughlin KA, Koenen KC, Friedman MJ, Ruscio AM, Karam EG, Shahly V, Stein DJ, Hill ED, Petukhova M, Alonso J, Andrade LH, Angermeyer MC, Borges G, de Girolamo G, de Graaf R, Demyttenaere K, Florescu SE, Mladenova M, Posada-Villa J, Scott KM, Takeshima T, Kessler RC. Biol Psychiatry. 2015; 77(4): 375-384.
Although only a few people exposed to a traumatic event (TE) develop posttraumatic stress disorder (PTSD), symptoms that do not meet full PTSD criteria are common and often clinically significant. Individuals with these symptoms sometimes have been characterized as having subthreshold PTSD, but no consensus exists on the optimal definition of this term. Data from a large cross-national epidemiologic survey are used in this study to provide a principled basis for such a definition. The World Health Organization World Mental Health Surveys administered fully structured psychiatric diagnostic interviews to community samples in 13 countries containing assessments of PTSD associated with randomly selected TEs. Focusing on the 23,936 respondents reporting lifetime TE exposure, associations of approximated DSM-5 PTSD symptom profiles with six outcomes (distress-impairment, suicidality, comorbid fear-distress disorders, and PTSD symptom duration) were examined to investigate implications of different subthreshold definitions. Although consistently highest outcomes for distress-impairment, suicidality, comorbidity, and PTSD symptom duration were observed among the 3.0% of respondents with DSM-5 PTSD rather than other symptom profiles, the additional 3.6% of respondents meeting two or three of DSM-5 criteria B-E also had significantly elevated scores for most outcomes. The proportion of cases with threshold versus subthreshold PTSD varied depending on TE type, with threshold PTSD more common following interpersonal violence and subthreshold PTSD more common following events happening to loved ones. Subthreshold DSM-5 PTSD is most usefully defined as meeting two or three of DSM-5 criteria B-E. Use of a consistent definition is critical to advance understanding of the prevalence, predictors, and clinical significance of subthreshold PTSD.

Gender Differences in the Long-term Associations between Posttraumatic Stress Disorder and Depression Symptoms: Findings from the Detroit Neighborhood Health Study
Horesh D, Lowe SR, Galea S, Uddin M, Koenen KC. Depress Anxiety. 2015; 32(1): 38-48.
Posttraumatic stress disorder (PTSD) and depression are known to be highly comorbid. However, previous findings regarding the nature of this comorbidity have been inconclusive. This study prospectively examined whether PTSD and depression are distinct constructs in an epidemiologic sample, as well as assessed the directionality of the PTSD-depression association across time. Nine hundred and forty-two Detroit residents (males: n = 387; females: n = 555) were interviewed by phone at three time points, 1 year apart. At each time point, they were assessed for PTSD (using the PCL-C), depression (PHQ-9), trauma exposure, and stressful life events. First, a confirmatory factor analysis showed PTSD and depression to be two distinct factors at all three waves of assessments (W1, W2, and W3). Second, chi-square analysis detected significant differences between observed and expected rates of comorbidity at each time point, with significantly more no-disorder and comorbid cases, and significantly fewer PTSD only and depression only cases, than would be expected by chance alone. Finally, a cross-lagged analysis revealed a bidirectional association between PTSD and depression symptoms across time for the entire sample, as well as for women separately, wherein PTSD symptoms at an early wave predicted later depression symptoms, and vice versa. For men, however, only the paths from PTSD symptoms to subsequent depression symptoms were significant. Across time, PTSD and depression are distinct, but correlated, constructs among a highly-exposed epidemiologic sample. Women and men differ in both the risk of these conditions, and the nature of the long-term associations between them.

Natural Course of Cannabis Use Disorders Farmer RF, Kosty DB, Seeley JR, Duncan SC, Lynskey MT, Rohde P, Klein DN, Lewinsohn PM. Psychol Med. 2015; 45(1): 63-72.
Despite its importance as a public health concern, relatively little is known about the natural course of cannabis use disorders (CUDs). The primary objective of this research was to provide descriptive data on the onset, recovery and recurrence functions of CUDs during the high-risk periods of adolescence, emerging adulthood and young adulthood based on data from a large prospective community sample.Probands (n = 816) from the Oregon Adolescent Depression Project (OADP) participated in four diagnostic assessments (T1-T4) between the ages of 16 and 30 years, during which current and past CUDs were assessed. The weighted lifetime prevalence of CUDs was 19.1% with an average onset age of 18.6 years. Although gender was not significantly related to the age of initial CUD onset, men were more likely to be diagnosed with a lifetime CUD. Of those diagnosed with a CUD episode, 81.8% eventually achieved recovery during the study period. Women achieved recovery significantly more quickly than men. The recurrence rate (27.7%) was relatively modest, and most likely to occur within the first 36 months following the offset of the first CUD episode. CUD recurrence was uncommon after 72 months of remission and recovery. CUDs are relatively common, affecting about one out of five persons in the OADP sample prior to the age of 30 years. Eventual recovery from index CUD episodes is the norm, although about 30% of those with a CUD exhibit a generally persistent pattern of problematic use extending 7 years or longer.

The Causes of Parent-offspring Transmission of Drug Abuse: A Swedish Population-based Study Kendler KS, Ohlsson H, Sundquist K, Sundquist J. Psychol Med. 2015; 45(1): 87-95.
While drug abuse (DA) is strongly familial, we still have limited knowledge about the causes of its cross-generational transmission. The authors examined DA ascertained from national registers in offspring of three family types from the Swedish population [intact (n = 2,111,074), not-lived-with;

(n = 165,315, where biological parents never lived with their offspring) and step; (n = 124,800 offspring)], which reflected, respectively, the effects of genes + rearing, genes only and rearing only. The authors replicated these results in three high-risk co-relative designs. Combined across mothers and fathers, the hazard ratio (HR) for DA in offspring given DA in parents was 3.52 in intact, 2.73 in; not-lived-with; and 1.79 in stepfamilies. In 968 biological full or half-sibling pairs one of whom was reared by and the other never lived with their parent with DA, the HR for DA was greater in the reared than ; not-lived-with; child (HR 1.57). In 64 offspring pairs of a parent with DA, the HR for DA was greater in a reared biological v. step-parented non-biological child (HR 3.33). In 321 pairs of offspring of a parent with DA one of whom was a not-lived-with biological child and the second a step-parented non-biological child, the HR for DA was greater in the biological v. stepchild (HR 1.80). Both genetic and environmental factors contribute substantially to parent-offspring resemblance for DA. The general population contains informative family constellations that can complement more traditional adoption designs in clarifying the sources of parent-offspring resemblance.

Influences of Motivational Contexts on Prescription Drug Misuse and Related Drug Problems Kelly BC, Rendina HJ, Vuolo M, Wells BE, Parsons JT. J Subst Abuse Treat. 2015; 48(1): 49-55.
Prescription drug misuse has emerged as a significant problem among young adults. While the effects of motivational contexts have been demonstrated for illicit drugs, the role of motivational contexts in prescription drug misuse remains understudied. Using data from 400 young adults recruited via time-space sampling, the authors examined the role of motivational contexts in the frequency of misuse of three prescription drug types as well as drug-related problems and symptoms of dependency. Both negative and positive motivations to use drugs are associated with increases in prescription drug misuse frequency. Only negative motivations are associated directly with drug problems and drug dependence, as well as indirectly via prescription pain killer misuse. Addressing positive and negative motivational contexts of prescription drug misuse may not only provide a means to reduce misuse and implement harm reduction measures, but may also inform the content of treatment plans for young adults with prescription drug misuse problems.

Genetic Variation In Personality Traits Explains Genetic Overlap Between Borderline Personality Features and Substance Use Disorders Few L, Grant JD, Trull TJ, Statham DJ, Martin NG, Lynskey MT, Agrawal A. Addiction. 2014; 109(12): 2118-2127.
The objective of this study was to examine the genetic overlap between borderline personality features (BPF) and substance use disorders (SUDs) and the extent to which variation in personality traits contributes to this covariance. Genetic structural equation modelling was used to partition the variance in and covariance between personality traits, BPF and SUDs into additive genetic, shared and individual-specific environmental factors. All participants were registered with the Australian Twin Registry. A total of 3127 Australian adult twins participated in the study. Diagnoses of DSM-IV alcohol and cannabis abuse/dependence (AAD; CAD) and nicotine dependence (ND) were derived via computer-assisted telephone interview. BPF and five-factor model personality traits were derived via self-report questionnaires. Personality traits, BPF and substance use disorders were partially influenced by genetic factors with heritability estimates ranging from 0.38 (neuroticism; 95% confidence interval: 0.30-0.45) to 0.78 (CAD; 95% confidence interval: 0.67-0.86). Genetic and individual-specific environmental correlations between BPF and SUDs ranged from 0.33 to 0.56 (95% CI = 0.19-0.74) and 0.19-0.32 (95% CI = 0.06-0.43), respectively. Overall, there was substantial support for genetic influences that were specific to AAD, ND and CAD (30.76-68.60%).

Finally, genetic variation in personality traits was responsible for 11.46% (extraversion for CAD) to 59.30% (neuroticism for AAD) of the correlation between BPF and SUDs. Both genetic and individual-specific environmental factors contribute to comorbidity between borderline personality features and substance use disorders. A substantial proportion of this comorbidity can be attributed to variation in normal personality traits, particularly neuroticism.

A Latent Growth Curve Analysis of Alcohol-use Specific Parenting and Adolescent Alcohol Use Zehe JM, Colder CR. Addict Behav. 2014; 39(12): 1701-1705.
This study investigates how changes in alcohol use-specific parenting were associated with adolescent drinking trajectories. Three waves of data from a longitudinal study investigating adolescent substance use were used. The community sample (N=378) was aged 10-13 at the first wave of assessment. The authors findings show that over time, parents are less likely to discipline their adolescents; drinking, more likely to grant their adolescent permission to drink, and less likely to communicate the consequences of alcohol use. Moreover, these changes are associated with escalation in adolescent alcohol use. Parental efficacy at preventing alcohol use declined, but did not relate to changes in adolescent drinking.

Global Epidemiology of HIV among Female Sex Workers: Influence of Structural Determinants Shannon K, Strathdee SA, Goldenberg SM, Duff P, Mwangi P, Rusakova M, Reza-Paul S, Lau J, Deering K, Pickles MR, Boily M-C. Lancet. 2015; 385(9962): 55-71.
Female sex workers (FSWs) bear a disproportionately large burden of HIV infection worldwide. Despite decades of research and programme activity, the epidemiology of HIV and the role that structural determinants have in mitigating or potentiating HIV epidemics and access to care for FSWs is poorly understood. The authors reviewed available published data for HIV prevalence and incidence, condom use, and structural determinants among this group. Only 87 (43%) of 204 unique studies reviewed explicitly examined structural determinants of HIV. Most studies were from Asia, with few from areas with a heavy burden of HIV such as sub-Saharan Africa, Russia, and Eastern Europe. To further explore the potential effect of structural determinants on the course of epidemics, the authors used a deterministic transmission model to simulate potential HIV infections averted through structural changes in regions with concentrated and generalized epidemics, and high HIV prevalence among FSWs. This modelling suggested that elimination of sexual violence alone could avert 17% of HIV infections in Kenya (95% uncertainty interval [UI] 1-31) and 20% in Canada (95% UI 3-39) through its immediate and sustained effect on non-condom use) among FSWs and their clients in the next decade. In Kenya, scaling up of access to antiretroviral therapy among FSWs and their clients to meet WHO eligibility of a CD4 cell count of less than 500 cells per *L could avert 34% (95% UI 25-42) of infections and even modest coverage of sex worker-led outreach could avert 20% (95% UI 8-36) of infections in the next decade. Decriminalization of sex work would have the greatest effect on the course of HIV epidemics across all settings, averting 33-46% of HIV infections in the next decade. Multipronged structural and community-led interventions are crucial to increase access to prevention and treatment and to promote human rights for FSWs worldwide.

Prevalence and Correlates of Nonmedical Prescription Opioid Use Among Cohort of Sex Workers in Vancouver, Canada Argento E, Chettiar J, Nguyen P, Montaner J, Shannon K. Int J Drug Policy. 2015; 26(1): 59-66.
The nonmedical use of prescription opioids (POs) is a major public health concern, causing extensive morbidity and mortality in North America. Canada has the second highest consumption rate of POs globally and data indicate nonmedical PO use (NPOU) is growing among key populations and increasingly available in street-level drug markets. Despite accumulating evidence documenting the rise of NPOU, few studies have systematically examined NPOU in Canada among key vulnerable populations, such as sex workers. This study prospectively evaluated the prevalence and correlates of NPOU within a Vancouver cohort of sex workers over three-year follow-up. Data were drawn from an open prospective cohort, AESHA (An Evaluation of Sex Workers Health Access) in Metro Vancouver, Canada (2010-2013). Women were recruited through outreach from outdoor street locations and indoor venues. Bivariate and multivariable logistic regression using Generalized Estimating Equations (GEE) were used to examine social and structural correlates of NPOU over 36 months. Of the 692 sex workers at baseline, close to one-fifth (n=130, 18.8%) reported NPOU (injection or non-injection) in the last six months. In multivariable GEE analyses, factors independently correlated with recent NPOU were: exchanging sex while high (AOR 3.26, 95%CI 2.29-4.64), police harassment/arrest (AOR 1.83, 95%CI 1.43-2.35), intimate partner injects drugs (AOR 1.66, 95%CI 1.11-2.49), and recent physical/sexual intimate partner violence (AOR 1.65, 95%CI 1.21-2.24). These results demonstrate that nearly one-fifth of sex workers in Metro Vancouver report NPOU. Factors independently statistically associated with NPOU included exchanging sex while high, police harassment/arrest, a drug injecting intimate partner and recent physical/sexual intimate partner violence. The high prevalence of NPOU use among sex workers underscores the need for further prevention and management strategies tailored to this key population. The correlates of NPOU uncovered here suggest that structural interventions may be further implemented to ameliorate this growing concern.

The Impact of Childhood Parental Loss on Risk for Mood, Anxiety and Substance Use Disorders In A Population-based Sample of Male Twins Otowa T, York TP, Gardner CO, Kendler KS, Hettema JM. Psychiatry Res. 2014; 220(1-2): 404-409.
Previous studies have identified the relationship between parental loss and psychopathology later in life. However, this relationship varied depending on the kind of loss, the parent involved, and the type of psychopathology. In the present study, the authors examined the association between parental loss (any loss, death, and separation) during childhood and lifetime risk for seven common psychiatric and substance use disorders in a sample of 2605 male twins from the Virginia population-based twin registry. Using structural equation modeling (SEM), we also examined the extent to which the influence of parental loss contributes to adult psychopathology. Parental separation was associated with a wide range of adult psychopathology, whereas parental death was specifically associated with phobia and alcohol dependence. Maternal and paternal separations were almost equally associated with most forms of psychopathology. SEM suggested that parental loss accounted for about 10% of the variance of adult psychopathology, of which parental separation had the strongest impacts on risk for depression and drug abuse/dependence (11% of the total variance). These findings suggest that early parental separation has stronger and wider effects on adult psychopathology than parental death.

Testing the Drug Substitution Switching-addictions Hypothesis. A Prospective Study In A Nationally Representative Sample Blanco C, Okuda M, Wang S, Liu S-M, Olfson M. JAMA Psychiatry. 2014; 71(11): 1246-1253.
Adults who remit from a substance use disorder (SUD) are often thought to be at increased risk for developing another SUD. A greater understanding of the prevalence and risk factors for drug substitution would inform clinical monitoring and management. The objective of this study was to determine whether remission from an SUD increases the risk of onset of a new SUD after a 3-year follow-up compared with lack of remission from an SUD and whether sociodemographic characteristics and psychiatric disorders, including personality disorders, independently predict a new-onset SUD. A prospective cohort study where data were drawn from a nationally representative sample of 34653 adults from the National Epidemiologic Survey on Alcohol and Related Conditions. Participants were interviewed twice, 3 years apart (wave 1, 2001-2002; wave 2, 2004-2005). The authors compared new-onset SUDs among individuals with at least 1 current SUD at wave 1 who did not remit from any SUDs at wave 2 (3275) and among individuals with at least 1 current SUD at wave 1 who remitted at wave 2 (2741).Approximately one-fifth (2741) of the total sample had developed a new-onset SUD at the wave 2 assessment. Individuals who remitted from 1 SUD during this period were significantly less likely than those who did not remit to develop a new SUD (13.1% vs 27.2%.001). Results were robust to sample specification. An exception was that remission from a drug use disorder increased the odds of a new SUD (odds ratio [OR]1.46; 95% CI, 1.11-1.92). However, after adjusting for the number of SUDs at baseline, remission from drug use disorders decreased the odds of a new-onset SUD (OR 0.66; 95% CI, 0.46-0.95) whereas the number of baseline SUDs increased those odds (OR=1.68; 95% CI, 1.43-1.98). Being male, younger in age, never married, having an earlier age at substance use onset, and psychiatric comorbidity significantly increased the odds of a new-onset SUD during the follow-up period. As compared with those who do not remit from an SUD, remitters have less than half the risk of developing a new SUD. Contrary to clinical lore, achieving remission does not typically lead to drug substitution but rather is associated with a lower risk of new SUD onsets.

Probability and Predictors of the Cannabis Gateway Effect: A National Study Secades-Villa R, Garcia-Rodriguez O, Jin CJ, Wang S, Blanco C. Int J Drug Policy. 2015; 26(2):135-142.
While several studies have shown a high association between cannabis use and use of other illicit drugs, the predictors of progression from cannabis to other illicit drugs remain largely unknown. This study aims to estimate the cumulative probability of progression to illicit drug use among individuals with lifetime history of cannabis use, and to identify predictors of progression from cannabis use to other illicit drugs use. Analyses were conducted on the sub-sample of participants in Wave 1of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) who started cannabis use before using any other drug (n=6624). Estimated projections of the cumulative probability of progression from cannabis use to use of any other illegal drug use in the general population were obtained by the standard actuarial method. Univariate and multivariable survival analyses with time-varying covariates were implemented to identify predictors of progression to any drug use. Lifetime cumulative probability estimates indicated that 44.7% of individuals with lifetime cannabis use progressed to other illicit drug use at some time in their lives. Several sociodemographic characteristics, internalizing and externalizing psychiatric disorders and indicators of substance use severity predicted progression from cannabis use to other illicit drugs use. A large proportion of individuals who use cannabis go on to use other illegal drugs. The increased risk of progression from cannabis use to other illicit drugs use among individuals with

mental disorders underscores the importance of considering the benefits and adverse effects of changes in cannabis regulations and of developing prevention and treatment strategies directed at curtailing cannabis use in these populations.

Psychosocial Vulnerability and HIV-Related Sexual Risk among Men Who Have Sex with Men and Women In the United States Dyer TP, Regan R, Pacek LR, Acheampong A, Khan MR. Arch Sex Behav. 2015; 44(2): 429-441.
In the U.S., HIV is concentrated among men who have sex with men (MSM), some of whom have had female partners (MSMW). MSMW are disproportionately impacted by psychosocial vulnerabilities, like depression and substance use that increase sexually transmitted infection (STI) and HIV risk. Research on psychosocial vulnerability and HIV-related sexual risk among MSMW is warranted to reduce infection transmission among MSM and to prevent bridging to female partners. The authors analyzed data from Wave IV (2007-2008) of the National Longitudinal Study of Adolescent Health to assess psychosocial vulnerability and HIV risk-taking among MSMW. Using lifetime and past year sexual activity, we classified men as ever having sex with: women only (MSW), men only (MSMO) or MSMW, with further refined categorization of MSMW with male only partners in the past 12months, only female partners in the past 12months, and both male and female partners in the past 12months (6,945). The authors compared psychosocial vulnerability characteristics and HIV-related risk behaviors among the five categories of men. MSMW were more likely to report depression, suicidality, substance use, and incarceration than MSW and MSMO. Compared to MSW, MSMW with current female partners had greater odds of unprotected sex, exchange sex, and STI. MSMW with male partners in the past year had greater odds of multiple or concurrent partners in the past year. HIV risk and psychosocial vulnerability factors are elevated among MSMW, a priority population for HIV risk reduction. HIV risk reduction interventions should address this and heterogeneity of sexual partnerships among MSMW.

Toward A Comprehensive Developmental Model Of Smoking Initiation and Nicotine Dependence Garcia-Rodriguez O, Blanco C, Wall MM, Wang S, Jin CJ, Kendler KS. Drug Alcohol Depend. 2014; 144: 160-169.
This study aims to identify predictors of smoking initiation and nicotine dependence (ND) to develop a comprehensive risk-factor model based on Kendlers development model for major depression. Data were drawn from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), Wave 2 (n=34,653). Risk factors were divided into five developmental tiers according to Kendlers model (childhood, early adolescence, late adolescence, adulthood, past-year). Hierarchical logistic regression models were built to predict the risk of smoking initiation and the risk of ND, given initiation. The continuation ratio (CR) was tested by ordinal logistic regression to examine whether the impact of the predictors was the same on smoking initiation or ND. The final models highlighted the importance of different tiers for each outcome. The CR identified substantial differences in the predictors of smoking initiation versus ND. Childhood tier appears to be more determinant for smoking initiation while the effect of more distal tiers (i.e. childhood and early adolescence) was tempered by more proximal ones (i.e. late adolescence, adulthood and past-year) in ND, with few sex differences. The differential effect of some predictors on each outcome shows the complexity of pathways from smoking initiation to ND. While some risk factors may be shared, others impact only at one stage or have even an inverse effect. An adaptation of Kendler developmental model for major depression showed high predictive power for smoking initiation and ND.

Nonmedical Stimulant Use Among Young Asian-Americans, Native Hawaiians/Pacific Islanders, And Mixed-race Individuals Aged 12-34 Years In the United States Wu L-T, Swartz MS, Brady KT, Blazer DG, Hoyle RH, NIDA AAPI Workgroup. J Psychiatr Res. 2014; 59: 189-199.

There are concerns over nonmedical use of prescription stimulants among youths, but little is known about the extent of use among young Asian-Americans, Native Hawaiians/Pacific Islanders (NHs/PIs), and mixed-race individuals-the fastest growing segments of the U.S. population. The authors examined prevalences and correlates of nonmedical stimulant use (NMSU) and disorder (StiUD) for these under recognized groups. Whites were included as a comparison. Data were from young individuals aged 12-34 years in the 2005-2012 National Surveys on Drug Use and Health. The authors used logistic regression to estimate odds of past-year NMSU status. Significant yearly increases in lifetime NMSU prevalence were noted in Whites only. NHs/PIs (lifetime 7.33%, past-year 2.72%) and mixed-race individuals (10.20%, 2.82%) did not differ from Whites in NMSU prevalence (11.68%, 3.15%). Asian-Americans (lifetime 3.83%, past-year 0.90%) had lower prevalence's than Whites. In each racial/ethnic group, "Methamphetamine/Desoxyn/Methedrine or Ritalin" was more commonly used than other stimulant groups; "got them from a friend/relative for free" and "bought them from a friends/relative" were among the most common sources. Females had greater odds than males of NMSU (among White, NH/PI, mixed-race individuals) and StiUD (among mixed-race individuals). Young adults (aged 18-25) had elevated odds of NMSU (White, NH/PI); adolescents had elevated odds of StiUD (White, mixed-race). Other substance use (especially marijuana, other prescription drugs) increased odds of NMSU and StiUD. NHs/PIs and mixed-race individuals were as likely as Whites to misuse stimulants. Research is needed to delineate health consequences of NMSU and inform prevention efforts for these understudied, rapidly-growing populations.

Assessing Differences In Groups Randomized By Recruitment Chain In A Respondent-driven Sample Of Seattle-area Injection Drug Users Burt RD, Thiede H. Ann Epidemiol. 2014; 24(11): 861-867.e14.

Respondent-driven sampling (RDS) is a form of peer-based study recruitment and analysis that incorporates features designed to limit and adjust for biases in traditional snowball sampling. It is being widely used in studies of hidden populations. The authors report an empirical evaluation of RDS consistency and variability, comparing groups recruited contemporaneously, by identical methods and using identical survey instruments. They randomized recruitment chains from the RDS-based 2012 National HIV Behavioral Surveillance survey of injection drug users in the Seattle area into two groups and compared them in terms of sociodemographic characteristics, drug-associated risk behaviors, sexual risk behaviors, human immunodeficiency virus (HIV) status and HIV testing frequency. The two groups differed in five of the 18 variables examined ($P<.001$): race (e.g., 60% white vs. 47%), gender (52% male vs. 67%), area of residence (32% downtown Seattle vs. 44%), an HIV test in the previous 12months (51% vs. 38%). The difference in serologic HIV status was particularly pronounced (4% positive vs. 18%). In four further randomizations, differences in one to five variables attained this level of significance, although the specific variables involved differed. The authors found some material differences between the randomized groups. Although the variability of the present study was less than has been reported in serial RDS surveys, these findings indicate caution in the interpretation of RDS results.

Factors Associated With Initiating Someone Into Illicit Drug Injection Bluthenthal RN, Wenger L, Chu D, Quinn B, Thing J, Kral AH. Drug Alcohol Depend. 2014; 144: 186-192.
Most people who inject drugs (PWID) were first initiated into injection by a current PWID. Few studies have examined PWID who assist others into drug injection. The authors' goal is to describe the prevalence of and risk factors for initiating someone into injection in the last 12 months. They recruited a cross-sectional sample of PWID (N=605) in California from 2011 to 2013. They examined bivariate and multivariate risk factors for initiating someone into injection with a focus on behaviors that might encourage injection initiation such as injecting in front of non-PWID, describing how to inject to non-PWID, and willingness to initiate someone into drug injection. Having initiated someone into injection was reported by 34% of PWID overall and 7% in the last 12 months. Forty-four PWID had assisted 431 people into injection in the past year. Factors independently associated with initiating someone into injection in the last 12 months were self-reported likelihood of initiating someone in the future (Adjusted Odds Ratio [AOR]=7.09; 95% Confidence Interval [CI]=3.40, 14.79), having injected another PWID in past month (AOR=4.05; 95% confidence interval [CI]=1.94, 8.47), having described how to inject to non-injectors (2.61; 95% CI=1.19, 5.71), and non-injection powder cocaine use in past month (AOR=4.97; 95% CI=2.08, 11.84) while controlling for study site. Active PWID are important in facilitating the process of drug injection uptake. Interventions to reduce initiation should include efforts to change behaviors and intentions among PWID that are associated with injection uptake among others.

High Risk and Little Knowledge: Overdose Experiences and Knowledge Among Young Adult Nonmedical Prescription Opioid Users Frank D, Mateu-Gelabert P, Guarino H, Bennett A, Wendel T, Jessell L, Teper A. Int J Drug Policy. 2015; 26(1): 84-91.
Opioid-involved overdoses in the United States have dramatically increased in the last 15 years, largely due to a rise in prescription opioid (PO) use. Yet few studies have examined the overdose knowledge and experience of nonmedical PO users. In depth, semi-structured, audio-recorded interviews were conducted with 46 New York City young adults (ages 18-32) who reported using POs none medically within the past 30 days. Verbatim interview transcripts were coded for key themes in an analytic process informed by grounded theory. Despite significant experience with overdose (including overdose deaths), either personally or within opioid-using networks, participants were relatively uninformed about overdose awareness, avoidance and response strategies, in particular the use of naloxone. Overdose experiences typically occurred when multiple pharmaceuticals were used (often in combination with alcohol) or after participants had transitioned to heroin injection. Participants tended to see themselves as distinct from traditional heroin users, and were often outside of the networks reached by traditional opioid safety/ overdose prevention services. Consequently, they were unlikely to utilize harm reduction services, such as syringe exchange programs (SEPs) that address drug user's health and safety. These findings suggest that many young adult nonmedical PO users are at high risk of both fatal and non-fatal overdose. There is a pressing need to develop innovative outreach strategies and overdose prevention programs to better reach and serve young PO users and their network contacts. Prevention efforts addressing risk for accidental overdose, including opioid safety/overdose reversal education and naloxone distribution, should be tailored for and targeted to this vulnerable group.

Nicotine-dependence-varying Effects Of Smoking Events On Momentary Mood Changes Among Adolescents Selya AS, Updegrove N, Rose JS, Dierker L, Tan X, Hedeker D, Li R, Mermelstein R. J. Addict Behav. 2015; 41: 65-71.
Theories of nicotine addiction emphasize the initial role of positive reinforcement in the development of regular smoking behavior, and the role of negative reinforcement at later stages. These theories are tested here by examining the effects of amount smoked per smoking event on smoking-related mood changes, and how nicotine dependence (ND) moderates this effect. The current study examines these questions within a sample of light adolescent smokers drawn from the metropolitan Chicago area (N=151, 55.6% female, mean 17.7years).Ecological momentary assessment data were collected via handheld computers, and additional variables were drawn from a traditional questionnaire. Effects of the amount smoked per event on changes in positive affect (PA) and negative affect (NA) after vs. before smoking were examined, while controlling for subject-averaged amount smoked, age, gender, and day of week. ND-varying effects were examined using varying effect models to elucidate their change across levels of ND. The effect of the amount smoked per event was significantly associated with an increase in PA among adolescents with low-to-moderate levels of ND, and was not significant at high ND. Conversely, the effect of the amount smoked was significantly associated with a decrease in NA only for adolescents with low levels of ND. These findings support the role of positive reinforcement in early stages of dependent smoking, but do not support the role of negative reinforcement beyond early stages of smoking. Other potential contributing factors to the relationship between smoking behavior and PA/NA change are discussed.

Patterns Of Opioid Use For Chronic Noncancer Pain In The Veterans Health Administration From 2009 To 2011 Edlund MJ, Austen MA, Sullivan MD, Martin BC, Williams JS, Fortney JC, Hudson T. J. Pain. 2014; 155(11): 2337-2343.
Although opioids are frequently prescribed for chronic noncancerous pain (CNCP) among Veterans Health Administration (VHA) patients, little has been reported on national opioid prescribing patterns in the VHA. The authors' objective was to better characterize the dosing and duration of opioid therapy for CNCP in the VHA. They analyzed national VHA administrative and pharmacy data for fiscal years 2009 to 2011. For individuals with CNCP diagnoses and any opioid use in the fiscal year, we calculated the distribution of individual mean daily opioid dose, individual total days covered with opioids in a year, and individual total opioid dose in a year. They also investigated the factors associated with being in the top 5% of individuals for total opioid dose in a year, which we term receipt of high-volume opioids. About half of the patients with CNCP received opioids in a given fiscal year. The median daily dose was 21mg morphine equivalents. Approximately 4.5% had a mean daily dose higher than 120mg morphine equivalents. The median days covered in a year was 115 to 120days in these years for those receiving opioids. Fifty-seven percent had at least 90days covered with opioids per year. Major depression and posttraumatic stress disorder were positively associated with receiving high-volume opioids, but non opioid substance use disorders were not. Among VHA patients with CNCP, chronic opioid therapy occurs frequently, but for most patients, the average daily dose is modest. Doses and duration of therapy were unchanged from 2009 to 2011.

Associations Between Childhood Adversity, Adult Stressful Life Events, and Past-year Drug Use Disorders In the National Epidemiological Study Of Alcohol and Related Conditions (NESARC) Myers B, McLaughlin K, Wang S, Blanco C, Stein D J. Psychol Addict Behav. 2014; 28(4): 1117-1126.
Stress sensitization, whereby CA lowers tolerance to later stressors, has been proposed as a potential mechanism explaining the association between exposure to childhood adversities (CA) and drug use disorders in adulthood. However, this mechanism remains untested. This paper begins to address this gap through exploring associations between CA exposure and stressful events in adulthood for predicting drug use disorders. The authors used data drawn from Wave 2 of the U.S. National Epidemiological Survey of Alcohol and Related Conditions (n = 34,653) to explore whether the association between past-year stressful life events and the 12-month prevalence of disordered cannabis, stimulant, and opiate use varied by the number of types of CA that an individual was exposed to. Past-year stressful life events were associated with an increased risk of cannabis, stimulant, and opiate use disorders among men and women. Exposure to CA was associated with increased risk for disordered cannabis use among men and women and opiate use among men only. Finally, the authors found significant associations between exposure to CA and past-year stressful life events in predicting disordered drug use, but only for women in relation to disordered stimulant and opiate use. Findings are suggestive of possible stress sensitization effects in predicting disordered stimulant and opiate use among women. Implications of these findings for the prevention and treatment of drug use disorders and for future research are discussed.

Associations Between Subjective Social Status and DSM-IV Mental Disorders: Results From the World Mental Health Surveys Scott KM, Al-Hamzawi AO, Andrade LH, Borges G, Caldas-de-Almeida JM, Fiestas F, Gureje O, Hu C, Karam EG, Kawakami N, Lee S, Levinson D, Lim CCW, Navarro-Mateu F, Okoliyski M, Posada-Villa Jose T, Yolanda W, David R, Zakhozha V, Kessler RC. JAMA Psychiatry. 2014; 71(12): 1400-1408.
The inverse social gradient in mental disorders is a well-established research finding with important implications for causal models and policy. This research has used traditional objective social status (OSS) measures, such as educational level, income, and occupation. Recently, subjective social status (SSS) measurement has been advocated to capture the perception of relative social status, but to our knowledge, there have been no studies of associations between SSS and mental disorders. To estimate associations of SSS with DSM-IV mental disorders in multiple countries and to investigate whether the associations persist after comprehensive adjustment of OSS. Face-to-face cross-sectional household surveys of community-dwelling adults in 18 countries in Asia, South Pacific, the Americas, Europe, and the Middle East (N=56,085). Subjective social status was assessed with a self-anchoring scale reflecting respondent evaluations of their place in the social hierarchies of their countries in terms of income, educational level, and occupation. Scores on the 1 to 10 SSS scale were categorized into 4 categories: low (scores 1-3), low-mid (scores 4-5), high-mid (scores 6-7), and high (scores 8-10). Objective social status was assessed with a wide range of fine-grained objective indicators of income, educational level, and occupation. The Composite International Diagnostic Interview assessed the 12-month prevalence of 16 DSM-IV mood, anxiety, and impulse control disorders. The weighted mean survey response rate was 75.2% (range, 55.1%-97.2%). Graded inverse associations were found between SSS and all 16 mental disorders. Gross odds ratios (lowest vs highest SSS categories) in the range of 1.8 to 9.0 were attenuated but remained significant for all 16 disorders (odds ratio, 1.4-4.9) after adjusting for OSS indicators. This pattern of inverse association between SSS and mental disorders was significant in 14 of 18 individual

countries, and in low-, middle-, and high-income country groups but was significantly stronger in high- vs lower-income countries. Significant inverse associations between SSS and numerous DSM-IV mental disorders exist across a wide range of countries even after comprehensive adjustment for OSS. Although it is unclear whether these associations are the result of social selection, social causation, or both, these results document clearly that research relying exclusively on standard OSS measures underestimates the steepness of the social gradient in mental disorders.

Hope As A Moderator Of the Associations Between Common Risk Factors and Frequency Of Substance Use Among Latino Adolescents Fite PJ, Gabrielli J, Cooley JL, Haas S, Frazer A, Rubens SL, Johnson-Motoyama M. J Psychopathol Behav Assess. 2014; 36(4): 653-662.
Ample research suggests that delinquency, depressive symptoms, and peer substance use are common risk factors associated with adolescent substance use. However, the factors that may help to buffer the deleterious effects of these risk factors on adolescent substance use, such as hope, have yet to be examined. The current study evaluated hope as a moderator of the associations between these common risk factors and frequency of substance use (alcohol, tobacco, and marijuana) in a sample of Latino high school students (Mage = 16.14years, SD = 1.30; 55% female). Findings indicated that the influence of delinquency on frequency of tobacco and marijuana use depended on levels of hope, with delinquency only positively associated with frequency of use when levels of hope were low. Additionally, hope moderated the association between depressive symptoms and alcohol use, such that depressive symptoms were only positively associated with frequency of alcohol use when levels of hope were low. Results and their implications for intervention are reviewed.

Childhood ADHD Potentiates the Association Between Problematic Drinking and Intimate Partner Violence Wymbs BT, Walther CAP, Cheong JW, Belendiuk KA, Pedersen SL, Gnagy EM, Pelham Jr, WE, Molina BSG. J Atten Disord. 2014.
Excessive alcohol consumption increases risk of perpetrating intimate partner violence (IPV). ADHD is associated with problematic drinking and IPV, but it is unclear whether problem drinkers with ADHD are more likely than those without ADHD to perpetrate IPV. The authors compared the strength of association between problem drinking trajectories and IPV perpetration among 19- to 24-year-old men with (n = 241) and without (n = 180) childhood ADHD. Men with ADHD who reported higher heavy episodic drinking or alcohol use problems at age 19, and slower decreases in alcohol use problems from age 19 to 24, were more likely to perpetrate IPV than problem drinkers without ADHD, among whom the same associations were non-significant. Associations between problem drinking and IPV were not attenuated in adults with ADHD upon controlling for antisocial personality disorder. Study findings highlight the heightened risk of problem drinkers with ADHD perpetrating IPV.

Exposure To Violence, Substance Use, and Neighborhood Context Fagan AA, Wright EM, Pinchevsky GM. Soc Sci Res. 2015; 49: 314-326.
Adolescent exposure to violence and substance use are both public health problems, but how neighborhood context contributes to these outcomes is unclear. This study uses prospective data from 1416 adolescents to examine the direct and interacting influences of victimization and neighborhood factors on adolescent substance use. Based on hierarchical Bernoulli regression models that controlled for prior substance use and multiple individual-level factors, exposure to violence significantly increased the likelihood of marijuana use but not alcohol use or binge

drinking. There was little evidence that community norms regarding adolescent substance use influenced rates of substance use or moderated the impact of victimization. Community disadvantage did not directly impact substance use, but the relationship between victimization and marijuana use was stronger for those in neighborhoods with greater disadvantage. The results suggest that victimization is particularly likely to affect adolescents; marijuana use, and that this relationship may be contingent upon neighborhood economic conditions.

Dynamic Associations Among Alcohol Use and Anxiety Symptoms In Early Adolescence
Pardee CS, Colder CR, Bowker JC. Psychol Addict Behav. 2014; 28(4): 1246-1252.
The relationship between anxiety and alcohol use in adolescence remains unclear, with evidence for no association and for risk and protective effects of anxiety. Considering developmental trajectories may be important for understanding the association between anxiety and alcohol use and may help clarify prior mixed findings. The present study examined trajectories of alcohol use, social anxiety symptoms, and general anxiety symptoms in early to middle adolescence through the use of univariate and parallel process growth models. Social anxiety and general anxiety symptoms declined, while alcohol use increased with age. Parallel process growth models suggested that less rapid declines in social anxiety and general anxiety symptoms were associated with more rapid escalation in alcohol use. These results suggest that young adolescents who do not show normative declines in social anxiety or general anxiety symptoms may be at risk for more rapid increases in alcohol use.

Social Contexts Of Substance Use Among U.S. High School Seniors: A Multicohort National Study McCabe SE, West BT, Veliz P, Frank KA, Boyd CJ. J Adolesc Health. 2014;55(6): 842-844.
The objective of this study was to determine the social contexts associated with the past-year substance use (multiple substances, alcohol, marijuana, and nonmedical use of prescription opioids, stimulants, and tranquilizers) among U.S. high school seniors. The study was a secondary analysis of nationally representative survey data from 10 cohorts (2002-2011) of the Monitoring the Future study, including 24,809 high school seniors. The social contexts associated with the past-year substance use varied considerably based on the substance used. The most prevalent location for alcohol, marijuana, and polydrug use was at a party, whereas nonmedical use of prescription stimulants, tranquilizers, and opioids was most likely to occur at home. Most types of substance use occurred in the presence of other people with the exception of nonmedical use of prescription stimulants, which was a more solitary behavior. These exploratory findings indicate that prevention efforts may need to account for differences in social contexts between types of substances used.

Association Between Mental Disorders and Subsequent Adult Onset Asthma Alonso J, de Jonge P, Lim CCW, Aguilar-Gaxiola S, Bruffaerts R, Caldas-de-Almeida JM, Liu Z, O'Neill S, Stein DJ, Viana MC, Al-Hamzawi AO, Angermeyer MC, Borges G, Ciutan M, de Girolamo G, Fiestas F, Haro JM, Hu C, Kessler RC, Lepine JP, Levinson D, Nakamura Y, Posada-Villa J, Wojtyniak BJ, Scott KM. J Psychiatr Res. 2014; 59: 179-188.
Associations between asthma and anxiety and mood disorders are well established, but little is known about their temporal sequence. The authors examined associations between a wide range of DSM-IV mental disorders with adult onset of asthma and whether observed associations remain after mental comorbidity adjustments. During face-to-face household surveys in community-dwelling adults (n = 52,095) of 19 countries, the WHO Composite International Diagnostic Interview retrospectively assessed lifetime prevalence and age at onset of 16 DSM-IV mental

disorders. Asthma was assessed by self-report of physician diagnosis together with age of onset. Survival analyses estimated associations between first onset of mental disorders and subsequent adult onset asthma, without and with comorbidity adjustment.1860 adult onset (21 years+) asthma cases were identified, representing a total of 2,096,486 person-years of follow up. After adjustment for comorbid mental disorders several mental disorders were associated with subsequent adult asthma onset: bipolar (OR = 1.8; 95%CI 1.3-2.5), panic (OR = 1.4; 95%CI 1.0-2.0), generalized anxiety (OR = 1.3; 95%CI 1.1-1.7), specific phobia (OR = 1.3; 95%CI 1.1-1.6); post-traumatic stress (OR = 1.5; 95%CI 1.1-1.9); binge eating (OR = 1.8; 95%CI 1.2-2.9) and alcohol abuse (OR = 1.5; 95%CI 1.1-2.0). Mental comorbidity linearly increased the association with adult asthma. The association with subsequent asthma was stronger for mental disorders with an early onset (before age 21). A wide range of temporally prior mental disorders are significantly associated with subsequent onset of asthma in adulthood. The extent to which asthma can be avoided or improved among those with early mental disorders deserves study.

Frequency Of Trauma Exposure and Post-Traumatic Stress Disorder In Italy: Analysis From the World Mental Health Survey Initiative Carmassi C, Dell'Osso L, Manni C, Candini V, Dagani J, Iozzino L, Koenen KC, de Girolamo G. J Psychiatr Res. 2014; 59: 77-84.
Epidemiological studies have examined the relative importance of Traumatic Events (TEs) in accounting for the societal burden of post-traumatic stress disorder (PTSD). However, most studies used the worst trauma experienced, which can lead to an overestimation of the conditional risk of PTSD. Although a number of epidemiological surveys on PTSD have been carried out in the United States, only a few studies in limited sample have been conducted in Italy. This study, carried out in the framework of the World Mental Health Survey Initiative, is a cross-sectional household survey of a representative sample of the Italian adult population. Lifetime prevalence of TEs and 12-month prevalence of PTSD were evaluated using the Composite International Diagnostic Interview (CIDI). Reports of PTSD associated with randomly selected TEs were weighted by the individual-level probabilities of TE selection to generate estimates of population-level PTSD risk associated with each TE. Network events was the most commonly reported class of TEs (29.4%). War events had the highest conditional risk of PTSD (12.2%). The TEs that contributed most to societal PTSD burden were unexpected death of a loved one (24.1%) and having seen atrocities (18.2%). Being female was related to high risk of PTSD after experiencing a TE. Exposure to network events is commonly reported among Italian adults, but two TEs are responsible for the highest burden associated with PTSD: the unexpected death of someone close and sexual assault. These results can help designing public health interventions to reduce the societal PTSD burden.

Attention Deficit Hyperactivity Disorder Symptoms and Smoking Trajectories: Race and Gender Differences Lee C-T, Clark TT, Kollins SH, McClernon FJ, Fuemmeler BF. Drug Alcohol Depend. 2015.
This study examined the influence of Attention Deficit Hyperactivity Disorder (ADHD) symptoms severity and directionality (hyperactive-impulsive symptoms relative to inattentive symptoms) on trajectories of the probability of current (past month) smoking and the number of cigarettes smoked from age 13 to 32. Racial and gender differences in the relationship of ADHD symptoms and smoking trajectories were also assessed. A subsample of 9719 youth (54.5% female) was drawn from the National Longitudinal Study of Adolescent to Adult Health (Add Health). Cohort sequential design and zero-inflated Poisson (ZIP) latent growth modeling were used to estimate the relationship between ADHD directionality and severity on smoking development. ADHD severity

effect on the likelihood of ever smoking cigarettes at the intercept (age 13) had a greater impact on White males than other groups. ADHD severity also had a stronger influence on the initial number of cigarettes smoked at age 13 among Hispanic participants. The relationships between ADHD directionality (hyperactive-impulsive symptoms relative to inattentive symptoms) and a higher number of cigarettes smoked at the intercept were stronger among Hispanic males than others. Gender differences manifested only among Whites. ADHD severity and directionality had unique effects on smoking trajectories. These results also highlight that the risk of ADHD symptoms may differ by race and gender.

PREVENTION RESEARCH

Couple-Based HIV Counseling and Testing: A Risk Reduction Intervention For US Drug-Involved Women and Their Primary Male Partners McMahon JM. Pouget ER, Tortu S, Volpe EM, Torres L, Rodriguez W. Prev Sci. 2014.
To help reduce the elevated risk of acquiring HIV for African-American and Latina women drug users in primary heterosexual relationships, the authors developed a brief couple-based HIV counseling and testing prevention intervention. The intervention was based on an integrated HIV risk behavior theory that incorporated elements of social exchange theory, the theory of gender and power, the stages-of-change model, and the information-motivation-behavior skills model. In this article, authors describe the development, content, and format of the couple-based HIV testing and counseling intervention, and its delivery to 110 couples (220 individuals) in a randomized effectiveness trial, the Harlem River Couples Project, conducted in New York City from 2005 to 2007. Components of the couple-based intervention included a personalized dyadic action plan based on the couples' risk profile and interactive exercises designed to help build interpersonal communication skills, and facilitated discussion of social norms regarding gender roles. The couple-based HIV testing and counseling intervention significantly reduced women's overall HIV risk compared to a standard-of-care individual HIV testing and counseling intervention. Experiences and perceptions of the intervention were positive among both clients and interventionists. The study was the first to demonstrate the effectiveness and feasibility of delivering a brief couple-based HIV counseling and testing intervention to reduce risk among drug-using heterosexual couples in high HIV prevalent urban communities in the USA. The intervention can be expanded to include new HIV prevention strategies, such as pre-exposure prophylaxis. Further research is needed to evaluate cost-effectiveness and implementation of the intervention in clinical settings.

Leading A Horse To Water: Facilitating Registration and Use Of A Prescription Drug Monitoring Program Deyo RA, Irvine JM, Hallvik SE, Hildebran C, Beran T, Millet LM, Marino M. Clin J Pain. 2014.
Prescription Drug Monitoring Programs (PDMPs) can help inform patient management, coordinate care, and identify drug safety risks, abuse, or diversion. However, many clinicians are not registered to use these systems, and use may be suboptimal. The authors sought to describe outreach efforts in one state (Oregon); quantify uptake of system use; identify barriers; and identify potential system improvements. Program reports of outreach efforts and operational metrics provided rates of registration and use. A statewide survey identified perceived barriers and potential improvements from users and non-users of the system. Even with extensive registration efforts, less than 25 percent of clinicians and pharmacists acquired PDMP accounts over 2 years of operation. Rapid increases in registration and use in 2013 corresponded to new requirements among large pharmacy chains that pharmacists register for and use the PDMP. Among surveyed PDMP non-users, nearly half were unaware they could register. Among users and non-users, over two-thirds indicated that time constraints were a major barrier and over half thought inability to delegate access was a major barrier. Desired improvements included linking state systems, faster entry of pharmacy data, and use of unique patient identifiers. Users also wanted better insurance coverage for mental health and addiction referrals. Increasing registration and use of PDMPs remains important. Clinician feedback indicates that program enhancements and healthcare system changes would facilitate using and responding to PDMP information. It appears premature to judge the efficacy of PDMPs until best practices for their use are identified and impacts are assessed.

Effects Of Multidimensional Treatment Foster Care On Psychotic Symptoms In Girls
Poulton R,Van Ryzin MJ, Harold GT, Chamberlain P, Fowler D, Cannon M, Arseneault L, Leve LD. J Am Acad Child Adolesc Psychiatry. 2014; 53(12): 1279-1287.
Neurodevelopmental theories of psychosis highlight the potential benefits of early intervention, prevention, and/or preemption. How early intervention should take place has not been established, nor whether interventions based on social learning principles can have preemptive effects. The objective was to test whether a comprehensive psychosocial intervention can significantly alter psychotic symptom trajectories during adolescence-a period of heightened risk for a wide range of psychopathology. This study was a randomized controlled trial (RCT) of Multidimensional Treatment Foster Care (MTFC) for delinquent adolescent girls. Assessment of psychotic symptoms took place at baseline and then 6, 12, 18, and 24 months post-baseline using a standardized self-report instrument (Brief Symptom Inventory). A second source of information about psychotic symptoms was obtained at baseline or 12 months, and again at 24 months using a structured diagnostic interview (the Diagnostic Interview Schedule for Children [DISC]). Significant benefits for MTFC over treatment as usual for psychosis symptoms were observed over a 24-month period. Findings were replicated across both measures. Effects were independent of substance use and initial symptom severity and persisted beyond the initial intervention period. Ameliorating nonclinical psychotic symptoms trajectories beginning in mid-adolescence via a multifaceted psychosocial intervention is possible. Developmental research on nonclinical psychotic symptoms and their prognostic value should be complemented by more psychosocial intervention research aimed at modifying these symptom trajectories early in their natural history. Clinical trial registration information-Juvenile Justice Girls Randomized Control Trial: Young Adult Follow-up; http://clinicaltrials.gov; NCT01341626.

Long-Term Effects Of Staying Connected With Your Teen ® On Drug Use Frequency At Age 20 Haggerty KP, Skinner ML, Catalano RF, Abbott RD, Crutchfield RD. Prev Sci. 2014.
Drug prevention interventions frequently target early adolescents in order to stop or delay initiation of substance use. However, the prevalence and frequency of drug use escalate and then peak during emerging adulthood, making it important to determine whether drug use prevention efforts in adolescence have lasting effects into adulthood. Additionally, given differences in drug use frequency between ethnic groups, intervention effects by race should be examined when possible. This study evaluates the efficacy of a family-focused prevention program, Staying Connected with Your Teen, delivered to parents and teens in the 8th grade, on family stressors during 9th and 10th grades, 10th-grade drug use (as potential mediators), and drug use frequency at age 20. Families (N=331; Black=163, White=168) were randomly assigned to three conditions: parent-adolescent group-administered (PA), self-administered with telephone support (SA), and no-treatment control (Haggerty et al. Prevention Science, 8: 249-260, 2007). The impact of the intervention was assessed using latent variable structural equation models. Age 20 drug use frequency was significantly higher among Whites than Blacks as expected. The PA intervention had direct effects on reducing drug use frequency for both Blacks and Whites. The SA intervention had an impact on family stressors during adolescence for Whites, but not for Blacks. Results suggest that both formats for delivery were modestly efficacious for Whites, but only direct delivery was modestly efficacious for Blacks. Given the substantial savings in cost of the self-administered program over the group-administered format, improving the efficacy of self-administered programming for Blacks is recommended.

Delinquency and Peer Acceptance In Adolescence: A Within-person Test Of Moffitt's Hypotheses Rulison KL, Kreager DA, Osgood DW. Dev Psychol. 2014; 50(11): 2437-2448.
The authors tested 2 hypotheses derived from Moffitt's (1993) taxonomic theory of antisocial behavior, both of which are central to her explanation for the rise in delinquency during adolescence. They tested whether persistently delinquent individuals become more accepted by their peers during adolescence and whether individuals who abstain from delinquent behavior become less accepted. Participants were 4,359 adolescents from 14 communities in the PROSPER study, which assessed friendship networks and delinquency from 6th (M = 11.8 years) to 9th (M = 15.3 years) grade. The authors operationalized peer acceptance as number of nominations received (in degree centrality), attractiveness as a friend (adjusted in degree centrality), and network bridging potential (betweenness centrality) and tested the hypotheses with multilevel modeling. Contrary to Moffitt's hypothesis, persistently delinquent youths did not become more accepted between early and middle adolescence, and although abstainers were less accepted in early adolescence, they became more accepted over time. Results were similar for boys and girls; when differences occurred, they provided no support for Moffitt's hypotheses for boys and were opposite of her hypotheses for girls. Sensitivity analyses in which alternative strategies and additional data were used to identify persistently delinquent adolescents produced similar results. The authors explore the implications of these results for Moffitt's assertions that social mimicry of persistently antisocial adolescents leads to increases in delinquency and that social isolation leads to abstention.

Probing the Smoking-suicide Association: Do Smoking Policy Interventions Affect Suicide Risk? Grucza RA, Plunk AD, Krauss MJ, Cavazos-Rehg PA, Deak J, Gebhardt K, Chaloupka FJ, Bierut LJ. Nicotine Tob Res. 2014; 16(11): 1487-1494.
Smoker's exhibit elevated risk for suicide, but it is unknown whether smoking interventions reduce suicide risk. The authors examined whether state-level policy interventions-increases in cigarette excise taxes and strengthening of smoke-free air laws-corresponded to a reduction in suicide risk during the 1990s and the early 2000s. They also examined whether the magnitude of such reductions correlated with individuals' predicted probability of smoking, which would be expected if the associations stemmed from changes in smoking behavior. The authors paired individual-level data on suicide deaths from the U.S. Multiple Cause of Death files, years 1990-2004, with living population data from the same period. These were linked with state data on cigarette excise taxes and smoke-free air policies. Utilizing a quasi-experimental analytical approach, the authors estimated the association between changes in policy and suicide risk. To examine whether associations correlated with individuals' probability of smoking, they used external survey data to derive a predicted probability of smoking function from demographic variables, which was then used to stratify the population by predicted smoking prevalence. Cigarette excise taxes, smoke-free air policies, and an index combining the two policies all exhibited protective associations with suicide. The associations were strongest in segments of the population where predicted smoking prevalence was the highest and weaker in segments of the population where predicted smoking prevalence was the lowest, suggesting that the protective associations were related to changes in smoking behavior. These results provide support for the proposition that population interventions for smoking could reduce risk for suicide.

Banning Cigarette Smoking On US Navy Submarines: A Case Study Lando HA, Michaud ME, Poston WSC; Jahnke SA, Williams L, Haddock CK. Tob Control. 2014.
The military has had a long pro-tobacco tradition. Despite official policy discouraging smoking, tobacco still is widely seen as part of military culture. While active smoking has presented a particular challenge for the military, in recent years there also has been increasing concern with secondhand smoke. This is especially true in closed environments and submarines may be deployed for months at a time. The current case study describes the successful implementation by the Navy of a comprehensive ban on smoking aboard submarines. The authors searched documents on the internet, popular media, military-based news outlets and the scientific literature. They also conducted interviews with Navy officers who were instrumental in policy implementation. Data demonstrating substantial exposure of non-smokers to tobacco smoke aboard submarines had major impact on successful adoption of the policy. A systematic and extended roll out of the ban included establishing a working group, soliciting input and active engagement from submarine personnel, and offering cessation assistance. Support was enlisted from Chief Petty Officers who could have been strongly opposed but who became strong proponents. Fewer problems were encountered than had been expected. In contrast to a previous unsuccessful attempt by a Navy captain to ban smoking on his ship, the ban was adopted without apparent tobacco industry interference. Lessons learned included the importance of strong empirical support, effective framing of the issue, setting a realistic timeline, soliciting support from key personnel and providing appropriate resources. These lessons have implications for those considering further tobacco policy changes in the military and elsewhere.

Replication RCT Of Early Universal Prevention Effects On Young Adult Substance Misuse
Spoth R, Trudeau L, Redmond C, Shin C. J Consult Clin Psychol. 2014; 82(6): 949-963.
For many substances, more frequent and problematic use occurs in young adulthood; these types of use are predicted by the timing of initiation during adolescence. The authors replicated and extended an earlier study examining whether delayed substance initiation during adolescence, resulting from universal preventive interventions implemented in middle school, reduces problematic use in young adulthood. Participants were middle school students from 36 Iowa schools randomly assigned to the Strengthening Families Program: For Parents and Youth 10-14 (Molgaard, Spoth, & Redmond, 2000) plus Life Skills Training (LST; Botvin, 1995, 2000), LST-only, or a control condition. Self-report questionnaires were collected at 11 time points, including 4 during young adulthood. The intercept (average level) and rate of change (slope) in young adult frequency measures (drunkenness, alcohol-related problems, cigarettes, and illicit drugs) across ages 19-22 were modeled as outcomes influenced by growth factors describing substance initiation during adolescence. Analyses entailed testing a 2-step hierarchical latent growth curve model; models included the effects of baseline risk, intervention condition assignment, and their interaction. showed significant indirect intervention effects on the average levels of all young adult outcomes, through effects on adolescent substance initiation growth factors, along with Intervention x Risk interaction effects favoring the higher risk subsample. Additional direct effects on young adult use were observed in some cases. Relative reduction rates were larger for the higher risk subsample at age 22, ranging from 5.8% to 36.4% on outcomes showing significant intervention effects. Universal preventive interventions implemented during early adolescence have the potential to decrease the rates of substance use and associated problems into young adulthood.

Group Motivational Interviewing For Adolescents: Change Talk and Alcohol and Marijuana Outcomes D'Amico EJ, Houck JM, Hunter SB, Miles JNV, Osilla KC, Ewing BA. J Consult Clin Psychol. 2015 Feb; 83(1): 68-80.
Little is known about what may distinguish effective and ineffective group interventions. Group motivational interviewing (MI) is a promising intervention for adolescent alcohol and other drug use; however, the mechanisms of change for group MI are unknown. One potential mechanism is change talk, which is client speech arguing for change. The present study describes the group process in adolescent group MI and effects of group-level change talk on individual alcohol and marijuana outcomes. The authors analyzed 129 group session audio recordings from a randomized clinical trial of adolescent group MI. Sequential coding was performed with the Motivational Interviewing Skill Code (MISC) and the CASAA Application for Coding Treatment Interactions software application. Outcomes included past-month intentions, frequency, and consequences of alcohol and marijuana use; motivation to change; and positive expectancies. Sequential analysis indicated that facilitator open-ended questions and reflections of change talk increased group change talk. Group change talk was then followed by more change talk. Multilevel models accounting for rolling group enrollment revealed group change talk was associated with decreased alcohol intentions, alcohol use, and heavy drinking 3 months later; group sustain talk was associated with decreased motivation to change, increased intentions to use marijuana, and increased positive alcohol and marijuana expectancies. Facilitator speech and peer responses each had effects on change and sustain talk in the group setting, which were then associated with individual changes. Selective reflection of change talk in adolescent group MI is suggested as a strategy to manage group dynamics and increase behavioral change.

Effects Of the Communities That Care Prevention System On Youth Reports Of Protective Factors Kim BKE, Gloppen KM, Rhew IC, Oesterle S, Hawkins JD. Prev Sci. 2014.
Many interventions seeking to reduce problem behaviors and promote healthy youth development target both risk and protective factors, yet few studies have examined the effect of preventive interventions on overall levels of protection community wide. In a community-randomized controlled trial, this study tested the effect of Communities That Care (CTC) on protective factors in 24 communities across seven states. Data on protective factors were collected from a panel of 4407 youths in CTC and control communities followed from grade 5 through grade 8. Hierarchical linear modeling compared mean levels of 15 protective factors derived from the social development model in CTC and control communities in grade 8, adjusted for individual and community characteristics and baseline levels of protective factors in grade 5. Global test statistics were calculated to examine effects on protection overall and by domain. Analyses across all protective factors found significantly higher levels of overall protection in CTC compared to control communities. Analyses by domain found significantly higher levels of protection in CTC than control communities in the community, school, and peer/individual domains, but not in the family domain. Significantly higher levels of opportunities for prosocial involvement in the community, recognition for prosocial involvement in school, interaction with prosocial peers, and social skills among CTC compared to control youth contributed to the overall and domain-specific results. This is consistent with CTC's theory of change, which posits that strengthening protective factors is a mechanism through which CTC prevents behavior problems.

Nonsupportive Parenting Affects Telomere Length In Young Adulthood Among African Americans: Mediation Through Substance Use Beach SRH, Lei MK, Brody GH, Yu T, Philibert RA. J Fam Psychol. 2014; 28(6): 967-972.
Telomere length (TL) is an indicator of age-related changes at the cellular level associated with heightened mortality risk. The effect of nonsupportive parenting (NSP) during late adolescence and young adulthood on TL 5 years later was examined in a sample of N = 183 young adult African Americans to determine if effects of NSP on TL were mediated by substance use. Results indicated that the effect of caregiver reported NSP on diminished TL was mediated by escalation of drinking and smoking in young adulthood, even after controlling effects of socioeconomic status risk, gender, BMI, young adult stress, and intervention status. Results suggest that prevention of NSP may influence later physical health consequences by influencing substance use trajectory.

Neighborhood Poverty and Allostatic Load In African American Youth Brody GH, Lei M-K, Chen E, Miller GE. Pediatrics. 2014; 134(5): e1362-1368.
This study was designed to determine whether living in a neighborhood in which poverty levels increase across adolescence is associated with heightened levels of allostatic load (AL), a biological composite reflecting cardio metabolic risk. The researchers also sought to determine whether receipt of emotional support could ameliorate the effects of increases in neighborhood poverty on AL. Neighborhood concentrations of poverty were obtained from the Census Bureau for 420 African American youth living in rural Georgia when they were 11 and 19 years of age. AL was measured at age 19 by using established protocols for children and adolescents. When youth were 18, caregivers reported parental emotional support and youth assessed receipt of peer and mentor emotional support. Covariates included family poverty status at ages 11 and 19, family financial stress, parental employment status, youth stress, and youths' unhealthful behaviors. Youth who lived in neighborhoods in which poverty levels increased from ages 11 to 19 evinced the highest levels of AL even after accounting for the individual-level covariates. The association of increasing neighborhood poverty across adolescence with AL was not significant for youth who received high emotional support. This study is the first to show an association between AL and residence in a neighborhood that increases in poverty. It also highlights the benefits of supportive relationships in ameliorating this association.

Adapting An Evidence-based Intervention For Homeless Women: Engaging The Community In Shared Decision-making Cederbaum JA, Song A, Hsu H-T, Tucker JS, Wenzel SL. J Health Care Poor Underserved. 2014; 25(4): 1552-1570.
As interest grows in the diffusion of evidence-based interventions (EBIs), there is increasing concern about how to mitigate implementation challenges; this paper concerns adapting an EBI for homeless women. Complementing earlier focus groups with homeless women, homeless service providers (n = 32) were engaged in focus groups to assess capacity, needs, and barriers with implementation of EBIs. Deductive analyses of data led to the selection of four EBIs. Six consensus groups were then undertaken; three each with homeless women (n = 24) and homeless service providers (n = 21). The selected EBI was adapted and pretested with homeless women (n = 9) and service providers (n = 6). The structured consensus group process provided great utility and affirmed the expertise of homeless women and service providers as experts in their domain. Engaging providers in the selection process reduced the structural barriers within agencies as obstacles to diffusion.

A Multi-level Examination Of How the Organizational Context Relates To Readiness To Implement Prevention and Evidence-based Programming In Community Settings Chilenski SM, Olson JR, Schulte JA, Perkins DF, Spoth R. Eval Program Plann. 2015; 48: 63-74.
Prior theoretical and empirical research suggests that multiple aspects of an organization's context are likely related to a number of factors, from their interest and ability to adopt new programming, to client outcomes. A limited amount of the prior research has taken a more community-wide perspective by examining factors that associate with community readiness for change, leaving how these findings generalize to community organizations that conduct prevention or positive youth development programs unknown. Thus for the current study, the authors examined how the organizational context of the Cooperative Extension System (CES) associates with current attitudes and practices regarding prevention and evidence-based programming. Attitudes and practices have been found in the empirical literature to be key indicators of an organization's readiness to adopt prevention and evidence-based programming. Based on multi-level mixed models, results indicate that organizational management practices distinct from program delivery may affect an organization's readiness to adopt and implement new prevention and evidence-based youth programs, thereby limiting the potential public health impact of evidence-based programs. Openness to change, openness of leadership, and communication were the strongest predictors identified within this study. An organization's morale was also found to be a strong predictor of an organization's readiness. The findings of the current study are discussed in terms of implications for prevention and intervention.

Effects Of A Youth Substance Use Prevention Program On Stealing, Fighting, And Weapon Use Nieri T, Apkarian J, Kulis S, Marsiglia FF. J Prim Prev. 2015; 36(1): 41-49.
Using a sample of sixth graders in 11 public schools in a large Southwestern city, this longitudinal study examined how a model substance use prevention program, keeping' it REAL, that was implemented in 7th grade, influenced three other problem behaviors (fighting, weapon use, stealing), measured in 8th grade. Using a non-equivalent control group design, the authors compared 259 students in the intervention to 322 students in a treatment-as-usual condition. At baseline, 37% of the sample reported fighting in the last 30 days; 31% reported stealing in the last 30 days, and 16% reported using a weapon in the last 30 days. Regression analyses adjusted for students nested in schools through multi-level modeling and for missing data through multiple imputation. The authors found that at posttest the rates of all three behaviors were lower in the intervention group than the control group at posttest: 35 versus 37% got into a fight in the last 30 days; 24 versus 31% stole something in the last 30 days; and 16 versus 25% used a weapon in the last 30 days. The program impact for fighting and stealing was not statistically significant and involved minimal effect sizes. The program impact for weapon use was not statistically significant but had an effect size comparable to that for other problem behavior interventions. Promoting positive development via life skills may be a key to broadening program impact.

Delinquency In Adolescent Girls: Using A Confluence Approach To Understand The Influences Of Parents and Peers Henneberger AK, Tolan PH, Hipwell AE, Keenan K. Crim Justice Behav. 2014; 41(11): 1327-1337.
Determining the interdependence of family and peer influences on the development of delinquency is critical to defining and implementing effective interventions. This study explored the longitudinal relationship among harsh punishment, positive parenting, peer delinquency, and adolescent delinquency using data from a sub-sample of the Pittsburgh Girls Study. Participants were 622

adolescent girls (42% European American, 53% African American); families living in low-income neighborhoods were oversampled. After controlling for the effects of race, living in a single parent household, and receipt of public assistance, harsh punishment and peer delinquency in early adolescence were positively related to delinquency in mid-adolescence. No significant main effects of positive parenting or interaction effects between parenting and peer delinquency were observed. Thus, the effects of harsh parenting and peer delinquency are independent and perhaps additive, rather than interdependent. Results indicate the continued importance of targeting both parenting and peer relationships to prevent delinquency in adolescent girls.

Change In Participant Engagement During A Family-based Preventive Intervention: Ups and Downs With Time and Tension Bamberger KT, Coatsworth JD, Fosco GM, Ram N. J Fam Psychol. 2014; 28(6): 811-820.
The efficacy of preventive interventions is related to both the delivery of content and the uptake of that content. Although much research has focused on the quality of delivery, few studies have examined the factors that influence uptake. This study examines how and why participants' engagement-conceptualized as a dynamic process wherein participants interact with each other, the interventionists, and the intervention curriculum-changes over time. The authors apply growth curve models to repeated measures of engagement obtained from 252 families during a 7-week intervention trial. In the models, they examine (a) whether and how engagement changes over time, and the extent of between-person differences in change; and (b) how those changes and differences are related to chronic and session-specific aspects of family tension, while also controlling for differences across parent sex and 2 versions of the Strengthening Families Program: For Parents and Youth Ages 10-14 (SFP 10-14). Results show that, on average, engagement increased over time, linearly with some deceleration, with substantial differences in both level and rates of change. Higher in-session chronic family tension was related to lower initial levels of engagement but not rates of change. Sessions when families displayed more session-specific tension were characterized by different levels of engagement for parents, depending on their level of chronic tension. Overall, these results highlight the importance of considering engagement as a dynamic construct that changes over time in complex ways. Further understanding of the many factors that influence engagement can promote both better delivery and better uptake of intervention curriculum.

Bidirectional Associations Between Parental Warmth, Callous Unemotional Behavior, and Behavior Problems In High-risk Preschoolers Waller R, Gardner F, Viding E, Shaw DS, Dishion TJ, Wilson MN, Hyde LW. J Abnorm Child Psychol. 2014; 42(8): 1275-1285.
Research suggests that parental warmth and positive parent-child interactions predict the development of conscience and empathy. Recent studies suggest that affective dimensions of parenting, including parental warmth, are associated with fewer behavior problems among children with high levels of callous-unemotional (CU) behavior. Evidence also suggests that CU behavior confers risk for behavior problems by uniquely shaping parenting. The current study examines reciprocal associations between parental warmth, CU behavior, and behavior problems among toddlers. Data from mother-child dyads (N=731; 49% female) were collected from a multi-ethnic, high-risk sample at ages 2 and 3. CU behavior was assessed using a previously validated measure (Hyde et al. 2013). Models were tested using two measures of parental warmth, the first from direct observations of warmth in the home, the second coded from 5-min speech samples. Three-way cross-lagged, simultaneous effects models showed that parental warmth predicted child CU behavior, over and above associations with behavior problems. There were cross-lagged

associations between directly observed parental warmth and child CU behavior, suggesting these behaviors show some malleability during toddlerhood and that parenting appears to reflect some adaptation to child behavior. The results have implications for models of early-starting behavior problems and preventative interventions for young children.

Do Specific Transitional Patterns Of Antisocial Behavior During Adolescence Increase Risk For Problems In Young Adulthood? Cook EC, Pflieger JC, Connell AM, Connell CM. J Abnorm Child Psychol. 2015; 43(1): 95-106.
Latent transition analysis was used to identify patterns and trajectories of antisocial behavior (ASB) and their association with young adult outcomes in a nationally representative sample of adolescents (N=5,422; 53.9% female). Participants were on average 13.96 years of age (SD=1.06) at wave 1 of the study. Latent class analysis identified four classes of ASB including a non-ASB class, an aggressive class, a petty theft class, and a serious ASB class. In general, youth who were classified as serious stable ASB were the most at risk for problematic functioning in young adulthood. Youth who escalated to more serious patterns of ASB or reduced involvement also were at greater risk of negative outcomes in young adulthood compared to stable non-ASB youth, although they generally fared better than youth involved in stable patterns of more serious ASB. Gender differences indicated that involvement in ASB was a greater risk factor for alcohol use among boys and a greater risk factor for depression among girls in young adulthood. Results are discussed in terms of the predictive validity of classes of ASB to functioning in young adulthood and the implications of this research for prevention efforts

Context-dependent Pathways Of the Transmission Of Risk From Communities To Individuals Lamont AE, Van Horn ML, Hawkins JD. Am J Community Psychol. 2014; 54(3-4): 384-396.
Research has consistently documented the role of environmental risk factors in the onset of delinquent behavior among youth. Less is known about the processes through which these contextual risks are translated to individual youth behavior. The aim of the current study is to examine the role of family risk factors in the transmission of community risk. Data was obtained from a nationally representative sample of over 30,000 middle school youth and community key informants (CKI). A multilevel, moderated mediation model was estimated with family risk as the moderator of the effect of CKI ratings of community risk on youth perceptions of risk. Results showed that when youth came from low risk families (measured by parental use of positive family management strategies), youth perceptions of risk mediated the effects of community risk on youth delinquency; however, there was no evidence of a significant mediated effect under conditions of high risk (measured by poor family management). This appears to be because youth from high-risk families perceived their neighborhoods as high-risk, regardless of actual levels of risk (as reported by CKI). This study finds that the relationship between communities and adolescent behavior is complex and interacts with the family environment.

Longitudinal Family Effects On Substance Use Among An At-risk Adolescent Sample Ewing BA, Osilla KC, Pedersen ER, Hunter SB, Miles JNV, D'Amico E J. Addict Behav. 2015; 41: 185-191.
Adult and peer factors may influence whether adolescents use alcohol and other drugs (AOD). This longitudinal study examined the direct effects of adult monitoring, perceived adult AOD use, and cultural values on adolescent AOD use. Participants were 193 at-risk adolescents referred to a California diversion program called Teen Court for a first-time AOD offense. The authors assessed

youth reports of past 30day AOD use (any alcohol use, heavy drinking, marijuana use), demographics, changes in parental monitoring and family values (from baseline to follow-up 180days later), as well as family structure and perceived adult substance use at follow-up. Adolescents who reported that a significant adult in their life used marijuana were more likely to have increased days of drinking, heavy drinking, and marijuana use at follow-up. Higher levels of families (importance the teen places on their family's needs over their own needs) and being in a nuclear family served as protective factors for future alcohol use. Additionally, poor family management was associated with increased alcohol use and heavy drinking. Findings highlight how family management and perceptions of adult marijuana use influence subsequent adolescent AOD use, and how an increase in families over time is associated with a decrease in adolescent drinking. Tailoring interventions, by including the teens' family and/or providing support to adults who use AOD may be crucial for improving interventions for adolescent AOD use.

Unpacking The Effect Of Parental Monitoring On Early Adolescent Problem Behavior: Mediation By Parental Knowledge And Moderation By Parent-Youth Warmth Lippold MA, Greenberg MT, Graham JW, Feinberg ME. J Fam Issues. 2014; 35(13): 1800-1823.
This study explores the monitoring process longitudinally among a sample of rural early adolescents and addresses two research questions (1) Does maternal knowledge mediate the relationship between three aspects of the parental monitoring process and adolescent problem behavior: active parent monitoring efforts, youth disclosure, and parental supervision? (2) Are these meditational pathways moderated by the affective quality of the parent-child relationship? Parent efforts to monitor youth and youth disclosure in the Fall of Grade 6 predicted substance use and delinquency in Grade 8. These relations were mediated by increases in maternal knowledge assessed in the Spring of Grade 6, suggesting that the protective effects of these constructs are partially indirect. Supervision was not significantly related to maternal knowledge or problem behavior. Parent efforts to monitor were more strongly related to maternal knowledge in families with high levels of positive affect than in families with low levels of positive affect.

Suicidal Behavior Outcomes Of Childhood Sexual Abuse: Longitudinal Study Of Adjudicated Girls Rabinovitch SM, Kerr DCR, Leve LD, Chamberlain P. Suicide Life Threat Behav. 2014.
Childhood sexual abuse (CSA) histories are prevalent among adolescent girls in the juvenile justice system (JJS) and may contribute to their high rates of suicidal behavior. Among 166 JJS girls who participated in an intervention trial, baseline CSA and covariates were examined as predictors of suicide attempt and nonsuicidal self-injury (NSSI) reported at long-term follow-up (7-12 years later). Early forced CSA was related to lifetime suicide attempt and NSSI history and (marginally) to post baseline attempt; effects were not mediated by anxiety or depressive symptoms. Findings suggest that earlier victimization and younger entry into JJS are linked with suicide attempt and NSSI.

Alcohol, Tobacco, and Other Drug Misuse Prevention and Cessation Programming For Alternative High School Youth: A Review Sussman S, Arriaza B, Grigsby TJ. J Sch Health. 2014; 84(11): 748-758.
Relative to youth in regular high schools, alternative high school (AHS) youth are at high risk for alcohol, tobacco, and other drug (ATOD) misuse. Prevention and cessation efforts are needed for this population. A systematic, exhaustive literature search was completed to identify ATOD misuse prevention and cessation research studies with AHS youth. For the AHS population, 23 ATOD

misuse prevention or cessation program evaluations were located. This review indicated that successful efforts have focused on instruction in motivation enhancement, life coping skills, and decision making. Alcohol, tobacco, and other drug misuse prevention and cessation programming for AHSs is effective, delivered in the classroom or as a school-based clinic. There is little evidence, though, that this programming is effective when delivered through other modalities such as via computer or bridging beyond the school setting. More research and application of evidence-based programming are recommended for youth in AHS settings.

How Group Factors Affect Adolescent Change Talk and Substance Use Outcomes: Implications For Motivational Interviewing Training Osilla KC, Ortiz JA, Miles JNV, Pedersen ER, Houck JM, D'Amico Elizabeth J. J Couns Psychol. 2015; 62(1): 79-86.
Clients who verbalize statements arguing for change (change talk [CT]) in psychotherapy are more likely to decrease alcohol and other drug use (AOD) compared with clients who voice statements in opposition of change (sustain talk [ST]). Little is known about how CT and ST are expressed in groups in which adolescents may vary in their AOD use severity and readiness to change. First, the authors examined how session content was associated with CT/ST, and then we looked at whether different subtypes of CT/ST were associated with subsequent AOD outcomes 3 months later. Audio recordings (N = 129 sessions) of a 6-session group motivational interviewing (MI) intervention, Free Talk, were coded. Session content was not associated with CT; however, some session content was associated with higher percentages of ST (e.g., normative feedback). Subtypes of CT (Commitment and Reason) were associated with improved AOD outcomes, whereas Ability subtype remarks were related to increased marijuana use, intentions, and consequences. Findings offer helpful guidance for clinical training and narrow in on the type of CT to try to elicit in Group MI sessions. Regardless of session content, adolescents can benefit from hearing CT during the group.

Impulsivity and the Association Between the Feedback-related Negativity and Performance On An Inhibitory Control Task In Young At-risk Children Roos LE, Pears K, Bruce J, Kim HK, Fisher PA. Psychophysiology. 2014.
Identifying neurocognitive processes associated with effective inhibitory control is particularly relevant for individuals at high risk for disruptive behaviors, such as maltreated children. Performance feedback processing during a flanker task was investigated in maltreated preschool-aged children (N=67) via an event-related potential component, the feedback-related negativity (FRN). The functionality of the FRN in children with high impulsivity was of interest, as impulsivity was associated with an exaggerated FRN in previous research. Results showed that high impulsivity was associated with an exaggerated FRN and greater post-error slowing. For children with high impulsivity, there was a correlation between the FRN and accuracy, which was not found in children with low impulsivity. This suggests that an exaggerated FRN is particularly important for children with high impulsivity to maintain effective inhibitory control.

Learning To Play It Safe (or Not): Stable and Evolving Neural Responses During Adolescent Risky Decision-making Kahn LE, Peake SJ, Dishion TJ, Stormshak EA, Pfeifer JH. J Cogn Neurosci. 2015; 27(1): 13-25.
Adolescent decision-making is a topic of great public and scientific interest. However, much of the neuroimaging research in this area contrasts only one facet of decision-making (e.g., neural responses to anticipation or receipt of monetary rewards). Few studies have directly examined the

processes that occur immediately before making a decision between two options that have varied and unpredictable potential rewards and penalties. Understanding adolescent decision-making from this vantage point may prove critical to ameliorating risky behavior and improving developmental outcomes. In this study, participants aged 14-16 years engaged in a driving simulation game while undergoing fMRI. Results indicated activity in ventral striatum preceded risky decisions and activity in right inferior frontal gyrus (rIFG) preceded safe decisions. Furthermore, participants who reported higher sensation-seeking and sensitivity to reward and punishment demonstrated lower rIFG activity during safe decisions. Finally, over successive games, rIFG activity preceding risky decisions decreased, whereas thalamus and caudate activity increased during positive feedback (taking a risk without crashing). These results indicate that regions traditionally associated with reward processing and inhibition not only drive risky decision-making in the moment but also contribute to learning about risk tradeoffs during adolescence.

The Effect Of Neighborhood Disadvantage, Social Ties, and Genetic Variation On the Antisocial Behavior Of African American Women: A Multilevel Analysis Lei M-K, Simons RL, Edmond MBond, Simons LG, Cutrona CE. Dev Psychopathol. 2014; 26(4 Pt 1): 1113-1128.
Social disorganization theory posits that individuals who live in disadvantaged neighborhoods are more likely to engage in antisocial behavior than are those who live in advantaged neighborhoods and that neighborhood disadvantage asserts this effect through its disruptive impact on social ties. Past research on this framework has been limited in two respects. First, most studies have concentrated on adolescent males. In contrast, the present study focused on a sample of adult African American females. Second, past research has largely ignored individual-level factors that might explain why people who grow up in disadvantaged neighborhoods often do not engage in antisocial behavior. The authors investigated the extent to which genetic variation contributes to heterogeneity of response to neighborhood conditions. They found that the impact of neighborhood disadvantage on antisocial behavior was mediated by neighborhood social ties. Further, the analysis indicated that the effects of neighborhood disadvantage and social ties on antisocial behavior were moderated by genetic polymorphisms. Examination of these moderating effects provided support for the differential susceptibility model of Gene x Environment. The effect of Gene x Neighborhood Disadvantage on antisocial behavior was mediated by the effect of Gene x Neighborhood Social Ties, providing support for an expanded view of social disorganization theory.

Genetic Basis Of Delay Discounting In Frequent Gamblers: Examination Of A Priori Candidates And Exploration Of A Panel Of Dopamine-related Loci Gray JC, MacKillop J. Brain Behav. 2014; 4(6): 812-821.
Delay discounting is a behavioral economic index of impulsivity that reflects preferences for small immediate rewards relative to larger delayed rewards. It has been consistently linked to pathological gambling and other forms of addictive behavior, and has been proposed to be a behavioral characteristic that may link genetic variation and risk of developing addictive disorders (i.e., an endophenotype). Studies to date have revealed significant associations with polymorphisms associated with dopamine neurotransmission. The current study examined associations between delay discounting and both previously linked variants and a novel panel of dopamine-related variants in a sample of frequent gamblers. Participants were 175 weekly gamblers of European ancestry who completed the Monetary Choice Questionnaire to assess delay discounting preferences and provided a DNA via saliva. In a priori tests, two loci previously associated with delayed reward discounting (rs1800497 and rs4680) were not replicated, however, the long form of DRD4 VNTR

was significantly associated with lower discounting of delayed rewards. Exploratory analysis of the dopamine-related panel revealed 11 additional significant associations in genes associated with dopamine synthesis, breakdown, reuptake, and receptor function (DRD3, SLC6A3, DDC, DBH, and SLC18A2). An aggregate genetic risk score from the nominally significant loci accounted for 17% of the variance in discounting. Mediational analyses largely supported the presence of indirect effects between the associated loci, delay discounting, and pathological gambling severity. These findings do not replicate previously reported associations but identify several novel candidates and provide preliminary support for a systems biology approach to understand the genetic basis of delay discounting.

Socioeconomic-related Risk and Sexually Transmitted Infection Among African-American Adolescent Females Sales JM, Smearman EL, Swartzendruber A, Brown JL, Brody G, DiClemente RJ. J Adolesc Health. 2014; 55(5): 698-704.
Virtually no studies have examined the potential role that chronic stress, particularly the stress associated with socioeconomic status (SES) strain, may play on sexually transmitted infection (STI) risk. This study examined the association between SES-related risk at baseline to STI acquisition and reinfection over 36 months of follow-up. Six hundred twenty-seven African-American female adolescents, ages 14-20 years, recruited from sexual health clinics in Atlanta, GA, participated in a randomized controlled HIV prevention trial and returned for at least one follow-up assessment. Following baseline assessment, six waves of data collection occurred prospectively over 36 months. Chronic SES-related risk was assessed as a sum of yes-no exposure to seven risk indicators. Laboratory-confirmed tests for Chlamydia trachomatis and Neisseria gonorrhoeae were performed at each follow-up. In multivariable regression analysis, SES-related risk significantly predicted STI acquisition over 36 months (adjusted odds ratio= 1.22) and STI reinfection (adjusted odds ratio= 1.16) above and beyond other known correlates of STI. Findings demonstrate that SES-related risk was predictive of both STI acquisition and reinfection among young African-American females. They are consistent with propositions that some health disparities observed in adulthood may be linked to earlier chronically stress-inducing life experiences, particularly experiences associated with low SES conditions. Although various explanations exist for the observed connection between SES-related risk and subsequent STI acquisition and/or reinfection across 36 months of follow-up, these findings highlight the need for further research to elucidate the exact pathway(s) by which SES-related risk influences later STI acquisition to refine STI prevention interventions for this population.

Maternal Abuse History and Self-regulation Difficulties In Preadolescence Delker BC, Noll LK, Kim HK, Fisher PA. Child Abuse Negl. 2014; 38(12): 2033-2043.
Although poor parenting is known to be closely linked to self-regulation difficulties in early childhood, comparatively little is understood about the role of other risk factors in the early caregiving environment (such as a parent's own experiences of childhood abuse) in developmental pathways of self-regulation into adolescence. Using a longitudinal design, this study aimed to examine how a mother's history of abuse in childhood relates to her offspring's self-regulation difficulties in preadolescence. Maternal controlling parenting and exposure to intimate partner aggression in the child's first 24-36 months were examined as important early social and environmental influences that may explain the proposed connection between maternal abuse history and preadolescent self-regulation. An ethnically diverse sample of mothers (N=488) who were identified as at-risk for child maltreatment was recruited at the time of their children's birth.

Mothers and their children were assessed annually from the child's birth through 36 months, and at age 9-11 years. Structural equation modeling and bootstrap tests of indirect effects were conducted to address the study aims. Findings indicated that maternal abuse history indirectly predicted their children's self-regulation difficulties in preadolescence mainly through maternal controlling parenting in early childhood, but not through maternal exposure to aggression by an intimate partner. Maternal history of childhood abuse and maternal controlling parenting in her child's early life may have long-term developmental implications for child self-regulation.

Psychological Intimate Partner Violence and Sexual Risk Behavior: Examining the Role Of Distinct Posttraumatic Stress Disorder Symptoms In the Partner Violence-sexual Risk Link
Overstreet NM, Willie TC, Hellmuth JC, Sullivan TP. Women's Health Issues. 2015; 25(1): 73-78.
Research has examined how physical and sexual intimate partner violence (IPV) victimization increases sexual risk behavior, yet research is lacking on 1) the effect of psychological IPV on sexual risk behavior and 2) factors through which psychological IPV may be linked to sexual risk behavior. The current study examined the relationship between psychological IPV and sexual risk behavior controlling for other forms of IPV (i.e., physical and sexual) in a sample of 186 human immunodeficiency virus (HIV)-negative community women currently experiencing IPV. Further, this study examined the potential mediating effects of four posttraumatic stress disorder (PTSD) symptom severity clusters (i.e., re-experiencing, avoidance, numbing, and hyper arousal) on this relationship. Results revealed that greater severity of psychological IPV was uniquely and directly related to greater sexual risk behavior. Additionally, of the four PTSD symptom severity clusters, only avoidance symptom severity mediated the relationship between psychological IPV and sexual risk behavior. Implications for addressing psychological IPV and PTSD to improve women's sexual health outcomes are discussed.

Associations Between Trajectories Of Perceived Racial Discrimination And Psychological Symptoms Among African American Adolescents Smith-Bynum MA, Lambert SF, English D, Ialongo NS. Dev Psychopathol. 2014; 26(4 Pt 1): 1049-1065.
Many African American adolescents experience racial discrimination, with adverse consequences; however, stability and change in these experiences over time have not been examined. The authors examined longitudinal patterns of perceived racial discrimination assessed in Grades 7-10 and how these discrimination trajectories related to patterns of change in depressive and anxious symptoms and aggressive behaviors assessed over the same 4-year period. Growth mixture modeling performed on a community epidemiologically defined sample of urban African American adolescents (n = 504) revealed three trajectories of discrimination: increasing, decreasing, and stable low. As predicted, African American boys were more frequent targets for racial discrimination as they aged, and they were more likely to be in the increasing group. The results of parallel process growth mixture modeling revealed that youth in the increasing racial discrimination group were four times more likely to be in an increasing depression trajectory than were youth in the low stable discrimination trajectory. Though youth in the increasing racial discrimination group were nearly twice as likely to be in the high aggression trajectory, results were not statistically significant. These results indicate an association between variation in the growth of perceived racial discrimination and youth behavior and psychological well-being over the adolescent years.

A Story Mapping Intervention To Improve Narrative Comprehension Deficits In Adolescents With ADHD Derefinko KJ, Hayden A, Sibley MH, Duvall J, Milich R, Lorch EP. School Ment Health. 2014; 6(4): 251-263.
The current study examined the effects of an 8-week Story Mapping Intervention (SMI) to improve narrative comprehension in adolescents with ADHD. Thirty 12 - 16 year-old adolescents with ADHD who were participating in a summer treatment program for adolescents with ADHD received the SMI instruction ten times and completed SMI homework ten times in a structured environment with teacher feedback. Recall of fables and story creation were assessed before and after the SMI. At post-test, fable recalls included more of the most important events, were more coherent, and included a greater number of plausible inferences than pre-test fable recalls. SMI homework scores accounted for increases in recall of important events and plausible inferences, suggesting that consistent practice and feedback with story mapping could contribute to important recall gains. In contrast, the inclusion of goal-based events and the rated coherence of created stories did not improve, suggesting that more explicit instruction in applying story mapping to story creation may be required.

The Moderating Effect Of Women's Alcohol Misuse On the Relationship Between Intimate Partner Violence Victimization and Postpartum Depression Hellmuth JC, Gordon KC, Moore TM, Stuart GL. Am J Addict. 2014; 23(6): 613-615.
The authors examined the moderating effect of women's alcohol misuse on the relationship between intimate partner violence (IPV) victimization and postpartum depression. Self-report data were collected from 122 women. Analyses controlled for women's baseline depression severity and partner alcohol misuse. Women's alcohol misuse moderated the relationship between psychological IPV victimization and postpartum depression only at high levels of the moderator. Findings highlight the mental health risk posed by the combination of psychological IPV and alcohol misuse postpartum. emphasize the need to investigate the understudied topic of women's postpartum alcohol misuse.

Cascading Effects Of Interparental Conflict In Adolescence: Linking Threat Appraisals, Self-efficacy, and Adjustment Fosco GM, Feinberg ME. Dev Psychopathol. 2015; 27(1): 239-252.
This study examined the longitudinal implications of adolescents' exposure to interparental conflict for their developmental success. In the proposed developmental cascade model, adolescents' perceptions of parental conflict as threatening is a risk factor for diminished self-efficacy, which would account for diminished adjustment. This study presents longitudinal data for 768 sixth-grade students and their families over four time points, ending in eighth grade. Analyses were conducted in three steps. First, replication of longitudinal support for threat as a mediator of the link between interparental conflict and emotional distress was found; however, findings did not support threat as a mediator of behavior problems or subjective well-being. Second, threat was found to mediate the longitudinal association between interparental conflict and self-efficacy. Third, a developmental cascade model supported a risk process in which interparental conflict was related to adolescents' threat appraisals, which undermined self-efficacy beliefs, and was then linked with emotional distress, behavior problems, and subjective well-being.

Intimate Partner Violence, Power, and Equity Among Adolescent Parents: Relation To Child Outcomes and Parenting Gibson C, Callands TA, Magriples U, Divney A, Kershaw T. Matern Child Health J. 2015; 19(1): 188-195.
Intimate partner violence (IPV) victimization and perpetration and power imbalances in parenting partners may result in poor outcomes for parents and children. Previous work in this area has focused on the maternal experiences, neglecting to examine paternal effects. The present study aimed to elucidate the role of IPV, power, and equity in parenting and child outcomes in an urban sample of adolescent parents. 159 male and 182 female parents in a relationship were recruited through university-affiliated hospitals. Power, equity, and IPV were measured at 6 months post-partum and were used as predictors for parenting and child outcomes 12 months post-partum using general estimating equations. Gender interactions and mediation effects of depression were also assessed. Higher perceived relationship equity was related to better infant temperament (B = 0.052, SE = 0.023, p = 0.02) whereas higher partner power was related to poorer social development (B = -0.201, SE = 0.088, p = 0.02) and fine motor development (B = -0.195, SE = 0.078, p = 0.01). IPV victimization was associated with poor infant temperament (B = -2.925, SE = 1.083, p = 0.007) and lower parenting competence (B = -3.508, SE = 1.142, p = 0.002). Depression mediated the relationship between IPV and parenting and IPV and infant temperament. No gender effects were found. IPV, inequities, and power imbalances were disadvantageous for parenting and child outcomes. These results suggest that these dynamics may negatively affect both males and females. Interventions to reduce violence in both partners and promote equity in relationships could benefit couples and their children.

Linking Childhood Maltreatment With Girls' Internalizing Symptoms: Early Puberty As A Tipping Point Mendle J, Leve LD, Van Ryzin M, Natsuaki MN. J Res Adolesc. 2014; 24(4): 689-702.
Early pubertal timing in girls is one of the most frequently replicated antecedents of adolescent emotional distress. Yet understanding the impact of pubertal timing in psychosocial development has presented something of a conundrum for develop mentalists, as earlier physical maturation may often be preceded by a range of early adversities and life stressors. The present paper disentangles these associations by investigating childhood maltreatment, adolescent internalizing symptoms, and perceived pubertal timing in girls who were residing in foster care at study entry (N = 100, M = 11.54 years old at Time 1). Girls were assessed at two time points two years apart. There were no significant direct effects of maltreatment on internalizing symptoms; rather, childhood sexual abuse predicted earlier perceived pubertal development at study onset which, in turn, was associated with higher levels of internalizing symptomatology. These higher levels of internalizing symptoms persisted over the two years of the study. This distinctive role for early pubertal timing - even within a sample subject to stressors and risks which far exceed the developmental norm - confirms the unique salience of pubertal timing in emotional adjustment, and suggests that the heightened sexual circumstances of puberty may be especially disturbing for girls whose lives have already been traumatically disrupted by inappropriate and unwanted sexual experiences.

Maternal Caregiving and Girls' Depressive Symptom and Antisocial Behavior Trajectories: An Examination Among High-risk Youth Harold GT, Leve LD, Kim HK, Mahedy L, Gaysina D, Thapar A, Collishaw S. Dev Psychopathol. 2014; 26(4 Pt 2): 1461-1475.
Past research has identified maternal depression and family of origin maltreatment as precursors to adolescent depression and antisocial behavior. Caregiving experiences have been identified as a

factor that may ameliorate or accentuate adolescent psychopathology trajectories. Using a multilevel approach that pools the unique attributes of two geographically diverse, yet complementary, longitudinal research designs, the present study examined the role of maternal caregiver involvement as a factor that promotes resilience-based trajectories related to depressive symptoms and antisocial behaviors among adolescent girls. The first sample comprises a group of US-based adolescent girls in foster care (n = 100; mean age = 11.50 years), each of whom had a history of childhood maltreatment and removal from their biological parent(s). The second sample comprises a group of UK-based adolescent girls at high familial risk for depression (n = 145; mean age = 11.70 years), with all girls having biological mothers who experienced recurrent depression. Analyses examined the role of maternal caregiving on girls' trajectories of depression and antisocial behavior, while controlling for levels of co-occurring psychopathology at each time point. Results suggest increasing levels of depressive symptoms for girls at familial risk for depression but decreasing levels of depression for girls in foster care. Foster girls' antisocial behavior also decreased over time. Maternal caregiver involvement was differentially related to intercept and slope parameters in both samples. Results are discussed with respect to the benefits of applying multilevel (multisample, multiple outcome) approaches to identifying family-level factors that can reduce negative developmental outcomes in high-risk youth.

Popularity As A Predictor Of Early Alcohol Use and Moderator Of Other Risk Processes
Guyll M, Madon S, Spoth R, Lannin DG. J Stud Alcohol Drugs. 2014; 75(6): 919-928.
This study tested the relationship between popularity and early adolescent alcohol use and examined whether popularity moderated the influence of several risk processes. Longitudinal data provided by 1,196 youth (590 girls) were analyzed to assess main and interactive effects of popularity, friends' alcohol use attitudes, own alcohol use attitude, risk taking, and aggressive-disruptive behavior on changes in alcohol use during seventh grade. When the authors controlled for demographic variables and baseline alcohol use, popularity and the other predictors of interest exhibited linear main effects on alcohol use, with popularity and the attitude variables also demonstrating curvilinear relationships. Further analysis indicated that popularity moderated the effect of aggressive-disruptive behavior, the latter being associated with greater alcohol use among more popular adolescents. Additional moderation results revealed that friends' favorable attitudes toward alcohol use also potentiated aggressive-disruptive behaviors' relationship with alcohol use and that male youth were more likely than female youth to use alcohol, but only among low risk takers. Popular youth may attempt to maintain status through early alcohol use, and their social competencies may facilitate risk processes associated with aggressive-disruptive behavior. Findings suggest the utility of providing universal prevention at developmentally crucial times to address substance use overall, and particularly to decrease early use among popular youth, which may serve to slow the growth of substance use in the larger cohort. Although aggressive-disruptive youth who are popular seem to be at particular risk, they may resist traditional interventions, indicating the potential value of less obvious intervention strategies.

Changes In Gender and Racial/ethnic Disparities In Rates Of Cigarette Use, Regular Heavy Episodic Drinking, and Marijuana Use: Ages 14 To 32 Evans-Polce RJ, Vasilenko SA, Lanza ST. Addict Behav. 2015; 41: 218-222.
The purpose of this study is to investigate disparities in substance use behaviors across gender and race/ethnicity as a flexible function of age from mid-adolescence through young adulthood. Using data from the National Longitudinal Study of Adolescent Health, the time-varying effect model

(TVEM) was used to examine gender and racial/ethnic differences in the prevalence of cigarette use, regular heavy episodic drinking (HED), and marijuana use as a smooth function of developmental age. Prevalence of cigarette use, regular HED, and marijuana use was higher for males than females overall, although gender differences varied with age. With regard to race, prevalence of each substance was higher for White than Hispanic or Black individuals; these differences increased considerably from ages 16 to 20, particularly for cigarette use. Differences in cigarette use by race/ethnicity were found across age, but were largest at age 18, when cigarette use peaks for White individuals, but continues to climb throughout the 20s among Hispanic and Black individuals. These results suggest that substance use, particularly for certain population subgroups, increases past early adolescence. Disparities in substance use behaviors fluctuate considerably throughout adolescence and young adulthood, suggesting that targeted intervention programs are more critical at particular ages. These findings also demonstrate that TVEM can advance our understanding of health risk behaviors and their correlates across developmental time.

Adolescent Pathways To Co-Occurring Problem Behavior: The Effects Of Peer Delinquency and Peer Substance Use Monahan KC, Rhew IC, Hawkins JD, Brown EC. J Res Adolesc. 2014; 24(4): 630-645.
Delinquency and substance use are more likely to co-occur in adolescence compared to earlier and later developmental periods. The present study examined developmental pathways to co-occurring problem behavior from 6th-10th grade (N=2,002), testing how peer delinquency and substance use were linked to transitioning between abstaining, delinquency, substance use, and co-occurring problem behavior. Developmentally, most youth transition from abstinence to delinquent behavior, and then escalate to co-occurring problem behavior. Once co-occurring problem behavior onsets, remitting to single problem behavior or abstinence is unlikely. The impact of peers on problem behavior are domain specific when individuals transition from abstaining to a single problem behavior, but are more general with respect to escalation of and desistance from problem behavior.

Family Functioning and High Risk Adolescents' Aggressive Behavior: Examining Effects By Ethnicity Henneberger AK, Varga SM, Moudy A, Tolan PH. J Youth Adolesc. 2014.
The relationship between family functioning and adolescents' physical aggression has been well established, but whether these relationships might differ by ethnicity has received less attention. Ethnic variations may be important for targeting prevention programs to specific youth and families. This study examined the longitudinal relationship between family cohesion, parental monitoring, and physical aggression using data from the Multisite Violence Prevention Project sample of high-risk youth (elevated aggression). Participants were 1,232 high-risk middle school students (65% male; 70% African American; 15% Hispanic). Meaningful demographic variations were identified. After controlling for intervention condition and study site, family cohesion was significantly negatively related to physical aggression, more so for Hispanic youth. Parental monitoring was negatively associated with physical aggression for African American youth only. These findings point to the importance of developing culturally sensitive family interventions to prevent physical aggression in middle school.

The Role Of Feared Possible Selves In the Relationship Between Peer Influence and Delinquency Pierce J, Schmidt C, Stoddard SA. J Adolesc. 2015; 38: 17-26.
This study explores the impact of a feared delinquent possible self on the relationship between exposure to negative peer behaviors and violent and non-violent self-reported delinquency. Previous research strongly supports that deviant peers influence adolescents' delinquent behavior. Yet, few studies have explored intrapersonal factors that may moderate this influence. Possible selves include what one hopes, expects and fears becoming and are believed to motivate behavior. Thus, it was hypothesized that adolescents who were exposed to deviant peers and also feared engaging in delinquency would be more likely to self-report delinquency. Seventh grade students (n=176) identified feared possible selves in the future, their exposure to negative peer behavior and self-reported violent and non-violent delinquent behavior. Findings suggest that exposure to negative peer behavior is associated with self-reported delinquent behavior. For violent behavior, possessing a feared delinquent possible self-moderates this relationship. Implications and suggestions for future research are discussed.

Country, Sex, and Parent Occupational Status: Moderators Of the Continuity Of Aggression From Childhood To Adulthood Kokko K, Simonton S, Dubow E, Lansford JE, Olson SL, Huesmann LR, Boxer P, Pulkkinen L, Bates JE, Dodge KA, Pettit GS. Aggress Behav. 2014; 40(6): 552-567.
Using data from two American and one Finnish long-term longitudinal studies, the authors examined continuity of general aggression from age 8 to physical aggression in early adulthood (age 21-30) and whether continuity of aggression differed by country, sex, and parent occupational status. In all samples, childhood aggression was assessed via peer nominations and early adulthood aggression via self-reports. Multi-group structural equation models revealed significant continuity in aggression in the American samples but not in the Finnish sample. These relations did not differ by sex but did differ by parent occupational status: whereas there was no significant continuity among American children from professional family-of-origin backgrounds, there was significant continuity among American children from non-professional backgrounds.

Alcohol Outlet Density and Related Use In An Urban Black Population In Philadelphia Public Housing Communities Cederbaum JA, Petering R, Hutchinson KM, He AS, Wilson JP, Jemmott Iii, JB, Sweet Jemmot L. Health Place. 2014; 31C: 31-38.
Adolescent alcohol use behaviors are influenced by familial patterns and neighborhood factors. This work explored the influence of individual, family, and environment on alcohol use. Baseline data from a randomized controlled trial with Black mothers son dyads (n=382) were paired with census tract and alcohol control board data. Among mothers, younger age, along with neighborhood factors of alcohol outlet density, race, and education were significantly associated with use. Among sons, older age and alcohol outlet density in the neighborhood predicted use. Findings highlight neighborhood influence, beyond family qualities, as a significant determinant of disadvantaged Black mothers' alcohol use. Implications for public health policy are discussed.

Emergence Of Mixed-sex Friendship Groups During Adolescence: Developmental Associations With Substance Use and Delinquency Molloy LE, Gest SD, Feinberg ME, Osgood DW. Dev Psychol. 2014; 50(11): 2449-2461.
Prospective longitudinal data from over 14,000 youth residing in 28 communities in the rural United States were analyzed to examine the emergence of mixed-sex friendship groups in early

adolescence. Youth were surveyed on 5 occasions between fall of 6th grade and spring of 9th grade. At each assessment, youth reported the names of up to 7 same-grade friends and described patterns of alcohol use, cigarette use, and delinquency. Approximately 800-900 friendship groups (M = 10.5 members) were identified at each assessment and categorized in terms of gender composition (all-girl, mostly-girl, mixed-sex, mostly-boy, all-boy). The proportion of groups categorized as mixed-sex increased with grade level (10% in 6th grade, 22% in 9th grade), but gender-homogenous groups predominated at all grade levels (76% in 6th grade, 51% in 9th grade). Mixed-sex groups were slightly larger than all-girl groups but the same size as all-boy groups. All-girl groups had the highest levels of tight-knittedness (i.e., density, reciprocity, and transitivity), with mixed-sex groups having the lowest levels and all-boy groups having intermediate levels. After controlling for demographic factors, future mixed-sex group membership was predicted by lower popularity, higher levels of delinquency, and lower levels of alcohol use; mixed-sex friendship group membership was associated with increased likelihood of cigarette use. Results are partially consistent with Dunphy's (1969) classic account of the emergence of mixed-sex groups in adolescence, but suggest that in early adolescence, mixed-sex group affiliation is significantly associated with deviant behavior and peripheral social status, not with popularity.

Examining the Link Between Traumatic Events and Delinquency Among Juvenile Delinquent Girls: A Longitudinal Study Marsiglio MC, Chronister KM, Gibson B, Leve LD. J Child Adolesc Trauma. 2014; 7(4): 217-225.
Researchers have postulated associations between childhood trauma and delinquency, but few have examined the direction of these relationships prospectively and, specifically, with samples of delinquent girls. The purpose of this study was to examine the relationship between traumatic events and delinquency for girls in the juvenile justice system using a cross-lagged model. Developmental differences in associations as a function of high school entry status were also examined. The sample included 166 girls in the juvenile justice systems that were mandated to community-based out-of-home care due to chronic delinquency. Overall, study results provide evidence that trauma and delinquency risk pathways vary according to high school entry status. Implications for future research and practice are discussed.

Exposure To Violence, Posttraumatic Stress Symptoms, and Borderline Personality Pathology Among Adolescents In Residential Psychiatric Treatment: The Influence Of Emotion Dysregulation Buckholdt KE, Weiss NH, Young J, Gratz KL. Child Psychiatry Hum Dev. 2014.
Exposure to violence during adolescence is a highly prevalent phenomenon associated with a range of deleterious outcomes. Theoretical literature suggests that emotion dysregulation is one consequence of exposure to violence associated with the manifestation of posttraumatic stress symptoms (PTSS) and borderline personality (BP) pathology. Thus, the goal of the present study was to examine the mediating role of emotion dysregulation in the relation between exposure to violence and both PTSS and BP pathology in a sample of 144 adolescents (age 10- to 17-years; 51% male; 55% African American) admitted to a psychiatric residential treatment center. Exposure to violence was associated with greater emotion dysregulation, which, in turn, was associated with greater PTSS and BP pathology. Furthermore, emotion dysregulation mediated the associations between exposure to violence and both PTSS and BP pathology. Findings suggest the importance of assessing and treating emotion dysregulation among violence-exposed adolescents in psychiatric residential treatment.

Identifying and Intervening With Substance-Using Women Exposed To Intimate Partner Violence: Phenomenology, Comorbidities, and Integrated Approaches Within Primary Care and Other Agency Settings Weaver TL, Gilbert L, El-Bassel N, Resnick HS, Noursi S. J Womens Health (Larchmt); In process - Epub 2015 Jan 2.
Substance use and/or disorders (SUDs) have been identified as a significant correlate of intimate partner violence (IPV) exposure and present complex issues that intersect with the topography of IPV, attendant mental health, and physical co-morbidities and may pose barriers to primary care- and other agency-based screening and intervention efforts. Despite substantial research indicating significantly higher rates of all types and severity of IPV victimization among women with SUDs and bidirectional associations between partner or self-use of drugs or alcohol and IPV victimization, effective screening, brief interventions, coordinated systems of care, and treatment approaches to address these co-occurring problems remain very limited. The authors integrated select research examining the intersection of IPV victimization and SUDs and several comorbidities that have significant public health impact and provided recommendations for scaling up targeted interventions to redress these co-occurring problems among women in primary, emergency, and other care settings.

Priorities Of Legislatively Active Veteran Services Organizations: A Content Analysis and Review For Health Promotion Initiatives Jahnke SA, Haddock CK, Carlos Poston WS, Jitnarin N. Mil Med. 2014; 179(11): 1331-1338.
Military and Veterans Service Organizations (MVSOs) have a unique opportunity to influence legislation and advocate for the interests of their members. However, little is known about what legislative priorities MVSOs see as important. Understanding the legislative priorities of MVSOs can inform efforts by health scientists to promote policy and laws designed to improve the health of our nation's veterans. Using a mixed methods approach, the authors conducted a thematic analysis of legislative priorities MVSOs promote with their legislative agendas. Most commonly, MVSOs addressed issues related to disability evaluations and ratings with the Veterans Administration and access to Veterans Administration services. Other common themes identified as priorities include benefits such as retirement, education, housing assistance for veterans, and TRICARE benefits. Findings highlight the broad range of topics MVSOs identify as legislative priorities as well as some health issues that receive relatively limited attention.

"Throwing A Rock At Their Armored Tank": Civilian Authority And Military Tobacco Control Grundy Q, Smith EA, Malone RE. BMC Public Health. 2014; 14: 1292.
Tobacco use is a major cause of chronic disease, disability and death among military personnel and veterans. However, civilian public health and tobacco control advocates have been relatively silent on the issue. Research on the tobacco industry shows a long history of interference in military tobacco policy through relationships with the United States (US) Congress. The military cannot autonomously implement tobacco control, but is subject to Congressional oversight. Thus, the primary obstacles to effective tobacco control in the military are Congressional political opposition and tobacco industry influence, and by extension, a lack of civilian awareness and support in the policy arena. As part of a larger project to explore the topic of civilian support for military tobacco control, we analyzed data from focus groups with public health professionals to better understand their sense of agency and authority in regards to military tobacco control. Researchers conducted 4 focus groups with a total of 36 public health professionals at key conferences for those working in public health and tobacco control. Data were coded and the research team developed an interpretive

account that captured patterns and variations in the data. Public health and tobacco control participants shared a sense of futility regarding civilian efforts to engage in military tobacco control. This stemmed from feeling ignorant of military culture and structure, identifying powerful discourses that opposed tobacco control, particularly in a military context, and the very-real presence of the tobacco industry lobby throughout the policy process. A strong public health voice on military tobacco control might serve to begin problematizing the tobacco industry's influence in the military policy arena. As the military moves to institute stronger tobacco control policy, public health and tobacco control professionals should work to engage with and aid its efforts from the outside. Only with such civilian side support can the goal of a tobacco free military be realized.

Addressing Confounding When Estimating the Effects Of Latent Classes On A Distal Outcome Schuler MS, Leoutsakos J-MS, Stuart EA. Health Serv Outcomes Res Methodol. 2014; 14(4): 232-254.
Confounding is widely recognized in settings where all variables are fully observed, yet recognition of and statistical methods to address confounding in the context of latent class regression are slowly emerging. In this study the authors focus on confounding when regressing a distal outcome on latent class; extending standard confounding methods is not straightforward when the treatment of interest is a latent variable. They describe a recent 1-step method, as well as two 3-step methods (modal and pseudoclass assignment) that incorporate propensity score weighting. Using simulated data, the authors compare the performance of these three adjusted methods to an unadjusted 1-step and unadjusted 3-step method. They also present an applied example regarding adolescent substance use treatment that examines the effect of treatment service class on subsequent substance use problems. The authors' simulations indicated that the adjusted 1-step method and both adjusted 3-step methods significantly reduced bias arising from confounding relative to the unadjusted 1-step and 3-step approaches. However, the adjusted 1-step method performed better than the adjusted 3-step methods with regard to bias and 95% CI coverage, particularly when class separation was poor. The authors' applied example also highlighted the importance of addressing confounding - both unadjusted methods indicated significant differences across treatment classes with respect to the outcome, yet these class differences were not significant when using any of the three adjusted methods. Potential confounding should be carefully considered when conducting latent class regression with a distal outcome; failure to do so may results in significantly biased effect estimates or incorrect inferences.

Low Dispositional Mindfulness Predicts Self-medication Of Negative Emotion With Prescription Opioids Garland EL, Hanley AW, Thomas EA, Knoll P, Ferraro J. J Addict Med. 2015; 9(1): 61-67.
Although evidence is mounting that opioids are abused to self-medicate negative emotions, little is known about the traits and factors linked to opioid self-medication. One potentially crucial psychological correlate is dispositional mindfulness. Thus, the purpose of this study was to describe the prevalence of opioid self-medication among a treatment-seeking sample of prescription opioid-dependent individuals and specifically examine the relationship between dispositional mindfulness and opioid self-medication. Participants in acute detoxification or intensive outpatient treatment for prescription opioid dependence (n = 79) were recruited from a regional hospital's addictions treatment unit for this cross-sectional study. Sociodemographic data were collected along with surveys of opioid self-medication, pain level, and dispositional mindfulness. Self-medication of negative affective states with opioids was quite common, with 94.9% of individual's sampled

reporting self-medication behaviors. In adjusted analyses, individuals engaging in more frequent opioid use tended to self-medicate negative emotions with opioids more often than those engaging in more intermittent opioid use (* = 0.33; P < 0.05). Importantly, irrespective of opioid use frequency and other clinical and sociodemographic covariates, dispositional mindfulness was inversely associated with opioid self-medication (* = -0.42; P < 0.001), such that less mindful individuals reported using opioids more frequently to self-medicate negative emotions. Self-medication of negative emotions with opioids was prevalent in this sample and related to low dispositional mindfulness. Plausibly, increasing mindfulness may decrease opioid self-medication. Addictive automaticity and emotion regulation are discussed as potential mechanisms linking low dispositional mindfulness and self-medication.

The Biobehavioral Women's Health CoOp In Pretoria, South Africa: Study Protocol For A Cluster-randomized Design Wechsberg WM, Zule WA, Ndirangu J, Kline TL, Rodman NF, Doherty IA, Novak SP, van der Horst CM. BMC Public Health. 2014; 14: 1074.
South Africa has 6.4 million adults over the age of 15 living with HIV. Gender inequality issues continue to drive the HIV epidemic in South Africa, where Black African women bear the greatest HIV burden. Limited access to services; little capacity to negotiate sex and condom use; and other legal, social, and economic inequities make women highly vulnerable to HIV infection. Behavioral interventions have been shown to decrease risk behaviors, but they have been less successful in reducing HIV incidence. Conversely, biomedical prevention strategies have proven to be successful in reducing HIV incidence, but require behavioral interventions to increase uptake and adherence. Consequently, there is a need for integrated approaches that combine biomedical and behavioral interventions. Effective combination prevention efforts should comprise biomedical, behavioral, and structural programming proven in randomized trials that focuses on the driving forces and key populations at higher risk of HIV infection and transmission. This prospective, geographically clustered randomized field experiment is enrolling participants into two arms: a control arm that receives standard HIV testing and referral for treatment; and an intervention arm that receives an evidence-based, woman-focused behavioral intervention that emphasizes risk reduction and retention, the Women’s Health CoOp. The authors divided the city of Pretoria into 14 mutually exclusive geographic zones and randomized these zones into either the control arm or the intervention arm. Outreach workers are recruiting drug-using women from each zone. At baseline, eligible participants complete a questionnaire and biological testing for HIV, recent drug use, and pregnancy. Follow-up interviews are completed at 6 and 12months.The bio behavioral intervention in this study merges an efficacious behavioral HIV prevention intervention for women with biomedical prevention through HIV treatment as prevention using a Seek, Test, Treat and Retain strategy. This combination bio behavioral intervention is designed to (1) improve the quality of life and reduce HIV infectiousness among women who are HIV positive, and (2) reduce HIV risk behaviors among women regardless of their HIV status. If efficacious, this intervention could help control the HIV epidemic in South Africa. Trial registration no: NCT01497405.

Using the Bollen-Stine Bootstrapping Method For Evaluating Approximate Fit Indices Kim H, Millsap R. Multivariate Behav Res. 2014; 49(6): 581-596.
Accepting that a model will not exactly fit any empirical data, global approximate fit indices quantify the degree of misfit. Recent research (Chen et al., 2008) has shown that using fixed conventional cut-points for approximate fit indices can lead to decision errors. Instead of using fixed cut-points for evaluating approximate fit indices, this study focuses on the meaning of

approximate fit and introduces a new method to evaluate approximate fit indices. Millsap (2012) introduced a simulation-based method to evaluate approximate fit indices. A limitation of Millsap's work was that a rather strong assumption of multivariate normality was implied in generating simulation data. In this study, the Bollen-Stine bootstrapping procedure (Bollen & Stine, 1993) is proposed to supplement the former study. When data are non-normal, the conclusions derived from Millsap's (2012) simulation method and the Bollen-Stine method can differ. Examples are given to illustrate the use of the Bollen-Stine bootstrapping procedure for evaluating RMSEA. Comparisons are made with the simulation method. The results are discussed, and suggestions are given for the use of proposed method.

Bidirectional Relationships Between Client and Counselor Speech: The Importance Of Reframing Barnett E, Spruijt-Metz D, Moyers TB, Smith C, Rohrbach LA, Sun P, Sussman S. Psychol Addict Behav. 2014; 28(4): 1212-1219.
In the study of motivational interviewing (MI), counselor skill has been posited to influence client language about change or "change talk." This study investigates the relationship between a specific counselor behavior, valenced reflective listening, and client change talk in a MI intervention with substance-using adolescents. A combination of recorded in-person and telephone (n = 223) sessions were sequentially coded using the Motivational Interviewing Skill Code 2.5. Reflections were categorized by valence, meaning they included content that was either moving toward (i.e., positive reflection) or away from change (i.e., negative reflection). Client language was coded as either moving toward change, away from change, or neutral about change. Probability analyses showed positive reflections were 11 times more likely to be followed by change talk and 71% less likely to be followed by counter change talk. Negative reflections were 19 times more likely to be followed by counter change talk and 65% less likely to be followed by change talk. Client language was also predictive of counselor reflections, such that positive reflections were 10 times more likely to occur after client change talk and negative reflections were 19 times more likely to follow counter change talk. Because the percentage of change talk expressed in a session has been shown to be positively related to improved behavioral outcomes, counselors should avoid unintentional reflections of counter change talk and use reframing techniques to change the valence of client change language. Implications for MI practice and training are discussed.

Neurophysiological Evidence For Remediation Of Reward Processing Deficits In Chronic Pain and Opioid Misuse Following Treatment With Mindfulness-Oriented Recovery Enhancement: Exploratory ERP Findings From A Pilot RCT Garland EL, Froeliger B, Howard MO. J Behav Med. 2014.
Dysregulated processing of natural rewards may be a central pathogenic process in the etiology and maintenance of prescription opioid misuse and addiction among chronic pain patients. This study examined whether a Mindfulness-Oriented Recovery Enhancement (MORE) intervention could augment natural reward processing through training in savoring as indicated by event-related brain potentials (ERPs). Participants were chronic pain patients at risk for opioid misuse who were randomized to 8 weeks of MORE (n=11) or a support group control condition (n=18). ERPs to images representing naturally rewarding stimuli (e.g., beautiful landscapes, intimate couples) and neutral images were measured before and after 8 weeks of treatment. Analyses focused on the late positive potential (LPP)-an ERP response in the 400-1,000 ms time window thought to index allocation of attention to emotional information. Treatment with MORE was associated with significant increases in LPP response to natural reward stimuli relative to neutral stimuli which

were correlated with enhanced positive affective cue-responses and reductions in opioid craving from pre- to post-treatment. Findings suggest that cognitive training regimens centered on strengthening attention to natural rewards may remediate reward processing deficits underpinning addictive behavior.

Assessment Of Mobile Device and SMS Use For Diet and Exercise Information Among Rural Mexican-American Adolescents Collins JL, Champion JD. J Pediatr Nurs. 2014; 29(6): 493-502.
This is a pilot study regarding the use of mobile technology and short message service (SMS) for diet and exercise among rural Mexican American adolescents (RMAA). Authors used convenience sampling to recruit RMAA seeking care at a rural healthcare clinic and conducted three focus groups (n=12). Content analysis was used to identify categories and subcategories. Participants applied diet and exercise information in their lives based on an interaction with community and through the use of use mobile devices. Culturally sensitive use of mobile devices and SMS may be a tool to provide rural adolescent populations with resources.

Is It Time For A Tobacco-free Military? Smith EA, Jahnke SA, Poston WSC, Williams LN, Haddock CK, Schroeder SA, Malone RE. N Engl J Med. 2014; 371(7): 589-591.
Achieving a tobacco-free military requires rethinking current perceptions of service members' tobacco use and unmasking the forces perpetuating those perceptions. Prohibiting tobacco use would be entirely consistent with other military requirements regarding health.

BEHAVIORAL AND INTEGRATIVE TREATMENT RESEARCH

Nicotine Concentrations with Electronic Cigarette Use: Effects of Sex and Flavor Oncken CA, Litt MD, McLaughlin LD, Burki NA. Nicotine Tob Res. 2015 Apr;17(4): 473-478.
This study examined overall changes in nicotine concentrations when using a popular e-cigarette and 18mg/mL nicotine e-Juice, and it further explored effects of sex and flavorings on these concentrations. The authors recruited nontreatment-seeking smokers who were willing to try e-cigarettes for 2 weeks and abstain from cigarette smoking. Subjects were randomized to either menthol tobacco or non-menthol tobacco-flavored e-cigarette use for 7-10 days, and the next week they were crossed over to the other condition. On the last day of e-cigarette use of each flavor, subjects completed a laboratory session in which they used the e-cigarette for 5min ad libitum. Nicotine concentrations were obtained 5min before and 5, 10, 15, 20, and 30min after the onset of e-cigarette use. Twenty subjects completed at least 1 monitoring session. Nicotine concentrations significantly increased from baseline to 5min by 4ng/mL at the first laboratory session ($p < .01$) and by 5.1ng/mL at the second laboratory session ($p < .01$). Combining sessions, there were no main effects of sex or preferred flavor (based on smoking history) on changes in nicotine concentrations. After adding preferred flavor, sex, and visit order to the model, there was a significant preferred flavor by sex interaction ($p < .01$), such that women who received nonpreferred flavors had lower nicotine concentrations and rated their e-cigarette as less likeable ($p < .01$). The authors found nicotine concentrations significantly increase after e-cigarette use for 5min, and flavor may impact nicotine concentrations with e-cigarette use in women.

Contingency Management Improves Smoking Cessation Treatment Outcomes among Highly Impulsive Adolescent Smokers Relative to Cognitive Behavioral Therapy Morean ME, Kong G, Camenga DR, Cavallo DA, Carroll KM, Pittman B, Krishnan-Sarin S. Addict Behav. 2015 Mar; 42:86-90.
Impulsive adolescents have difficulty quitting smoking. The authors examined if treatments that provide behavioral incentives for abstinence improve treatment outcomes among impulsive adolescent smokers, who have been shown to be highly sensitive to reward. They ran secondary data analyses on 64 teen smokers (mean age=16.36 [1.44]; cigarettes/day=13.97 [6.61]; 53.1% female; 90.6% Caucasian) who completed a four-week smoking cessation trial to determine whether impulsive adolescents differentially benefit from receiving cognitive behavioral therapy (CBT), contingency management (CM), or the combination of the two (CM/CBT). Indices of treatment efficacy included self-report percent days abstinent and end of treatment biochemically-confirmed 7-day point prevalence abstinence (EOT abstinence). The authors assessed self-reported impulsivity using the Brief Barratt Impulsiveness Scale. They used univariate Generalized Linear Modeling to examine main effects and interactions of impulsivity and treatment condition as predictors of self-reported abstinence, and exact logistic regression to examine EOT abstinence. CM/CBT and CM were comparably effective in promoting abstinence, so analyses were conducted comparing the efficacy of CBT to treatments with a CM component (i.e., CM and CM/CBT). CBT and deficient self-regulation predicted lower self-reported abstinence rates within the total analytic sample. Treatments containing CM were more effective than CBT in predicting 1) self-reported abstinence among behaviorally impulsive adolescents (% days abstinent: CM 77%; CM/CBT 81%; CBT 30%) and 2) EOT point prevalence abstinence among behaviorally impulsive adolescents and adolescents with significant deficits in self-regulation. CM-based interventions may improve the low smoking cessation rates previously observed among impulsive adolescent smokers.

Adding an Internet-delivered Treatment to an Efficacious Treatment Package for Opioid Dependence Christensen DR, Landes RD, Jackson L, Marsch LA, Mancino MJ, Chopra MP, Bickel WK. J Consult Clin Psychol. 2014 Dec; 82(6):964-972.
The objective of this study was to examine the benefit of adding an Internet-delivered behavior therapy to a buprenorphine medication program and voucher-based motivational incentives. A block-randomized, unblinded, parallel, 12-week treatment trial was conducted with 170 opioid-dependent adult patients (mean age = 34.3 years; 54.1% male; 95.3% White). Participants received an Internet-based community reinforcement approach intervention plus contingency management (CRA+) and buprenorphine or contingency management alone (CM-alone) plus buprenorphine. The primary outcomes, measured over the course of treatment, were longest continuous abstinence, total abstinence, and days retained in treatment. Compared to those receiving CM-alone, CRA+ recipients exhibited, on average, 9.7 total days more of abstinence (95% confidence interval [CI = 2.3, 17.2]) and had a reduced hazard of dropping out of treatment (hazard ratio = 0.47; 95% CI [0.26, 0.85]). Prior treatment for opioid dependence significantly moderated the additional improvement of CRA+ for longest continuous days of abstinence. These results provide further evidence that an Internet-based CRA+ treatment is efficacious and adds clinical benefits to a contingency management/medication based program for opioid dependence.

Does Impulsiveness Moderate Response to Financial Incentives for Smoking Cessation among Pregnant and Newly Postpartum Women? Lopez AA, Skelly JM, White TJ, Higgins ST. Exp Clin Psychopharmacol. 2015 Mar. [Epub ahead of print].
The authors examined whether impulsiveness moderates response to financial incentives for cessation among pregnant smokers. Participants were randomized to receive financial incentives delivered contingent on smoking abstinence or to a control condition wherein incentives were delivered independent of smoking status. The study was conducted in two steps: First, they examined associations between baseline impulsiveness and abstinence at late pregnancy and 24-weeks-postpartum as part of a planned prospective study of this topic using data from a recently completed, randomized controlled clinical trial (N = 118). Next, to increase statistical power, they conducted a second analysis collapsing results across that recent trial and two prior trials involving the same study conditions (N = 236). Impulsivity was assessed using a delay discounting (DD) of hypothetical monetary rewards task in all three trials and Barratt Impulsiveness Scale (BIS) in the most recent trial. Neither DD nor BIS predicted smoking status in the single or combined trials. Receiving abstinence-contingent incentives, lower baseline smoking rate, and a history of quit attempts prepregnancy predicted greater odds of antepartum abstinence across the single and combined trials. No variable predicted postpartum abstinence across the single and combined trials, although a history of antepartum quit attempts and receiving abstinence-contingent incentives predicted in the single and combined trials, respectively. Overall, this study provides no evidence that impulsiveness as assessed by DD or BIS moderates response to this treatment approach while underscoring a substantial association of smoking rate and prior quit attempts with abstinence across the contingent incentives and control treatment conditions.

Initial Abstinence Status and Contingency Management Treatment Outcomes: Does Race Matter? Montgomery L, Carroll KM, Petry NM. J Consult Clin Psychol. 2015 Mar. [Epub ahead of print].
Limited research has evaluated African American substance users' response to evidence-based treatments. This study examined the efficacy of contingency management (CM) in African American and White cocaine users. A secondary analysis evaluated effects of race, treatment condition, and baseline cocaine urine sample results on treatment outcomes of African American (n = 444) and White (n = 403) cocaine abusers participating in one of six randomized clinical trials comparing CM to standard care. African American and White patients who initiated treatment with a cocaine-negative urine sample remained in treatment for similar durations and submitted a comparable proportion of negative samples during treatment regardless of treatment type; CM was efficacious in both races in terms of engendering longer durations of abstinence in patients who began treatment abstinent. Whites who began treatment with a cocaine positive sample remained in treatment longer and submitted a higher proportion of negative samples when assigned to CM than standard care. African Americans who initiated treatment with a cocaine positive sample, however, did not remain in treatment longer with CM compared with standard care, and gains in terms of drug use outcomes were muted in nature relative to Whites. This interaction effect persisted through the 9-month follow-up period. The authors conclude that CM is not equally effective in reducing drug use among all subgroups, specifically African American patients who are using cocaine upon treatment entry. Future research on improving treatment outcomes in this population is needed.

A Comparison of Three Interventions for Homeless Youth Evidencing Substance Use Disorders: Results of a Randomized Clinical Trial Slesnick N, Guo X, Brakenhoff B, Bantchevska D. J Subst Abuse Treat. 2015 Feb. [Epub ahead of print].
While research on homeless adolescents and young adults evidencing substance use disorder is increasing, there is a dearth of information regarding effective interventions, and more research is needed to guide those who serve this population. The current study builds upon prior research showing promising findings of the community reinforcement approach (CRA) (Slesnick, Prestopnik, Meyers, & Glassman, 2007). Homeless adolescents and young adults between the ages of 14 to 20years were randomized to one of three theoretically distinct interventions: (1) CRA (n=93), (2) motivational enhancement therapy (MET, n=86), or (3) case management (CM, n=91). The relative effectiveness of these interventions was evaluated at 3, 6, and 12months post-baseline. Findings indicated that substance use and associated problems were significantly reduced in all three interventions across time. Several moderating effects were found, especially for sex and history of childhood abuse. Findings show little evidence of superiority or inferiority of the three interventions and suggest that drop-in centers have choices for addressing the range of problems that these adolescents and young adults face.

Predictors of Depression Outcomes among Abstinent Methamphetamine-dependent Individuals Exposed to an Exercise Intervention Haglund M, Ang A, Mooney L, Gonzales R, Chudzynski J, Cooper CB, Dolezal BA, Gitlin M, Rawson RA. Am J Addict. 2014 Dec. [Epub ahead of print].
This paper expands on a study investigating depression outcomes in response to an 8-week exercise intervention among methamphetamine (MA) dependent individuals in early recovery. A total of 135 MA-dependent individuals enrolled in residential treatment were randomly assigned to either a structured exercise intervention or a structured health education control group. Both groups were

similar in format: 60-minute sessions, offered three times a week over an 8-week study period. Results showed that at the 8-week trial endpoint, participants randomized to the exercise intervention showed significantly greater reduction in depression symptom scores than participants randomized to the health education group, and that participants who attended the greatest number of exercise sessions derived the greatest benefit. This paper further analyzes study data to uncover individual predictors of depression response to exercise and finds that among participants randomized to exercise treatment, individuals with the most severe medical, psychiatric, and addiction disease burden at baseline showed the most significant improvement in depressive symptoms by study endpoint. These findings suggest that exercise in moderate dose is effective at treating depressive symptoms in individuals in early recovery from addiction, and furthermore, that treatment with exercise appears to be particularly beneficial to individuals who suffer from severe medical, psychiatric, and addictive disorders.

A Randomized Trial of Computerized vs. In-person Brief Intervention for Illicit Drug Use in Primary Care: Outcomes through 12 Months Gryczynski J, Mitchell SG, Gonzales A, Moseley A, Peterson TR, Ondersma SJ, O'Grady KE, Schwartz RP. J Subst Abuse Treat. 2015 Mar; 50:3-10. This study examined outcomes through 12 months from a randomized trial comparing computerized brief intervention (CBI) vs. in-person brief intervention (IBI) delivered by behavioral health counselors for adult community health center patients with moderate-level drug misuse (N=360). Data were collected at baseline, 3-, 6-, and 12-month follow-up, and included the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) and laboratory analysis of hair samples. Repeated measures analyses examined differential change over time. There were no significant differences in drug-positive hair tests over time or by condition. Global ASSIST scores decreased in both conditions ($p<.001$), but there were no significant differences between conditions in overall change across 12 months of follow-up ($p=.13$). CBI produced greater overall reductions in alcohol ($p=.04$) and cocaine ($p=.02$) ASSIST scores than IBI, with initial differences dissipating over time. Computerized brief interventions present a viable alternative to traditional in-person brief interventions.

Real-time Mobile Detection of Drug Use with Wearable Biosensors: A Pilot Study Carreiro S, Smelson D, Ranney M, Horvath KJ, Picard RW, Boudreaux ED, Hayes R, Boyer EW. J Med Toxicol. 2015 Mar;11(1): 73-79.
While reliable detection of illicit drug use is paramount to the field of addiction, current methods involving self-report and urine drug screens have substantial limitations that hinder their utility. Wearable biosensors may fill a void by providing valuable objective data regarding the timing and contexts of drug use. This is a preliminary observational study of four emergency department patients receiving parenteral opioids and one individual using cocaine in a natural environment. A portable biosensor was placed on the inner wrist of each subject, to continuously measure electrodermal activity (EDA), skin temperature, and acceleration. Data were continuously recorded for at least 5 min prior to drug administration, during administration, and for at least 30 min afterward. Overall trends in biophysiometric parameters were assessed. Injection of opioids and cocaine use were associated with rises in EDA. Cocaine injection was also associated with a decrease in skin temperature. Opioid tolerance appeared to be associated with a blunted physiologic response as measured by the biosensor. Laterality may be an important factor, as magnitude of response varied between dominant and nondominant wrists in a single patient with bilateral wrist measurements. Changes in EDA and skin temperature are temporally associated with intravenous

administration of opioids and cocaine; the intensity of response, however, may vary depending on history and extent of prior use.

Chronic Pain and Depression among Primary Care Patients Treated with Buprenorphine
Stein MD, Herman DS, Bailey GL, Straus J, Anderson BJ, Uebelacker LA, Weisberg RB. J Gen Intern Med. 2015 Feb. [Epub ahead of print].
Pain and depression are each prevalent among opioid dependent patients receiving maintenance buprenorphine, but their interaction has not been studied in primary care patients. The authors set out to examine the relationship between chronic pain, depression, and ongoing substance use, among persons maintained on buprenorphine in primary care settings. Between September 2012 and December 2013, they interviewed buprenorphine patients at three practice sites. Participants were opioid dependent persons at two private internal medicine offices and a federally qualified health center participated in the study. Pain was measured in terms of chronicity, with chronic pain being defined as pain lasting at least 6 months; and in terms of severity, as measured by self-reported pain in the past week, measured on a 0-100 scale. The authors defined mild chronic pain as pain severity between 0 and 39 and lasting at least 6 months, and moderate/severe chronic pain as severity ≥ 40 and lasting at least 6 months. To assess depression, they used the Center for Epidemiologic Studies Depression (CESD) ten-item symptom scale and the two-item Patient Health Questionnaire (PHQ-2). Among 328 participants, 169 reported no chronic pain, 56 reported mild chronic pain, and 103 reported moderate/severe chronic pain. Participants with moderate/severe chronic pain commonly used non-opioid pain medications (56.3 %) and antidepressants (44.7 %), yet also used marijuana, alcohol, or cocaine (40.8 %) to help relieve pain. Mean CESD scores were 7.1 (±6.8), 8.3 (±6.0), and 13.6 (±7.6) in the no chronic, mild, and moderate/severe pain groups, respectively. Controlling for covariates, higher CESD scores were associated with a higher likelihood of moderate/severe chronic pain relative to both no chronic pain ($OR = 1.09$, $p < 0.001$) and mild chronic pain ($OR = 1.06$, $p = 0.04$). Many buprenorphine patients are receiving over-the-counter or prescribed pain medications, as well as antidepressants, and yet continue to have significant and disabling pain and depressive symptoms. There is a clear need to address the pain-depression nexus in novel ways.

RESEARCH ON PHARMACOTHERAPIES FOR DRUG ABUSE

The Anti-(+)-Methamphetamine Monoclonal Antibody Mab7F9 Attenuates Acute (+)-Methamphetamine Effects On Intracranial Self-Stimulation In Rats Harris AC, LeSage MG, Shelley D, Perry JL, Pentel PR, Owens SM. PLoS One. 2015; 10(3): e0118787.
Passive immunization with monoclonal antibodies (mAbs) against (+)-methamphetamine (METH) is being evaluated for the treatment of METH addiction. A human/mouse chimeric form of the murine anti-METH mAb7F9 has entered clinical trials. This study examined the effects of murine mAb7F9 on certain addiction-related behavioral effects of METH in rats as measured using intracranial self-stimulation (ICSS). Initial studies indicated that acute METH (0.1-0. 56 mg/kg, s.c.) lowered the minimal (threshold) stimulation intensity that maintained ICSS. METH (0.3 mg/kg, s.c.) also blocked elevations in ICSS thresholds (anhedonia-like behavior) during spontaneous withdrawal from a chronic METH infusion (10 mg/kg/day x 7 days). In studies examining effects of i. v. pretreatment with mAb7F9 (at 30, 100, or 200 mg/kg), 200 mg/kg blocked the ability of an initial injection of METH (0.3 mg/kg, s.c.) to reduce baseline ICSS thresholds, but was less capable of attenuating the effect of subsequent daily injections of METH. MAb7F9 (200 mg/kg) also produced a small but significant reduction in the ability of METH (0.3 mg/kg, s.c.) to reverse METH withdrawal-induced elevations in ICSS thresholds. These studies demonstrate that mAb7F9 can partially attenuate some addiction-related effects of acute METH in an ICSS model, and provide some support for the therapeutic potential of mAb7F9 for the treatment of METH addiction.

Pharmacokinetic Correlates Of the Effects Of A Heroin Vaccine On Heroin Self-Administration In Rats Raleigh MD, Pentel PR, LeSage MG. PLoS One. 2014; 9(12): e115696.
The purpose of this study was to evaluate the effects of a morphine-conjugate vaccine (M-KLH) on the acquisition, maintenance, and reinstatement of heroin self-administration (HSA) in rats, and on heroin and metabolite distribution during heroin administration that approximated the self-administered dosing rate. Vaccination with M-KLH blocked heroin-primed reinstatement of heroin responding. Vaccination also decreased HSA at low heroin unit doses but produced a compensatory increase in heroin self-administration at high unit doses. Vaccination shifted the heroin dose-response curve to the right, indicating reduced heroin potency, and behavioral economic demand curve analysis further confirmed this effect. In a separate experiment heroin was administered at rates simulating heroin exposure during HSA. Heroin and its active metabolites, 6-acetylmorphine (6-AM) and morphine, were retained in plasma and metabolite concentrations were reduced in brain in vaccinated rats compared to controls. Reductions in 6-AM concentrations in brain after vaccination were consistent with the changes in HSA rates accompanying vaccination. These data provide evidence that 6-AM is the principal mediator of heroin reinforcement, and the principal target of the M-KLH vaccine, in this model. While heroin vaccines may have potential as therapies for heroin addiction, high antibody to drug ratios appear to be important for obtaining maximal efficacy.

Flagellin As Carrier And Adjuvant In Cocaine Vaccine Development Lockner JW, Eubanks LM, Choi JL, Lively JM, Schlosburg JE, Collins KC, Globisch D, Rosenfeld-Gunn RJ, Wilson IA, Janda KD. Mol Pharm. 2015 Feb; 12(2): 653-662.
Cocaine abuse is problematic, directly and indirectly impacting the lives of millions, and yet existing therapies are inadequate and usually ineffective. A cocaine vaccine would be a promising

alternative therapeutic option, but efficacy is hampered by variable production of anticocaine antibodies. Thus, new tactics and strategies for boosting cocaine vaccine immunogenicity must be explored. Flagellin is a bacterial protein that stimulates the innate immune response via binding to extracellular Toll-like receptor 5 (TLR5) and also via interaction with intracellular NOD-like receptor C4 (NLRC4), leading to production of pro-inflammatory cytokines. Reasoning that flagellin could serve as both carrier and adjuvant, we modified recombinant flagellin protein to display a cocaine hapten termed GNE. The resulting conjugates exhibited dose-dependent stimulation of anti-GNE antibody production. Moreover, when adjuvanted with alum, but not with liposomal MPLA, GNE-FliC was found to be better than our benchmark GNE-KLH. This work represents a new avenue for exploration in the use of hapten-flagellin conjugates to elicit antihapten immune responses.

AM841, A Covalent Cannabinoid Ligand, Powerfully Slows Gastrointestinal Motility In Normal and Stressed Mice In A Peripherally-Restricted Manner Keenan CM, Storr MA, Thakur GA, Wood JT, Wager-Miller J, Straiker A, Eno MR, Nikas SP, Bashashati M, Hu H, Mackie K, Makriyannis A, Sharkey KA. Br J Pharmacol. 2015 Jan; [Epub ahead of print].
Cannabinoid ligands have been demonstrated to have utility as novel therapeutic agents for the treatment of pain, metabolic conditions and gastrointestinal (GI) disorders. However, many of these ligands are centrally active, which limits their usefulness. Here the authors examine a unique novel covalent cannabinoid receptor ligand, AM841, to assess its potential for use in physiological and pathophysiological in vivo studies. The covalent nature of AM841 was determined in vitro using electrophysiological and receptor internalization studies on isolated cultured hippocampal neurons. Mouse models were used for behavioural analysis of analgesia, hypothermia and hypolocomotion. Motility of the small and large intestine was assessed in vivo under normal conditions and after acute stress. Brain penetration of AM841 was also determined. AM841 behaves as an irreversible cannabinoid (CB)1 receptor agonist in vitro. AM841 potently reduces GI motility through an action on CB1 receptors in the small (EC50 0. 004 mg/kg) and large (EC50 0.03 mg/kg) intestine under physiological conditions. AM841 is even more potent under conditions of acute stress, and was shown to normalize accelerated GI motility under these conditions. This compound behaves as a peripherally-restricted ligand, showing very little brain penetration and no characteristic centrally-mediated CB1 receptor-mediated effects (analgesia, hypothermia or hypolocomotion). AM841, a novel peripherally-restricted covalent CB1 receptor ligand that possess remarkable potency represents a new class of potential therapeutic agents for the treatment of functional GI disorders.

Cannabinoid Withdrawal In Mice: Inverse Agonist Vs Neutral Antagonist Tai S, Nikas SP, Shukla VG, Vemuri K, Makriyannis A, Järbe TU. Psychopharmacology (Berl). 2015 Mar; [Epub ahead of print].
Previous reports shows rimonabant's inverse properties may be a limiting factor for treating cannabinoid dependence. To overcome this limitation, neutral antagonists were developed, to address mechanisms by which an inverse agonist and neutral antagonist elicit withdrawal. The objective of this study is to introduce an animal model to study cannabinoid dependence by incorporating traditional methodologies and profiling novel cannabinoid ligands with distinct pharmacological properties/modes of action by evaluating their pharmacological effects on CB1-receptor (CB1R) related physiological/behavioral endpoints. The cannabinergic AM2389 was acutely characterized in the tetrad (locomotor activity, analgesia, inverted screen/catalepsy bar test, and temperature), with some comparisons made to Δ(9)-tetrahydrocannabinol (THC). Tolerance

was measured in mice repeatedly administered AM2389. Antagonist-precipitated withdrawal was characterized in cannabinoid-adapted mice induced by either centrally acting antagonists, rimonabant and AM4113, or an antagonist with limited brain penetration, AM6545. In the tetrad, AM2389 was more potent and longer acting than THC, suggesting a novel approach for inducing dependence. Repeated administration of AM2389 led to tolerance by attenuating hypothermia that was induced by acute AM2389 administration. Antagonist-precipitated withdrawal signs were induced by rimonabant or AM4113, but not by AM6545. Antagonist-precipitated withdrawal was reversed by reinstating AM2389 or THC. These findings suggest cannabinoid-precipitated withdrawal may not be ascribed to the inverse properties of rimonabant, but rather to rapid competition with the agonist at the CB1R. This withdrawal syndrome is likely centrally mediated, since only the centrally acting CB1R antagonists elicited withdrawal, i.e., such responses were absent after the purported peripherally selective CB1R antagonist AM6545.

Chronic Cannabinoid Receptor 2 Activation Reverses Paclitaxel Neuropathy Without Tolerance Or Cannabinoid Receptor 1-Dependent Withdrawal Deng L, Guindon J, Cornett BL, Makriyannis A, Mackie K, Hohmann AG. Biol Psychiatry. 2015 Mar;77(5): 475-487.
Mixed cannabinoid receptor 1 and 2 (CB1 and CB2) agonists such as Δ(9)-tetrahydrocannabinol (Δ(9)-THC) can produce tolerance, physical withdrawal, and unwanted CB1-mediated central nervous system side effects. Whether repeated systemic administration of a CB2-preferring agonist engages CB1 receptors or produces CB1-mediated side effects is unknown. The authors evaluated antiallodynic efficacy, possible tolerance, and cannabimimetic side effects of repeated dosing with a CB2-preferring agonist AM1710 in a model of chemotherapy-induced neuropathy produced by paclitaxel using CB1 knockout (CB1KO), CB2 knockout (CB2KO), and wild-type (WT) mice. Comparisons were made with the prototypic classic cannabinoid Δ(9)-THC. The authors also explored the site and possible mechanism of action of AM1710. Paclitaxel-induced mechanical and cold allodynia developed to an equivalent degree in CB1KO, CB2KO, and WT mice. Both AM1710 and Δ(9)-THC suppressed established paclitaxel-induced allodynia in WT mice. In contrast to Δ(9)-THC, chronic administration of AM1710 did not engage CB1 activity or produce antinociceptive tolerance, CB1-mediated cannabinoid withdrawal, hypothermia, or motor dysfunction. Antiallodynic efficacy of systemic administration of AM1710 was absent in CB2KO mice and WT mice receiving the CB2 antagonist AM630, administered either systemically or intrathecally. Intrathecal administration of AM1710 also attenuated paclitaxel-induced allodynia in WT mice, but not CB2KO mice, implicating a possible role for spinal CB2 receptors in AM1710 antiallodynic efficacy. Finally, both acute and chronic administration of AM1710 decreased messenger RNA levels of tumor necrosis factor-α and monocyte chemoattractant protein 1 in lumbar spinal cord of paclitaxel-treated WT mice. These results highlight the potential of prolonged use of CB2 agonists for managing chemotherapy-induced allodynia with a favorable therapeutic ratio marked by sustained efficacy and absence of tolerance, physical withdrawal, or CB1-mediated side effects.

Discriminative-Stimulus Effects Of Second Generation Synthetic Cathinones In Methamphetamine-Trained Rats Naylor JE, Freeman KB, Blough BE, Woolverton WL, Huskinson SL. Drug Alcohol Depend. 2015 Apr; 149[Epub ahead of print] 280-284.
Synthetic cathinones are beta-ketophenethylamine analogs manufactured to avoid legal restrictions placed on illicit stimulants like methamphetamine. Regulating these "emerging" designer drugs require scientific evidence of abuse potential. The present study evaluated the discriminative-stimulus effects of three synthetic cathinones, recently identified in commercial and confiscated

products, in male Sprague-Dawley rats trained to discriminate methamphetamine (1.0mg/kg) from saline under a fixed-ratio (FR) 20 schedule of food delivery. Three synthetic cathinones, 4-methyl-N-ethylcathinone (4-MEC; 1.0-8. 0mg/kg), 4-methyl-alpha-pyrrolidinopropiophenone (4-MePPP; 4.0-16. 0mg/kg), and alpha-pyrrolidinopentiophenone (alpha-PVP; 0.25-2.0mg/kg) were tested for their ability to substitute for methamphetamine. Full substitution for the training dose of methamphetamine occurred at the highest doses for both 4-MePPP and alpha-PVP, and 4-MEC did not substitute at any dose tested. The present findings show that two synthetic cathinones, 4-MePPP and alpha-PVP, produced subjective effects similar to those of methamphetamine. The synthetic cathinone, 4-MEC, did not produce subjective effects similar to those of methamphetamine with the parameters used in the current experiment. Based on findings here and by others, these three compounds warrant further tests of abuse potential.

Effects Of Fatty Acid Amide Hydrolase (FAAH) Inhibitors In Non-Human Primate Models Of Nicotine Reward and Relapse Justinova Z, Panlilio LV, Moreno-Sanz G, Redhi GH, Auber A, Secci ME, Mascia P, Bandiera T, Armirotti A, Bertorelli R, Chefer SI, Barnes C, Yasar S, Piomelli D, Goldberg SR. Neuropsychopharmacology. 2015 Mar; [Epub ahead of print].
Inhibition of the enzyme fatty acid amide hydrolase (FAAH) counteracts reward-related effects of nicotine in rats, but has not been tested for this purpose in non-human primates. Therefore, the authors studied the effects of the first- and second-generation O-arylcarbamate-based FAAH inhibitors, URB597 (cyclohexyl carbamic acid 3'-carbamoyl-3-yl ester) and URB694 (6-hydroxy-[1,1'-biphenyl]-3-yl-cyclohexylcarbamate), in squirrel monkeys. Both FAAH inhibitors: 1) blocked FAAH activity in brain and liver, increasing levels of endogenous ligands for cannabinoid and alpha-type peroxisome proliferator-activated (PPAR-α) receptors; 2) shifted nicotine self-administration dose-response functions in a manner consistent with reduced nicotine reward; 3) blocked reinstatement of nicotine seeking induced by re-exposure to either nicotine priming or nicotine-associated cues; and 4) had no effect on cocaine or food self-administration. The effects of FAAH inhibition on nicotine self-administration and nicotine priming-induced reinstatement were reversed by the PPAR-α antagonist, MK886. Unlike URB597, which was not self-administered by monkeys in an earlier study, URB694 was self-administered at a moderate rate. URB694 self-administration was blocked by pretreatment with an antagonist for either PPAR-α (MK886) or cannabinoid CB1 receptors (rimonabant). In additional experiments in rats, URB694 was devoid of THC-like or nicotine-like interoceptive effects under drug-discrimination procedures, and neither FAAH inhibitor induced dopamine release in the nucleus accumbens shell-consistent with their lack of robust reinforcing effects in monkeys. Overall, both URB597 and URB694 show promise for the initialization and maintenance of smoking cessation, due to their ability to block the rewarding effects of nicotine and prevent nicotine priming-induced and cue-induced reinstatement. Neuropsychopharmacology accepted article preview online, 10 March 2015. doi:10. 1038/npp. 2015. 62.

Effects Of Pramipexole On the Acquisition Of Responding With Opioid-Conditioned Reinforcement In the Rat Bertz JW, Chen J, Woods JH. Psychopharmacology (Berl). 2015 Jan; 232(1): 209-221.
Dopamine D3 receptor-preferring ligands may be able to modify the conditioned reinforcing effects of drug-associated stimuli. In evaluating the effects of these compounds, it is important to clarify the extent to which responding depends on (1) conditioned reinforcement vs. other behavioral mechanisms and (2) dopamine D3 vs. D2 receptor activity. To use behaviorally stringent new-

response acquisition procedures to characterize the effects of the D3-preferring agonist, pramipexole, on the conditioned reinforcing effects of a stimulus paired with the opioid agonist, remifentanil. First, in Pavlovian conditioning (PAV) sessions, rats received response-independent IV injections of remifentanil and presentations of a light-noise stimulus. In separate groups, injections and stimuli either always co-occurred ("paired PAV") or occurred with no consistent relationship ("random PAV" control). Next, in instrumental acquisition (ACQ) sessions, all animals could respond in two nose-poke manipulanda: an active nose-poke, which produced the stimulus alone, or an inactive nose-poke. Pramipexole was injected SC prior to ACQ sessions with or without pretreatments of the D3-preferring antagonist, SB-277011A, or the D2-preferring antagonist, L-741,626. After paired PAV, but not random PAV, rats acquired nose-poke responding during ACQ (i. e. , active > inactive). Pramipexole dose-dependently increased active responding without changing inactive responding. Pramipexole-induced increases in responding were blocked by pretreatment with L-741,626, but not SB-277011A. Pramipexole specifically enhanced remifentanil-conditioned reinforcement: active responding was selectively increased only after the stimulus was paired with remifentanil. Although pramipexole is D3-preferring, the antagonist effects obtained presently suggest an important role for the D2 receptor in opioid-conditioned reinforcement.

Effects Of the Triple Monoamine Uptake Inhibitor Amitifadine On Pain-Related Depression Of Behavior and Mesolimbic Dopamine Release In Rats Miller LL, Leitl MD, Banks ML, Blough BE, Negus SS. Pain. 2015 Jan; 156(1):175-184.
Pain-related depression of behavior and mood is a key therapeutic target in the treatment of pain. Clinical evidence suggests a role for decreased dopamine (DA) signaling in pain-related depression of behavior and mood. Similarly, in rats, intraperitoneal injection of dilute lactic acid (IP acid) serves as a chemical noxious stimulus to produce analgesic-reversible decreases in both (1) extracellular DA levels in nucleus accumbens (NAc) and (2) intracranial self-stimulation (ICSS), an operant behavior reliant on NAc DA. Intraperitonial acid-induced depression of ICSS is blocked by DA transporter (DAT) inhibitors, but clinical viability of selective DAT inhibitors as analgesics is limited by abuse potential. Drugs that produce combined inhibition of both DA and serotonin transporters may retain efficacy to block pain-related behavioral depression with reduced abuse liability. Amitifadine is a "triple uptake inhibitor" that inhibits DAT with approximately 5- to 10-fold weaker potency than it inhibits serotonin and norepinephrine transporters. This study compared amitifadine effects on IP acid-induced depression of NAc DA and ICSS and IP acid-stimulated stretching in male Sprague-Dawley rats. Amitifadine blocked IP acid-induced depression of both NAc DA and ICSS and IP acid-stimulated stretching. In the absence of the noxious stimulus, amitifadine increased NAc levels of both DA and serotonin, and behaviorally, amitifadine produced significant but weak abuse-related ICSS facilitation. Moreover, amitifadine was more potent to block IP acid-induced depression of ICSS than to facilitate control ICSS. These results support consideration of amitifadine and related monoamine uptake inhibitors as candidate analgesics for treatment of pain-related behavioral depression.

Kinetic Characterization Of A Cocaine Hydrolase Engineered From Mouse Butyrylcholinesterase Chen X, Huang X, Geng L, Xue L, Hou S, Zheng X, Brimijoin S, Zheng F, Zhan CG. Biochem J. 2015 Mar; 466(2): 243-251.
Mouse butyrylcholinesterase (mBChE) and an mBChE-based cocaine hydrolase (mCocH, i.e., the A199S/S227A/S287G/A328W/Y332G mutant) have been characterized for their catalytic activities

against cocaine, i. e. naturally occurring (-)-cocaine, in comparison with the corresponding human BChE (hBChE) and an hBChE-based cocaine hydrolase (hCocH, i.e., the A199S/F227A/S287G/ A328W/Y332G mutant). It has been demonstrated that mCocH and hCocH have improved the catalytic efficiency of mBChE and hBChE against (-)-cocaine by ~8- and ~2000-fold respectively, although the catalytic efficiencies of mCocH and hCocH against other substrates, including acetylcholine (ACh) and butyrylthiocholine (BTC), are close to those of the corresponding wild-type enzymes mBChE and hBChE. According to the kinetic data, the catalytic efficiency (kcat/KM) of mBChE against (-)-cocaine is comparable with that of hBChE, but the catalytic efficiency of mCocH against (-)-cocaine is remarkably lower than that of hCocH by ~250-fold. The remarkable difference in the catalytic activity between mCocH and hCocH is consistent with the difference between the enzyme-(-)-cocaine binding modes obtained from molecular modelling. Further, both mBChE and hBChE demonstrated substrate activation for all of the examined substrates [(-)-cocaine, ACh and BTC] at high concentrations, whereas both mCocH and hCocH showed substrate inhibition for all three substrates at high concentrations. The amino-acid mutations have remarkably converted substrate activation of the enzymes into substrate inhibition, implying that the rate-determining step of the reaction in mCocH and hCocH might be different from that in mBChE and hBChE.

Novel 4-Substituted-N,N-Dimethyltetrahydronaphthalen-2-Amines: Synthesis, Affinity, and In Silico Docking Studies At Serotonin 5-HT2-Type and Histamine H1 G Protein-Coupled Receptors Sakhuja R, Kondabolu K, Córdova-Sintjago T, Travers S, Vincek AS, Kim MS, Abboud KA, Fang L, Sun Z, Canal CE, Booth RG. Bioorg Med Chem. 2015 Apr; 23(7): 1588-1600. Syntheses were undertaken of derivatives of (2S,4R)-(-)-trans-4-phenyl-N,N-dimethyl-1,2,3,4-tetrahydronaphthalen-2-amine (4-phenyl-2-dimethylaminotetralin, PAT), a stereospecific agonist at the serotonin 5-HT2C G protein-coupled receptor (GPCR), with inverse agonist activity at 5-HT2A and 5-HT2B GPCRs. Molecular changes were made at the PAT C(4)-position, while preserving N,N-dimethyl substitution at the 2-position as well as trans-stereochemistry, structural features previously shown to be optimal for 5-HT2 binding. Affinities of analogs were determined at recombinant human 5-HT2 GPCRs in comparison to the phylogenetically closely-related histamine H1 GPCR, and in silico ligand docking studies were conducted at receptor molecular models to help interpret pharmacological results and guide future ligand design. In most cases, C(4)-substituted PAT analogs exhibited the same stereoselectivity ([-]-trans>[+]-trans) as the parent PAT across 5-HT2 and H1 GPCRs, albeit, with variable receptor selectivity. 4-(4'-substituted)-PAT analogs, however, demonstrated reversed stereoselectivity ([2S,4R]-[+]-trans>[2S,4R]-[-]-trans), with absolute configuration confirmed by single X-ray crystallographic data for the 4-(4'-Cl)-PAT analog. Pharmacological affinity results and computational results herein support further PAT drug development studies and provide a basis for predicting and interpreting translational results, including, for (+)-trans-4-(4'-Cl)-PAT and (-)-trans-4-(3'-Br)-PAT that were previously shown to be more potent and efficacious than their corresponding enantiomers in rodent models of psychoses, psychostimulant-induced behaviors, and compulsive feeding ('binge-eating').

O-(Triazolyl)Methyl Carbamates As A Novel And Potent Class Of Fatty Acid Amide Hydrolase (FAAH) Inhibitors Colombano G, Albani C, Ottonello G, Ribeiro A, Scarpelli R, Tarozzo G, Daglian J, Jung KM, Piomelli D, Bandiera T. ChemMedChem. 2015 Feb; 10(2): 380-395.
Inhibition of fatty acid amide hydrolase (FAAH) activity is under investigation as a valuable strategy for the treatment of several disorders, including pain and drug addiction. A number of potent FAAH inhibitors belonging to different chemical classes have been disclosed to date; O-aryl carbamates are one of the most representative families. In the search for novel FAAH inhibitors, a series of O-(1,2,3-triazol-4-yl)methyl carbamate derivatives were designed and synthesized exploiting a copper- catalyzed [3+2] cycloaddition reaction between azides and alkynes (click chemistry). Exploration of the structure-activity relationships within this new class of compounds identified potent inhibitors of both rat and human FAAH with IC50 values in the single-digit nanomolar range. In addition, these derivatives showed improved stability in rat plasma and kinetic solubility in buffer with respect to the lead compound. Based on the results of the study, the novel analogues identified can be considered to be promising starting point for the development of new FAAH inhibitors with improved drug-like properties.

A Peripheral Endocannabinoid Mechanism Contributes To Glucocorticoid-Mediated Metabolic Syndrome Bowles NP, Karatsoreos IN, Li X, Vemuri VK, Wood JA, Li Z, Tamashiro KL, Schwartz GJ, Makriyannis AM, Kunos G, Hillard CJ, McEwen BS, Hill MN. Proc Natl Acad Sci USA. 2015 Jan; 112(1): 285-290.
Glucocorticoids are known to promote the development of metabolic syndrome through the modulation of both feeding pathways and metabolic processes; however, the precise mechanisms of these effects are not well-understood. Recent evidence shows that glucocorticoids possess the ability to increase endocannabinoid signaling, which is known to regulate appetite, energy balance, and metabolic processes through both central and peripheral pathways. The aim of this study was to determine the role of endocannabinoid signaling in glucocorticoid-mediated obesity and metabolic syndrome. Using a mouse model of excess corticosterone exposure, the authors found that the ability of glucocorticoids to increase adiposity, weight gain, hormonal dysregulation, hepatic steatosis, and dyslipidemia was reduced or reversed in mice lacking the cannabinoid CB1 receptor as well as mice treated with the global CB1 receptor antagonist AM251. Similarly, a neutral, peripherally restricted CB1 receptor antagonist (AM6545) was able to attenuate the metabolic phenotype caused by chronic corticosterone, suggesting a peripheral mechanism for these effects. Biochemical analyses showed that chronic excess glucocorticoid exposure produced a significant increase in hepatic and circulating levels of the endocannabinoid anandamide, whereas no effect was observed in the hypothalamus. To test the role of the liver, specific and exclusive deletion of hepatic CB1 receptor resulted in a rescue of the dyslipidemic effects of glucocorticoid exposure, while not affecting the obesity phenotype or the elevations in insulin and leptin. Together, these data indicate that glucocorticoids recruit peripheral endocannabinoid signaling to promote metabolic dysregulation, with hepatic endocannabinoid signaling being especially important for changes in lipid metabolism.

Preclinical Assessment Of Lisdexamfetamine As An Agonist Medication Candidate For Cocaine Addiction: Effects In Rhesus Monkeys Trained To Discriminate Cocaine Or To Self-Administer Cocaine In A Cocaine Versus Food Choice Procedure Banks ML, Hutsell BA, Blough BE, Poklis JL, Negus SS. Int J Neuropsychopharmacol. 2015 Jan; [Epub ahead of print]. Chronic amphetamine treatment decreases cocaine consumption in preclinical and human laboratory studies and in clinical trials. Lisdexamfetamine is an amphetamine prodrug in which L-lysine is conjugated to the terminal nitrogen of d-amphetamine. Prodrugs may be advantageous relative to their active metabolites due to slower onsets and longer durations of action; however, lisdexamfetamine treatment's efficacy in decreasing cocaine consumption is unknown. This study compared lisdexamfetamine and d-amphetamine effects in rhesus monkeys using two behavioral procedures: (1) a cocaine discrimination procedure (training dose = 0.32mg/kg cocaine, i.m.); and (2) a cocaine-versus-food choice self-administration procedure. In the cocaine-discrimination procedure, lisdexamfetamine (0.32-3.2mg/kg, i.m.) substituted for cocaine with lower potency, slower onset, and longer duration of action than d-amphetamine (0.032-0.32mg/kg, i.m.). Consistent with the function of lisdexamfetamine as an inactive prodrug for amphetamine, the time course of lisdexamfetamine effects was related to d-amphetamine plasma levels by a counter-clockwise hysteresis loop. In the choice procedure, cocaine (0-0.1mg/kg/injection, i.v.) and food (1g banana-flavored pellets) were concurrently available, and cocaine maintained a dose-dependent increase in cocaine choice under baseline conditions. Treatment for 7 consecutive days with lisdexamfetamine (0.32-3.2mg/kg/day, i.m.) or d-amphetamine (0.032-0.1mg/kg/h, i.v.) produced similar dose-dependent rightward shifts in cocaine dose-effect curves and decreases in preference for 0. 032mg/kg/injection cocaine. Lisdexamfetamine has a slower onset and longer duration of action than amphetamine but retains amphetamine's efficacy to reduce the choice of cocaine in rhesus monkeys. These results support further consideration of lisdexamfetamine as an agonist-based medication candidate for cocaine addiction.

Serotonin-2C Receptor Agonists Decrease Potassium-Stimulated GABA Release In The Nucleus Accumbens Kasper JM, Booth RG, Peris J. Synapse. 2015 Feb; 69(2): 78-85. The serotonin 5-HT2C receptor has shown promise in vivo as a pharmacotherapeutic target for alcoholism. For example, recently, a novel 4-phenyl-2-N,N-dimethylaminotetralin (PAT) drug candidate, that demonstrates 5-HT2C receptor agonist activity together with 5-HT2A/2B receptor inverse agonist activity, was shown to reduce operant responding for ethanol after peripheral administration to rats. Previous studies have shown that the 5-HT2C receptor is found throughout the mesoaccumbens pathway and that 5-HT2C receptor agonism causes activation of ventral tegmental area (VTA) GABA neurons. It is unknown what effect 5-HT2C receptor modulation has on GABA release in the nucleus accumbens core (NAcc). To this end, microdialysis coupled to capillary electrophoresis with laser-induced fluorescence was used to quantify extracellular neurotransmitter concentrations in the NAcc under basal and after potassium stimulation conditions, in response to PAT analogs and other 5-HT2C receptor modulators administered by reverse dialysis to rats. 5-HT2C receptor agonists specifically attenuated stimulated GABA release in the NAcc while 5-HT2C antagonists or inverse agonists had no effect. Agents with activity at 5-HT2A receptors had no effect on GABA release. Thus, in contrast to results reported for the VTA, current results suggest 5-HT2C receptor agonists decrease stimulated GABA release in the NAcc, and provide a possible mechanism of action for 5HT2C -mediated negative modulation of ethanol self-administration.

Synthesis, Pharmacological Evaluation and Molecular Modeling Studies Of Triazole Containing Dopamine D3 Receptor Ligands Peng X, Wang Q, Mishra Y, Xu J, Reichert DE, Malik M, Taylor M, Luedtke RR, Mach RH. Bioorg Med Chem Lett. 2015 Feb; 25(3): 519-523.
A series of 2-methoxyphenyl piperazine analogues containing a triazole ring were synthesized and their in vitro binding affinities at human dopamine D2 and D3 receptors were evaluated. Compounds 5b, 5c, 5d, and 4g, demonstrate high affinity for dopamine D3 receptors and moderate selectivity for the dopamine D3 versus D2 receptor subtypes. To further examine their potential as therapeutic agents, their intrinsic efficacy at both D2 and D3 receptors was determined using a forskolin-dependent adenylyl cyclase inhibition assay. Affinity at dopamine D4 and serotonin 5-HT1A receptors was also determined. In addition, information from previous molecular modeling studies of the binding of a panel of 163 structurally-related benzamide analogues at dopamine D2 and D3 receptors was applied to this series of compounds. The results of the modeling studies were consistent with our previous experimental data. More importantly, the modeling study results explained why the replacement of the amide linkage with the hetero-aromatic ring leads to a reduction in the affinity of these compounds at D3 receptors.

Differential Effects Of the Dopamine D3 Receptor Antagonist PG01037 On Cocaine and Methamphetamine Self-Administration In Rhesus Monkeys John WS, Newman AH, Nader MA. Neuropharmacology. 2015 May; 92: 34-43. doi: 10.1016/j.neuropharm.2014.12.024. Epub 2015 Jan 6.
The dopamine D3 receptor (D3R) has been shown to mediate many of the behavioral effects of psychostimulants associated with high abuse potential. This study extended the assessment of the highly selective D3R antagonist PG01037 on cocaine and methamphetamine (MA) self-administration to include a food-drug choice procedure. Eight male rhesus monkeys (n = 4/group) served as subjects in which complete cocaine and MA dose-response curves were determined daily in each session. When choice was stable, monkeys received acute and five-day treatment of PG01037 (1.0-5.6 mg/kg, i.v.). Acute administration of PG01037 was effective in reallocating choice from cocaine to food and decreasing cocaine intake, however, tolerance developed by day 5 of treatment. Up to doses that disrupted responding, MA choice and intake were not affected by PG01037 treatment. PG01037 decreased total reinforcers earned per session and the behavioral potency was significantly greater on MA-food choice compared to cocaine-food choice. Furthermore, the acute efficacy of PG01037 was correlated with the sensitivity of the D3/D2R agonist quinpirole to elicit yawning. These data suggest (1) that efficacy of D3R compounds in decreasing drug choice is greater in subjects with lower D3R, perhaps suggesting that it is percent occupancy that is the critical variable in determining efficacy and (2) differences in D3R activity in chronic cocaine vs. MA users. Although tolerance developed to the effects of PG01037 treatment on cocaine choice, tolerance did not develop to the disruptive effects on food-maintained responding. These findings suggest that combination treatments that decrease cocaine-induced elevations in DA may enhance the efficacy of D3R antagonists on cocaine self-administration.

Effects Of Buspirone and the Dopamine D3 Receptor Compound PG619 On Cocaine and Methamphetamine Self-Administration In Rhesus Monkeys Using A Food-Drug Choice Paradigm John WS, Banala AK, Newman AH, Nader MA. Psychopharmacology (Berl). 2015 Apr; 232(7): 1279-1289. doi: 10.1007/s00213-014-3760-6. Epub 2014 Oct 21.
The dopamine (DA) D2 and D3 receptors have been associated with cocaine abuse. A recent study with the D3 receptor (D3R) partial agonist PG619 found that it attenuated cocaine-induced

reinstatement and the D2-like receptor antagonist buspirone has shown positive outcomes in two studies of cocaine abuse in monkeys. However, a recent clinical trial indicated that buspirone did not improve abstinence in treatment-seeking cocaine abusers. The objective of the study was to examine PG619 and buspirone under a food-drug choice paradigm in order to better model the clinical findings. In addition, the authors extended the characterization of both compounds to include methamphetamine (MA) self-administration (SA). Six adult male rhesus monkeys were trained to respond under a concurrent food (1.0-g pellets) and drug (0.01-0.3 mg/kg/injection cocaine or MA) choice paradigm in which complete SA dose-response curves were determined each session (N = 3/group). Monkeys received 5 days of treatment with either PG619 (0.1-3.0 mg/kg, i.v.) or buspirone (0.01-1.0 mg/kg, i.m.). In a follow-up study, the SA doses were reduced (0.003-0.1 mg/kg/injection) to increase reinforcement frequency and buspirone was retested. PG619 did not affect cocaine or MA choice, while buspirone increased low-dose cocaine choice. Changing the SA doses increased the number of reinforcers received each session, but buspirone did not decrease drug choice. Consistent with clinical findings, these results do not support the use of buspirone for psychostimulant abuse and suggest that food-drug choice paradigms may have greater predictive validity than the use of other schedules of reinforcement.

Simultaneous Inhibition Of Fatty Acid Amide Hydrolase (FAAH) and Monoacylglycerol Lipase (MAGL) Shares Discriminative Stimulus Effects With Δ9-THC In Mice Hruba L, Seillier A, Zaki A, Cravatt BF, Lichtman AH, Giuffrida A, McMahon LR. J Pharmacol Exp Ther. 2015 Feb 24. pii: jpet.115.222836. [Epub ahead of print].
Monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH) inhibitors exert pre-clinical effects indicative of therapeutic potential (i.e., analgesia). However, the extent to which MAGL and FAAH inhibitors produce unwanted effects remains unclear. Here, FAAH and MAGL inhibition was examined separately and together in a Δ9-tetrahydrocannabinol (Δ9-THC; 5.6 mg/kg i.p.) discrimination assay predictive of subjective effects associated with cannabis use, and the relative contribution of N-arachidonoyl ethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) in the prefrontal cortex, hippocampus, and caudate putamen to those effects was examined. Δ9-THC dose-dependently increased Δ9-THC appropriate responses (ED50 value = 3.1 mg/kg), whereas the FAAH inhibitors PF-3845 and URB597 or a MAGL inhibitor JZL184 alone did not substitute for the Δ9-THC discriminative stimulus. The non-selective FAAH/MAGL inhibitors SA-57 and JZL195 fully substituted for Δ9-THC with ED50 values equal to 2.7 and 21.8 mg/kg, respectively. Full substitution for Δ9-THC also was produced by a combination of JZL184 and PF-3845, but not by a combination of JZL184 and URB597 (i.e., 52% maximum). The CB1 receptor antagonist rimonabant attenuated the discriminative stimulus effects of Δ9-THC, SA-57, JZL195, and the combined effects of JZL184 and PF-3845. Full substitution for the Δ9-THC discriminative stimulus occurred only when both 2-AG and AEA were significantly elevated, and the patterns of increased endocannabinoid content were similar among brain regions. Overall, these results suggest that increasing both endogenous 2-AG and AEA produces qualitatively unique effects (i.e., the subjective effects of cannabis) that are not obtained from increasing either 2-AG or AEA separately

Effects Of Environmental Manipulations and Treatment With Bupropion and Risperidone On Choice Between Methamphetamine and Food In Rhesus Monkeys Banks ML, Blough BE. Neuropsychopharmacology. 2015 Mar 6. doi: 10.1038/npp.2015.63. [Epub ahead of print].
Preclinical and human laboratory choice procedures have been invaluable in improving our knowledge of the neurobiological mechanisms of drug reinforcement and in the drug development

process for candidate medications to treat drug addiction. However, little is known about the neuropharmacological mechanisms of methamphetamine vs. food choice. The aims of this study were to develop a methamphetamine vs. food choice procedure and determine treatment effects with two clinically relevant compounds: the monoamine uptake inhibitor bupropion and the dopamine antagonist risperidone. Rhesus monkeys (n=6) responded under a concurrent schedule of food delivery (1-g pellets, fixed-ratio (FR) 100 schedule) and intravenous methamphetamine injections (0-0.32 mg/kg/injection, FR10 schedule) during 7-day bupropion (0.32-1.8 mg/kg/h) and risperidone (0.001-0.0056 mg/kg/h) treatment periods. For comparison, effects of removing food pellets or methamphetamine injections and FR response requirement manipulations were also examined. Under saline treatment conditions, food was preferred over no methamphetamine or small unit methamphetamine doses (0.01-0.032 mg/kg/injection). Larger methamphetamine doses resulted in greater methamphetamine preference and 0.32 mg/kg/injection methamphetamine maintained near exclusive preference. Removing food availability increased methamphetamine choice, whereas removing methamphetamine availability decreased methamphetamine choice. Methamphetamine choice was not significantly altered when the FR response requirements for food and drug were the same (FR100:FR100 or FR10:FR10). Risperidone treatment increased methamphetamine choice, whereas bupropion treatment did not alter methamphetamine choice up to doses that decreased rates of operant behavior. Overall, these negative results with bupropion and risperidone are concordant with previous human laboratory and clinical trials and support the potential validity of this preclinical methamphetamine vs. food choice model.

A Generalized Matching Law Analysis Of Cocaine VS. Food Choice In Rhesus Monkeys: Effects Of Candidate 'Agonist-Based' Medications On Sensitivity To Reinforcement Hutsell BA, Negus SS, Banks ML. Drug Alcohol Depend. 2015 Jan 1;146:52-60. doi: 10.1016/j.drugalcdep.2014.11.003. Epub 2014 Nov 20.

The authors have previously demonstrated reductions in cocaine choice produced by either continuous 14-day phendimetrazine and d-amphetamine treatment or removing cocaine availability under a cocaine vs. food choice procedure in rhesus monkeys. The aim of the present investigation was to apply the concatenated generalized matching law (GML) to cocaine vs. food choice dose-effect functions incorporating sensitivity to both the relative magnitude and price of each reinforcer. The authors' goal was to determine potential behavioral mechanisms underlying pharmacological treatment efficacy to decrease cocaine choice. A multi-model comparison approach was used to characterize dose- and time-course effects of both pharmacological and environmental manipulations on sensitivity to reinforcement. GML models provided an excellent fit of the cocaine choice dose-effect functions in individual monkeys. Reductions in cocaine choice by both pharmacological and environmental manipulations were principally produced by systematic decreases in sensitivity to reinforcer price and non-systematic changes in sensitivity to reinforcer magnitude. The modeling approach used provides a theoretical link between the experimental analysis of choice and pharmacological treatments being evaluated as candidate 'agonist-based' medications for cocaine addiction. The analysis suggests that monoamine releaser treatment efficacy to decrease cocaine choice was mediated by selectively increasing the relative price of cocaine. Overall, the net behavioral effect of these pharmacological treatments was to increase substitutability of food pellets, a nondrug reinforcer, for cocaine.

Supraspinal Actions Of N/OFQ, Morphine and Substance P In Regulating Pain and Itch in Nonhuman Primates Ding H, Hayashida K, Suto T, Sukhtankar DD, Kimura M, Mendenhall V, Ko MC. Br J Pharmacol. 2015 Mar 5. doi: 10.1111/bph.13124. [Epub ahead of print].
Nociceptin/orphanin FQ (N/OFQ) peptide (NOP) receptor agonists display a promising analgesic profile in preclinical studies. However, supraspinal N/OFQ produced hyperalgesia in rodents and such an effect has not been addressed in primates. Thus, the aim of this study was to investigate the effects of centrally administered ligands on regulating pain and itch in nonhuman primates. In particular, nociceptive thresholds affected by intracisternal N/OFQ were compared to morphine and substance P, known to provide analgesia and mediate hyperalgesia, respectively, in humans. An intrathecal catheterization was established to enable intracisternal and lumbar intrathecal administration in awake and unanesthetized rhesus monkeys. Nociceptive responses were measured by using the warm water tail-withdrawal assay. Itch scratching responses were scored from video tapes recording behavioral activities of monkeys in their home cages. Antagonist studies were conducted to validate the receptor mechanisms underlying intracisternally-elicited behavioral responses. Intracisternal morphine 100 nmol elicited more head scratches as compared to those of intrathecal morphine. Distinct dermatomal scratching locations between the two routes suggest a corresponding activation of supraspinal and spinal mu opioid receptors. Unlike intracisternal substance P-induced hyperalgesia, intracisternal N/OFQ 100 nmol produced NOP receptor-mediated antinociceptive effects; both peptides did not increase scratching responses. Collectively, these results demonstrate differential actions of ligands in the primate supraspinal region in regulating pain and itch. This study not only improves scientific understanding of the N/OFQ-NOP receptor system in pain processing, but also supports the therapeutic potential of NOP-related ligands as analgesics.

Biochemical Estimation Of Noncompliance With Smoking Of Very Low Nicotine Content Cigarettes Benowitz N, Nardone N, Hatsukami D, Donny E. Cancer Epidemiol Biomarkers Prev. 2015; 24(2): 331-335.
The reduction of the nicotine content of cigarettes to non-addicting levels is a potential federal regulatory intervention to reduce the prevalence of cigarette smoking and related disease. Many clinical trials on the effects and safety of nicotine reduction are ongoing. An important methodologic concern is noncompliance with reduced nicotine content cigarettes in the context of freely available conventional cigarettes. The authors propose two approaches using biomarkers to estimate noncompliance in smokers of very low nicotine content (VLNC) cigarettes in a clinical trial. Data from 50 subjects in a study of gradual nicotine reduction were analyzed. Using plasma cotinine concentrations measured at baseline and while smoking VLNC cigarettes, the authors compared within-subject ratios of plasma cotinine comparing usual brand to VLNC in relation to nicotine content of these cigarettes. In another approach, they used nicotine pharmacokinetic data to estimate absolute plasma cotinine/cigarettes per day (CPD) threshold values for compliance based on the nicotine content of VLNC. The two approaches showed concordance, indicating at least 60% noncompliance with smoking VLNC. In a sensitivity analysis assuming extreme compensation and extreme values for nicotine metabolic parameters, noncompliance was still at least 40%, much higher than self-reported noncompliance. Biomarker analysis demonstrates a high degree of noncompliance with smoking VLNC cigarettes, indicating that smokers are supplementing these with conventional cigarettes. The authors propose a practical approach to assessing compliance with smoking VLNC in clinical trials of nicotine reduction.

A Translational Investigation Targeting Stress-reactivity and Prefrontal Cognitive Control With Guanfacine For Smoking Cessation McKee S, Potenza M, Kober H, Sofuoglu M, Arnsten A, Picciotto M, Weinberger A, Ashare R, Sinha R. J Psychopharmacol. 2015; 29(3): 300-311. Stress and prefrontal cognitive dysfunction have key roles in driving smoking; however, there are no therapeutics for smoking cessation that attenuate the effects of stress on smoking and enhance cognition. Central noradrenergic pathways are involved in stress-induced reinstatement to nicotine and in the prefrontal executive control of adaptive behaviors. The authors used a novel translational approach employing a validated laboratory analogue of stress-precipitated smoking, functional magnetic resonance imaging (fMRI), and a proof-of-concept treatment period to evaluate whether the noradrenergic α2a agonist guanfacine (3 mg/day) versus placebo (0 mg/day) reduced stress-precipitated smoking in the laboratory, altered cortico-striatal activation during the Stroop cognitive-control task, and reduced smoking following a quit attempt. In nicotine-deprived smokers (n=33), stress versus a neutral condition significantly decreased the latency to smoke, and increased tobacco craving, ad-libitum smoking, and systolic blood pressure in placebo-treated subjects, and these effects were absent or reduced in guanfacine-treated subjects. Following stress, placebo-treated subjects demonstrated decreased cortisol levels whereas guanfacine-treated subjects demonstrated increased levels. Guanfacine, compared with placebo, altered prefrontal activity during a cognitive-control task, and reduced cigarette use but did not increase complete abstinence during treatment. These preliminary laboratory, neuroimaging, and clinical outcome data were consistent and complementary and support further development of guanfacine for smoking cessation.

UGT1A and UGT2B Genetic Variation Alters Nicotine and Nitrosamine Glucuronidation In European and African American Smokers Wassenaar C, Conti D, Das S, Chen P, Cook E, Ratain M, Benowitz N, Tyndale R. Cancer Epidemiol Biomarkers Prev. 2015; 24(1): 94-104. Identifying sources of variation in the nicotine and nitrosamine metabolic inactivation pathways is important to understanding the relationship between smoking and cancer risk. Numerous UGT1A and UGT2B enzymes are implicated in nicotine and nitrosamine metabolism in vitro; however, little is known about their roles in vivo. Within UGT1A1, UGT1A4, UGT1A9, UGT2B7, UGT2B10, and UGT2B17, 47 variants were genotyped, including UGT2B10*2 and UGT2B17*2. The association between variation in these UGTs and glucuronidation activity within European and African American current smokers (n = 128), quantified as urinary ratios of the glucuronide over unconjugated compound for nicotine, cotinine, trans-3'-hydroxycotinine, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), was investigated in regression models assuming a dominant effect of variant alleles. Correcting for multiple testing, three UGT2B10 variants were associated with cotinine glucuronidation, rs2331559 and rs11726322 in European Americans and rs835309 in African Americans ($P \leq 0.0002$). Additional variants predominantly in UGT2B10 were nominally associated with nicotine ($P = 0.008$-0.04) and cotinine ($P = <0.001$-0.02) glucuronidation in both ethnicities in addition to UGT2B10*2 in European Americans ($P = 0.01$, $P < 0.001$). UGT2B17*2 ($P = 0.03$) in European Americans and UGT2B7 variants ($P = 0.02$-0.04) in African Americans were nominally associated with 3HC glucuronidation. UGT1A ($P = 0.007$-0.01), UGT2B10 ($P = 0.02$), and UGT2B7 ($P = 0.02$-0.03) variants in African Americans were nominally associated with NNAL glucuronidation. Findings from this initial in vivo study support a role for multiple UGTs in the glucuronidation of tobacco-related compounds in vivo, in particular UGT2B10 and cotinine glucuronidation. Findings also provide insight into ethnic differences in

glucuronidation activity, which could be contributing to ethnic disparities in the risk for smoking-related cancers.

Weak Ventral Striatal Responses To Monetary Outcomes Predict An Unwillingness To Resist Cigarette Smoking Wilson S, Delgado M, McKee S, Grigson P, MacLean R, Nichols T, Henry S. Cogn Affect Behav Neurosci. 2014; 14(4): 1196-1207.
As a group, cigarette smokers exhibit blunted subjective, behavioral, and neurobiological responses to nondrug incentives and rewards, relative to nonsmokers. Findings from recent studies suggest, however, that there are large individual differences in the devaluation of nondrug rewards among smokers. Moreover, this variability appears to have significant clinical implications, since reduced sensitivity to nondrug rewards is associated with poorer smoking cessation outcomes. Currently, little is known about the neurobiological mechanisms that underlie these individual differences in the responsiveness to nondrug rewards. Here, the authors tested the hypothesis that individual variability in reward devaluation among smokers is linked to the functioning of the striatum. Specifically, functional magnetic resonance imaging was used to examine variability in the neural response to monetary outcomes in nicotine-deprived smokers anticipating an opportunity to smoke-circumstances found to heighten the devaluation of nondrug rewards by smokers in prior work. The authors also investigated whether individual differences in reward-related brain activity in those expecting to have access to cigarettes were associated with the degree to which the same individuals subsequently were willing to resist smoking in order to earn additional money. The key finding was that deprived smokers who exhibited the weakest response to rewards (i.e., monetary gains) in the ventral striatum were least willing to refrain from smoking for monetary reinforcement. These results provide evidence that outcome-related signals in the ventral striatum serve as a marker for clinically meaningful individual differences in reward-motivated behavior among nicotine-deprived smokers.

Compensatory Smoking From Gradual and Immediate Reduction In Cigarette Nicotine Content Hatsukami D, Donny E, Koopmeiners J, Benowitz N. Cancer Epidemiol Biomarkers Prev. 2015; 24(2): 472-476.
Reducing the addictiveness of cigarettes by reducing their nicotine content can potentially have a profound impact on public health. Two different approaches to nicotine reduction have been proposed: gradual and immediate. To determine if either of these approaches results in significant compensatory smoking behavior, which might lead to safety concerns, the authors performed a secondary analysis of data from studies that have utilized these two approaches. The number of cigarettes smoked per day, carbon monoxide exposure, and cotinine levels in plasma or urine were assessed while participants smoked reduced nicotine content cigarettes and compared with when they smoked their usual brand cigarettes. The results showed that in general, these two approaches led to minimal compensatory smoking and reduced levels of cotinine over the course of the experimental period, suggesting that neither of these approaches poses a major safety concern.

Organic Cation Transporter Variation and Response To Smoking Cessation Therapies
Bergen A, Javitz H, Krasnow R, Michel M, Nishita D, Conti, D, Edlund C, Kwok PY, McClure J, Kim R, Hall S, Tyndale R, Baker T, Benowitz, N, Swan G. Nicotine Tob Res. 2014; 16(12): 1638-1646.
The authors evaluated chr6q25.3 organic cation transporter gene (SLC22A1, SLC22A2, SLC22A3) variation and response to smoking cessation therapies. The corresponding proteins are low-affinity

transporters of choline, acetylcholine and monoamines, and smoking cessation pharmacotherapies expressed in multiple tissues. The authors selected 7 common polymorphisms for mega-regression analysis. They assessed additive model association of polymorphisms with 7-day point prevalence abstinence overall and by assigned pharmacotherapy at end of treatment and at 6 months among European-ancestry participants of 7 randomized controlled trials adjusted for demographic, population genetic, and trial covariates. Initial results were obtained in 6 trials with 1,839 participants. Nominally statistically significant associations of 2 SLC22A2 polymorphisms were observed: (1) with rs316019 at 6 months, overall ([c.808T>G; p.Ser270Ala], OR = 1.306, 95% CI = 1.034-1.649, p = .025), and among those randomized to nicotine replacement therapy (NRT) (OR = 1.784, 95% CI = 1.072-2.970, p = .026); and (2) with rs316006 (c.1502-529A>T) among those randomized to varenicline (OR = 1.420, 95% CI = 1.038-1.944, p = .028, OR = 1.362, 95% CI = 1.001-1.853, p = .04) at end of treatment and 6 months. Individuals randomized to NRT from a seventh trial were genotyped for rs316019; rs316019 was associated with a nominally statistically significant effect on abstinence overall at 6 months among 2,233 participants (OR = 1.249, 95% CI = 1.007-1.550, p = .043). The functional OCT2 Ser270Ala polymorphism is nominally statistically significantly associated with abstinence among European-ancestry treatment-seeking smokers after adjustments for pharmacotherapy, demographics, population genetics, and without adjustment for multiple testing of 7 SNPs. Replication of these preliminary findings in additional randomized controlled trials of smoking cessation therapies and from multiple continental populations would describe another pharmacogenetic role for SLC22A2/OCT2.

Bupropion For the Treatment Of Methamphetamine Dependence In Non-Daily Users: A Randomized, Double-Blind, Placebo-Controlled Trial Anderson AL, Li SH, Markova D, Holmes TH, Chiang N, Kahn R, Campbell J, Dickerson DL, Galloway GP, Haning W, Roache JD, Stock C, Elkashef AM. Drug Alcohol Depend. 2015 Feb 7. pii: S0376-8716(15)00056-3. doi: 10.1016/j.drugalcdep.2015.01.036. [Epub ahead of print]
Bupropion was tested for efficacy to achieve methamphetamine (MA) abstinence in dependent, non-daily users. A randomized, double-blind, placebo-controlled trial, with 12-week treatment and 4-week follow-up, was conducted with 204 treatment-seeking participants having MA dependence per DSM-IV, who used MA on a less-than-daily basis. 104 were randomized to matched placebo and 100 to bupropion, sustained-release 150mg, twice daily. Participants were seen three times weekly to obtain urine for MA and bupropion assays, study assessments, and thrice weekly, 90-min, group psychotherapy. There was no biomarker for placebo adherence. The primary outcome was achievement of abstinence throughout the last two weeks of treatment; 'success' requiring at least two urine samples during each of Weeks 11 and 12, and all samples MA-negative (<300ng/mL). Bupropion and placebo groups did not differ significantly in the percentage achieving abstinence for the last 2 weeks of treatment (chi-square, p=0.32). Subgroup analysis of participants with lower baseline MA use (≤18 of last 30 days before consent) also revealed no difference in success between groups (p=0.73). Medication adherence per protocol (detectable bupropion, >5ng/mL, in ≥50% of urine samples from Study Weeks 1-10 and ≥66% of urine samples from Weeks 11 to 12) was achieved by 47% of participants taking bupropion. These data indicate that bupropion did not increase abstinence in dependent participants who were using MA less-than-daily. Medication non-adherence was a limitation in this trial. Psychosocial therapy remains the mainstay of treatment for MA dependence. Further research on subgroups who may respond to bupropion may be warranted.

Naltrexone and Bupropion, Alone Or Combined, Do Not Alter the Reinforcing Effects Of Intranasal Methamphetamine Stoops WW, Pike E, Hays LR, Glaser PE, Rush CR. Pharmacol Biochem Behav. 2015 Feb; 129[Epub ahead of print]c45-50.
Naltrexone and bupropion, when administered alone in clinical trials, modestly reduce amphetamine use. Whether combining these drugs would result in greater reductions in methamphetamine taking relative to either drug alone is undetermined. This study examined the influence of naltrexone, bupropion and a naltrexone-bupropion combination on methamphetamine self-administration in humans. Seven subjects reporting recent illicit stimulant use completed a placebo-controlled, crossover, double-blind study in which the reinforcing, subject-rated and physiological effects of intranasal methamphetamine (0, 10 and 30 mg) were assessed during maintenance on placebo, naltrexone (50 mg), bupropion (300 mg/day), and naltrexone combined with bupropion. Methamphetamine maintained responding and produced prototypic subjective and physiological effects (e.g., increased ratings of good effects, elevated systolic blood pressure). Maintenance doses were well tolerated and generally devoid of effects. No maintenance condition reduced methamphetamine self-administration or systematically altered the subject-rated effects of methamphetamine. These outcomes demonstrate the robust behavioral effects of methamphetamine that could make it resistant to pharmacological manipulation. Although these outcomes indicate that this combination may be ineffective for managing methamphetamine use disorder, future work should evaluate longer maintenance dosing, individuals with different levels of amphetamine use, adding this combination to a behavioral platform and other pharmacotherapy combinations for reducing methamphetamine use.

Bupropion-Varenicline Interactions and Nicotine Self-Administration Behavior In Rats Hall B, Slade, S, Wells C, Rose J, Levin E. Pharmacol Biochem Behav. 2015; 130: 84-89.
Varenicline and bupropion each have been shown to significantly improve cessation of tobacco addiction in humans. They act through different mechanisms and the question about the potential added efficacy with their combined used has arisen. Preclinical animal models of nicotine addiction can help with the evaluation of this combined approach and what dose combinations of varenicline and bupropion may be useful for enhancing tobacco cessation. In this study, the authors investigated the interacting dose-effect functions of varenicline and bupropion in a rat model of nicotine self-administration. Young adult female Sprague-Dawley rats were allowed to self-administer nicotine in 1-h sessions under an FR1 reinforcement schedule. Varenicline (0.3, 1.3mg/kg) and bupropion (8.33, 25, 75mg/kg) were administered alone or together 15min before each session. The vehicle saline was the control. Higher doses of each drug alone reduced nicotine self-administration compared to control with reductions of 62% and 75% with 3mg/kg varenicline and 75mg/kg bupropion respectively. Lower dose varenicline which does not by itself reduce nicotine self-administration, significantly augmented bupropion effects. The 0.3mg/kg varenicline dose combined with the 25 and 75mg/kg bupropion doses caused greater reductions of nicotine self-administration than either dose of bupropion given alone. However, higher dose varenicline did not have this effect. Lower dose bupropion did not augment varenicline effects. Only the high bupropion dose significantly enhanced the varenicline effect. Likewise, combining 1mg/kg varenicline with 75mg/kg bupropion reduced self-administration to a greater extent than either dose alone. These results demonstrate that combination therapy with varenicline and bupropion may be more beneficial than monotherapy with either drug alone.

CYP2A6 Reduced Activity Gene Variants Confer Reduction In Lung Cancer Risk In African American Smokers--findings From Two Independent Populations Wassenaar C, Ye Y, Cai Q, Aldrich M, Knight J, Spitz M, Wu X, Blot W, Tyndale R. Carcinogenesis. 2015; 36(1): 99-103.
The authors investigated genetic variation in CYP2A6 in relation to lung cancer risk among African American smokers, a high-risk population. Previously, they found that CYP2A6, a nicotine/nitrosamine metabolism gene, was associated with lung cancer risk in European Americans, but smoking habits, lung cancer risk and CYP2A6 gene variants differ significantly between European and African ancestry populations. Herein, African American ever-smokers, drawn from two independent lung cancer case-control studies, were genotyped for reduced activity CYP2A6 alleles and grouped by predicted metabolic activity. Lung cancer risk in the Southern Community Cohort Study (n = 494) was lower among CYP2A6 reduced versus normal metabolizers, as estimated by multivariate conditional logistic regression [odds ratio (OR) = 0.44; 95% confidence interval (CI) = 0.26-0.73] and by unconditional logistic regression (OR = 0.62; 95% CI = 0.41-0.94). The association was replicated in an independent study from MD Anderson Cancer Center (n = 407) (OR = 0.64; 95% CI = 0.42-0.98), and pooling the studies yielded an OR of 0.64 (95% CI = 0.48-0.86). Exploratory analyses revealed a significant interaction between CYP2A6 genotype and sex on the risk for lung cancer (Southern Community Cohort Study: P = 0.04; MD Anderson: P = 0.03; Pooled studies: P = 0.002) with a CYP2A6 effect in men only. These findings support a contribution of genetic variation in CYP2A6 to lung cancer risk among African American smokers, particularly men, whereby CYP2A6 genotypes associated with reduced metabolic activity confer a lower risk of developing lung cancer.

E-Cigarettes and Smoking Cessation: Insights and Cautions From A Secondary Analysis Of Data From A Study Of Online Treatment-Seeking Smokers Pearson J, Stanton C, Cha S, Niaura R, Luta G,Graham A. Nicotine Tob Res. 2014; doi: 10.1093/ntr/ntu269.
Evidence from observational studies regarding the association between electronic cigarette (e-cigarette) use and cessation is mixed and difficult to interpret. Utilizing 2 analytic methods, this study illustrates challenges common in analyses of observational data, highlights measurement challenges, and reports associations between e-cigarette use and smoking cessation. Data were drawn from an ongoing web-based smoking cessation trial. The sample was comprised of 2,123 participants with complete 3-month follow-up data. Logistic regression models with and without entropy balancing to control for confounds were conducted to evaluate the association between e-cigarette use and 30-day cigarette smoking abstinence. At follow-up, 31.7% of participants reported using e-cigarettes to quit in the past 3 months. E-cigarette users differed from nonusers on baseline characteristics including cigarettes per day, Fagerstrom score, quit attempt in the past year, and previous use of e-cigarettes to quit. At follow-up, e-cigarette users made more quit attempts and employed more cessation aids than smokers who did not use e-cigarettes to quit. E-cigarette use was negatively associated with abstinence after adjustment for baseline characteristics; however, the association was not significant after additional adjustment for use of other cessation aids at 3 months. The magnitude and significance of the estimated association between e-cigarette use and cessation in this study were dependent upon the analytical approach. Observational studies should employ multiple analytic approaches to address threats to validity. Future research should employ better measures of patterns of and reasons for e-cigarette use, frequency of e-cigarette use, and concurrent use of cessation aids.

Nicotine Levels In Electronic Cigarette Refill Solutions: A Comparative Analysis Of Products From the US, Korea, and Poland Goniewicz ML, Gupta R, Lee YH, Reinhardt S, Kim S, Kim B, Kosmider L, Sobczak A. Int J Drug Policy. 2015; doi: 10.1016/j.drugpo.2015.01.020.
Electronic cigarettes vaporize nicotine dissolved in glycerine and/or propylene glycol (e-liquid). Due to a lack of regulations, e-liquids may contain inaccurately labelled nicotine levels. The authors' aim was to test nicotine levels in samples of e-liquids from three countries. They measured nicotine concentration in 32, 29 and 30 e-liquids purchased between 2013 and 2014 from locations in the United States (US), South Korea, and Poland, respectively. Nicotine concentration in the US products varied from 0 to 36.6mg/mL. Traces of nicotine were found in three US products labelled as 'nicotine free'. Two-thirds of South Korean products did not contain detectable amounts of nicotine, whereas nicotine concentration in other products varied from 6.4±0.7 to 150.3±7.9 (labelled as 'pure nicotine') mg/mL. In products from Poland, nicotine concentration varied from 0 to 24.7±0.1mg/mL. Overall, the authors found significant discrepancies (>20%) in the labelled nicotine concentrations in 19% of analysed e-liquids. Most of the analysed samples had no significant discrepancies in labelled nicotine concentrations and contained low nicotine levels. However some products labelled as 'nicotine-free' had detectable levels of the substance, suggesting insufficient manufacturing quality control. The authors identified a single product labelled as 'pure nicotine' which contained significantly higher concentration of the drug, increasing the risk of accidental poisoning. The study reveals the need for quality standards of these new nicotine containing products.

Safety and Pharmacokinetics Of Oral Cannabidiol When Administered Concomitantly With Intravenous Fentanyl In Humans Manini AF, Yiannoulos G, Bergamaschi MM, Hernandez S, Olmedo R, Barnes AJ, Winkel G, Sinha R, Jutras-Aswad D, Huestis MA, Hurd YL. J Addict Med. 2015 Mar; [Epub ahead of print].
Cannabidiol (CBD) is hypothesized as a potential treatment for opioid addiction, with safety studies an important first step for medication development. The authors determined CBD safety and pharmacokinetics when administered concomitantly with a high-potency opioid in healthy subjects. This double-blind, placebo-controlled cross-over study of CBD, co-administered with intravenous fentanyl, was conducted at the Clinical Research Center in Mount Sinai Hospital, a tertiary care medical center in New York City. Participants were healthy volunteers aged 21 to 65 years with prior opioid exposure, regardless of the route. Blood samples were obtained before and after 400 or 800 mg of CBD pretreatment, followed by a single 0. 5 (session 1) or 1.0 μg/kg (session 2) of intravenous fentanyl dose. The primary outcome was the Systematic Assessment for Treatment Emergent Events (SAFTEE) to assess safety and adverse effects. CBD peak plasma concentrations, time to reach peak plasma concentrations (tmax), and area under the curve (AUC) were measured. SAFTEE data were similar between groups without respiratory depression or cardiovascular complications during any test session. After low-dose CBD, tmax occurred at 3 and 1.5 hours in sessions 1 and 2, respectively. After high-dose CBD, tmax occurred at 3 and 4 hours in sessions 1 and 2, respectively. There were no significant differences in plasma CBD or cortisol (AUC P = NS) between sessions. Cannabidiol does not exacerbate adverse effects associated with intravenous fentanyl administration. Coadministration of CBD and opioids was safe and well tolerated. These data provide the foundation for future studies examining CBD as a potential treatment for opioid abuse.

Clinical Interpretation Of Opioid Tolerance Versus Opioid-Induced Hyperalgesia Chen L, Sein M, Vo T, Amhmed S, Zhang Y, Hilaire KS, Houghton M, Mao J. J Opioid Manag.; 10(6): 383-393.
Opioid analgesics are commonly used to manage moderate to severe pain. However, the long-term use of opioids could lead to opioid tolerance (OT) and opioid-induced hyperalgesia (OIH). Distinguishing OIH from OT would impact the practice of opioid therapy because opioid dose adjustment may differentially influence OT and OIH. Currently, there are no standard criteria of OT versus OIH causing considerable ambiguity in clinical interpretation and management of these conditions. The authors designed a practitioner-based survey consisting of 20 targeted questions. Answering these questions would require responders' actual clinical experiences with opioid therapy. The survey was conducted between 2011 and 2012 through direct mails or e-mails to 1,408 physicians who are currently practicing in the United States. The authors find that certain clinical characteristics (eg, increased pain despite opioid dose escalation) are often used by practitioners to make differential diagnosis of OT and OIH despite some overlap in their clinical presentation. A key difference in clinical outcome is that OT and OIH could be improved and exacerbated by opioid dose escalation, respectively. The survey results revealed a significant knowledge gap in some responders regarding differential diagnosis and management of OT and OIH. The results also identified several issues, such as opioid dose adjustment and clinical comorbidities related to OT and OIH, which require future patient-based studies.

Pharmacotherapies For Cannabis Dependence Marshall K, Gowing L, Ali R, Le Foll B. Cochrane Database Syst Rev. 2014 ; 12[Epub ahead of print]CD008940.
Cannabis is the most prevalent illicit drug in the world. Demand for treatment of cannabis use disorders is increasing. There are currently no pharmacotherapies approved for treatment of cannabis use disorders. The objective of this study was to assess the effectiveness and safety of pharmacotherapies as compared with each other, placebo or supportive care for reducing symptoms of cannabis withdrawal and promoting cessation or reduction of cannabis use. The authors searched the Cochrane Central Register of Controlled Trials (CENTRAL) (to 4 March 2014), MEDLINE (to week 3 February 2014), EMBASE (to 3 March 2014) and PsycINFO (to week 4 February 2014). They also searched reference lists of articles, electronic sources of ongoing trials and conference proceedings, and contacted selected researchers active in the area. Randomized and quasi-randomized controlled trials involving the use of medications to reduce the symptoms and signs of cannabis withdrawal or to promote cessation or reduction of cannabis use, or both, in comparison with other medications, placebo or no medication (supportive care) in participants diagnosed as cannabis dependent or who were likely to be dependent. The authors used standard methodological procedures expected by The Cochrane Collaboration. Two review authors assessed studies for inclusion and extracted data. All review authors confirmed the inclusion decisions and the overall process. The authors included 14 randomised controlled trials involving 958 participants. For 10 studies the average age was 33 years; two studies targeted young people; and age data were not available for two studies. Approximately 80% of study participants were male. The studies were at low risk of selection, performance, detection and selective outcome reporting bias. Three studies were at risk of attrition bias. All studies involved comparison of active medication and placebo. The medications included preparations containing tetrahydrocannabinol (THC) (two studies), selective serotonin reuptake inhibitor (SSRI) antidepressants (two studies), mixed action antidepressants (three studies), anticonvulsants and mood stabilizers (three studies), an atypical antidepressant (two studies), an anxiolytic (one study), a norepinephrine reuptake inhibitor (one study) and a

glutamatergic modulator (one study). One study examined more than one medication. Diversity in the medications and the outcomes reported limited the extent that analysis was possible. Insufficient data were available to assess the utility of most of the medications to promote cannabis abstinence at the end of treatment. There was moderate quality evidence that completion of treatment was more likely with preparations containing THC compared to placebo (RR 1.29, 95% CI 1.08 to 1.55; 2 studies, 207 participants, P = 0.006). There was some evidence that treatment with preparations containing THC was associated with reduced cannabis withdrawal symptoms and craving, but this latter outcome could not be quantified. For mixed action antidepressants compared with placebo (2 studies, 179 participants) there was very low quality evidence on the likelihood of abstinence from cannabis at the end of follow-up (RR 0.82, 95% CI 0.12 to 5.41), and moderate quality evidence on the likelihood of treatment completion (RR 0.93, 95% CI 0.71 to 1.21). For this same outcome there was very low quality evidence for the effects of SSRI antidepressants (RR 0.82, 95% CI 0.44 to 1.53; 2 studies, 122 participants), anticonvulsants and mood stabilizers (RR 0.78, 95% CI 0.42 to 1.46; 2 studies, 75 participants), and the atypical antidepressant, bupropion (RR 1.06, 95% CI 0.67 to 1.67; 2 studies, 92 participants). Available evidence on gabapentin (anticonvulsant) and N-acetylcysteine (glutamatergic modulator) was insufficient for quantitative estimates of their effectiveness, but these medications may be worth further investigation. There is incomplete evidence for all of the pharmacotherapies investigated, and for many of the outcomes the quality was downgraded due to small sample sizes, inconsistency and risk of attrition bias. The quantitative analyses that were possible, combined with general findings of the studies reviewed, indicate that SSRI antidepressants, mixed action antidepressants, atypical antidepressants (bupropion), anxiolytics (buspirone) and norepinephrine reuptake inhibitors (atomoxetine) are probably of little value in the treatment of cannabis dependence. Preparations containing THC are of potential value but, given the limited evidence, this application of THC preparations should be considered still experimental. Further studies should compare different preparations of THC, dose and duration of treatment, adjunct medications and therapies. The evidence base for the anticonvulsant gabapentin and the glutamatergic modulator N-acetylcysteine is weak, but these medications are also worth further investigation.

Naltrexone and Bupropion, Alone Or Combined, Do Not Alter the Reinforcing Effects Of Intranasal Methamphetamine Stoops WW, Pike E, Hays LR, Glaser PE, Rush CR. Pharmacol Biochem Behav. 2015 Feb; 129[Epub ahead of print] 45-50.
Naltrexone and bupropion, when administered alone in clinical trials, modestly reduce amphetamine use. Whether combining these drugs would result in greater reductions in methamphetamine taking relative to either drug alone is undetermined. This study examined the influence of naltrexone, bupropion and a naltrexone-bupropion combination on methamphetamine self-administration in humans. Seven subjects reporting recent illicit stimulant use completed a placebo-controlled, crossover, double-blind study in which the reinforcing, subject-rated and physiological effects of intranasal methamphetamine (0, 10 and 30 mg) were assessed during maintenance on placebo, naltrexone (50 mg), bupropion (300 mg/day), and naltrexone combined with bupropion. Methamphetamine maintained responding and produced prototypic subjective and physiological effects (e. g. , increased ratings of good effects, elevated systolic blood pressure). Maintenance doses were well tolerated and generally devoid of effects. No maintenance condition reduced methamphetamine self-administration or systematically altered the subject-rated effects of methamphetamine. These outcomes demonstrate the robust behavioral effects of methamphetamine that could make it resistant to pharmacological manipulation. Although these outcomes indicate that

this combination may be ineffective for managing methamphetamine use disorder, future work should evaluate longer maintenance dosing, individuals with different levels of amphetamine use, adding this combination to a behavioral platform and other pharmacotherapy combinations for reducing methamphetamine use.

Test-Retest Reliability Of Eye Tracking During the Visual Probe Task In Cocaine-Using Adults Marks KR, Pike E, Stoops WW, Rush CR. Drug Alcohol Depend. 2014 Dec; 145[Epub ahead of print] 235-237.
Stimuli associated with cocaine use capture attention. Evidence suggests that fixation time measured on the visual probe task is a valid measure of cocaine cue attentional bias. The aim of this experiment was to demonstrate the test-retest reliability of cocaine cue attentional bias as measured by fixation time during the visual probe task. In a within-subject, repeated-measures design, thirty-six non-treatment seeking cocaine-using adults completed a visual probe task with eye tracking. Participants displayed an attentional bias to cocaine-related images as measured by fixation time across two occasions ($F (1, 35) = 56. 5, p < 0. 0001$). A Pearson correlation indicated significant test-retest reliability for this effect ($r = 0. 51, p = 0. 001$). Response time failed to detect an attentional bias and test-retest reliability was low ($r = 0. 24, p = 0. 16$). Fixation time during the visual probe task is a reliable measure of cocaine cue attentional bias in cocaine-using adults across time.

A Comparison Of Impulsivity, Depressive Symptoms, Lifetime Stress and Sensation Seeking In Healthy Controls Versus Participants With Cocaine Or Methamphetamine Use Disorders Mahoney JJ, Thompson-Lake DG, Cooper K, Verrico CD, Newton TF, De La Garza R. J Psychopharmacol. 2015 Jan; 29(1): 50-56.
Previous research has focused on developing theories of addiction that may explain behavior in cocaine- and methamphetamine-dependent individuals. The primary goal of this report was to compare and contrast the prevalence of self-reported measures of impulsivity, depression, lifetime stress and sensation-seeking in healthy controls versus individuals with cocaine or methamphetamine use disorders. Twenty-nine individuals with cocaine use disorders and 31 individuals with methamphetamine use disorders were matched with 31 healthy control participants on several demographic variables. All participants were administered behavioral questionnaires including the Barrett Impulsiveness Scale (assessing impulsivity), Beck Depression Inventory II (assessing depression), Life Stressor Checklist-Revised (assessing lifetime stress) and the Impulsive Sensation Seeking Scale (assessing sensation-seeking). When compared to healthy controls, individuals with cocaine and methamphetamine use disorders had significantly higher levels of impulsivity and sensation-seeking. In addition, when compared to healthy controls, individuals with cocaine use disorders had significantly higher Beck Depression Inventory II scores, while individuals with methamphetamine use disorders had significantly higher Life Stressor Checklist-Revised scores. The results revealed that there were significantly higher levels of impulsivity, depression and sensation-seeking in cocaine users and significantly higher impulsivity, lifetime stress and sensation-seeking in methamphetamine users when compared to healthy controls.

Butyrylcholinesterase Levels and Subjective Effects Of Smoked Cocaine In Healthy Cocaine Users Askalsky P, Kalapatapu RK, Foltin RW, Comer SD. Am J Drug Alcohol Abuse. 2015 Mar; 41(2): 161-165.

Butyrylcholinesterase (BChE) is beginning to attract attention as a possible target for cocaine abuse treatment because of its role in metabolizing cocaine. The purpose of this analysis was to assess whether endogenous BChE levels are associated with the subjective effects of cocaine. Data from 28 participants in five inpatient cocaine self-administration studies were included in the present analysis. Four minutes after each smoked cocaine dose, participants rated their drug-related effects from 0-100 using a computerized self-report Visual Analogue Scale (VAS). The main outcome measures were nine change-in-VAS ratings between a baseline placebo dose and a 25-mg smoked cocaine dose. After controlling for age, sex, total years of cocaine use, total milligrams of cocaine administered before the 25-mg dose being analyzed, and baseline diastolic blood pressure, endogenous BChE was not significantly associated with any of the nine change-in-VAS ratings. Though BChE appears to be a possible target for cocaine abuse treatment, these data suggest that endogenous levels of BChE may not play a role in modifying the subjective effects of cocaine. Future larger studies of BChE in respect to the subjective effects produced by cocaine are needed to confirm or refute these findings.

Methamphetamine Self-Administration In Humans During D-Amphetamine Maintenance Pike E, Stoops WW, Hays LR, Glaser PE, Rush CR. J Clin Psychopharmacol. 2014 Dec; 34(6): 675-681.

Agonist replacement may be a viable treatment approach for managing stimulant use disorders. This study sought to determine the effects of D-amphetamine maintenance on methamphetamine self-administration in stimulant using human participants. The authors predicted that D-amphetamine maintenance would reduce methamphetamine self-administration. Eight participants completed the protocol, which tested 2 D-amphetamine maintenance conditions in counterbalanced order (0 and 40 mg/d). Participants completed 4 experimental sessions under each maintenance condition in which they first sampled 1 of 4 doses of intranasal methamphetamine (0, 10, 20, or 30 mg). Participants then had the opportunity to respond on a computerized progressive-ratio task to earn portions of the sampled methamphetamine dose. Subject-rated drug effect and physiological measures were completed at regular intervals prior to and after sampling methamphetamine. Methamphetamine was self-administered as an orderly function of dose regardless of the maintenance condition. Methamphetamine produced prototypical subject-rated effects on 12 items of the drug-effects questionnaires, 8 of which were attenuated by D-amphetamine maintenance (eg, increased ratings were attenuated on items such as Any Effect, Like Drug, and Willing to Take Again on the Drug Effect Questionnaire). Methamphetamine produced significant increases in systolic blood pressure, which were attenuated by D-amphetamine maintenance compared to placebo maintenance. Methamphetamine was well tolerated during D-amphetamine maintenance and no adverse events occurred. Although D-amphetamine attenuated some subject-rated effects of methamphetamine, the self-administration results are concordant with those of clinical trials showing that D-amphetamine did not reduce methamphetamine use. Unique pharmacological approaches may be needed for treating amphetamine use disorders.

Separate and Combined Effects Of the GABAa Positive Allosteric Modulator Diazepam and Δ^9-THC In Humans Discriminating Δ^9-THC Lile JA, Kelly TH, Hays LR. Drug Alcohol Depend. 2014 Oct; 143[Epub ahead of print] 141-148.
The authors' previous research suggested the involvement of γ-aminobutyric acid (GABA), in particular the GABAB receptor subtype, in the interoceptive effects of Δ(9)-tetrahydrocannabinol (Δ(9)-THC). The aim of the present study was to determine the potential involvement of the GABAA receptor subtype by assessing the separate and combined effects of the GABAA positive allosteric modulator diazepam and Δ(9)-THC using pharmacologically selective drug-discrimination procedures. Ten cannabis users learned to discriminate 30 mg oral Δ(9)-THC from placebo and then received diazepam (5 and 10mg), Δ(9)-THC (5, 15 and 30 mg) and placebo, alone and in combination. Self-report, task performance and physiological measures were also collected. Δ(9)-THC functioned as a discriminative stimulus, produced subjective effects typically associated with cannabinoids (e. g. , High, Stoned, Like Drug) and elevated heart rate. Diazepam alone impaired performance on psychomotor performance tasks and increased ratings on a limited number of self-report questionnaire items (e.g., Any Effect, Sedated), but did not substitute for the Δ(9)-THC discriminative stimulus or alter the Δ(9)-THC discrimination dose-response function. Similarly, diazepam had limited impact on the other behavioral effects of Δ(9)-THC. These results suggest that the GABAA receptor subtype has minimal involvement in the interoceptive effects of Δ(9)-THC, and by extension cannabis, in humans.

The Relationship Between Sleep and Drug Use Characteristics In Participants With Cocaine Or Methamphetamine Use Disorders Mahoney JJ, De La Garza R, Jackson BJ, Verrico CD, Ho A, Iqbal T, Newton TF. Psychiatry Res. 2014 Oct; 219(2): 367-371.
The goal of this project was to evaluate the relationship between self-reported sleep habits, daytime sleepiness, and drug use variables in individuals with cocaine and methamphetamine (METH) use disorders. Participants with a cocaine or meth use disorder completed questionnaires, including the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and a demographic/drug use form. Participants with a cocaine (N=51) or meth use disorder (N=85) were separated into those with either high or low sleep deficits. In participants with a cocaine use disorder, ANOVA revealed significantly higher ESS scores among those defined as "poor sleepers" (with a PSQI score >5) when compared to those defined as "good sleepers" (with a PSQI score ≤5). In addition, poor sleepers reported using cocaine for more days out of the past 30 when compared to good sleepers. Interestingly, good sleepers reported using more grams of cocaine/day compared to poor sleepers. In participants with a METH use disorder, ANOVA revealed significantly higher ESS scores among poor sleepers when compared to good sleepers. Finally, individuals with a METH use disorder that endorsed elevated daytime sleepiness also had significantly higher PSQI scores when compared to those with normal daytime sleepiness. The results indicate that drug use variables, such as recent and daily use, may affect sleep quality and daytime sleepiness in individuals with stimulant use disorders; however, further investigations (i. e. in cocaine and METH users that do not meet criteria for a cocaine or METH use disorder) must be conducted in order to provide more conclusive evidence of the impact these usage variables may have on these sleep characteristics.

RESEARCH ON THE MEDICAL CONSEQUENCES OF DRUG ABUSE AND CO-OCCURRING INFECTIONS

Chronic Administration Of Δ9-Tetrahydrocannabinol Induces Intestinal Anti-Inflammatory MicroRNA Expression During Acute Simian Immunodeficiency Virus Infection Of Rhesus Macaques Chandra LC, Kumar V, Torben W, Vande Stouwe C, Winsauer P, Amedee A, Molina PE, Mohan M. J Virol. 2015 Jan 15; 89(2):1168-1181. Epub 2014 Nov 5.
Recreational and medical use of cannabis among human immunodeficiency virus (HIV)-infected individuals has increased in recent years. In simian immunodeficiency virus (SIV)-infected macaques, chronic administration of Δ9-tetrahydrocannabinol (Δ9-THC) inhibited viral replication and intestinal inflammation and slowed disease progression. Persistent gastrointestinal disease/inflammation has been proposed to facilitate microbial translocation and systemic immune activation and promote disease progression. Cannabinoids including Δ9-THC attenuated intestinal inflammation in mouse colitis models and SIV-infected rhesus macaques. To determine if the anti-inflammatory effects of Δ9-THC involved differential microRNA (miRNA) modulation, the authors profiled miRNA expression at 14, 30, and 60 days postinfection (days p.i.) in the intestine of uninfected macaques receiving Δ9-THC (n=3) and SIV-infected macaques administered either vehicle (VEH/SIV; n=4) or THC (THC/SIV; n=4). Chronic Δ9-THC administration to uninfected macaques significantly and positively modulated intestinal miRNA expression by increasing the total number of differentially expressed miRNAs from 14 to 60 days p.i. At 60 days p.i., ~28% of miRNAs showed decreased expression in the VEH/SIV group compared to none showing decrease in the THC/SIV group. Furthermore, compared to the VEH/SIV group, THC selectively upregulated the expression of miR-10a, miR-24, miR-99b, miR-145, miR-149, and miR-187, previously been shown to target proinflammatory molecules. NOX4, a potent reactive oxygen species generator, was confirmed as a direct miR-99b target. A significant increase in NOX4+ crypt epithelial cells was detected in VEH/SIV macaques compared to the THC/SIV group. The authors speculate that miR-99b-mediated NOX4 downregulation may protect the intestinal epithelium from oxidative stress-induced damage. These results support a role for differential miRNA induction in THC-mediated suppression of intestinal inflammation. Whether similar miRNA modulation occurs in other tissues requires further investigation. Gastrointestinal (GI) tract disease/inflammation is a hallmark of HIV/SIV infection. Previously, the authors showed that chronic treatment of SIV-infected macaques with Δ9-tetrahydrocannabinol (Δ9-THC) increased survival and decreased viral replication and infection-induced gastrointestinal inflammation. Here, they show that chronic THC administration to SIV-infected macaques induced an anti-inflammatory microRNA expression profile in the intestine at 60 days p.i. These included several miRNAs bioinformatically predicted to directly target CXCL12, a chemokine known to regulate lymphocyte and macrophage trafficking into the intestine. Specifically, miR-99b was significantly upregulated in THC-treated SIV-infected macaques and confirmed to directly target NADPH oxidase 4 (NOX4), a reactive oxygen species generator known to damage intestinal epithelial cells. Elevated miR-99b expression was associated with a significantly decreased number of NOX4+ epithelial cells in the intestines of THC-treated SIV-infected macaques. Overall, these results show that selective upregulation of anti-inflammatory miRNA expression contributes to THC-mediated suppression of gastrointestinal inflammation and maintenance of intestinal homeostasis.

The Causal Effect Of Opioid Substitution Treatment On HAART Medication Refill Adherence Nosyk B, Min JE, Colley G, Lima VD, Yip B, Milloy M-JS, Wood E, Montaner JSG AIDS: Post Acceptance: March 23, 2015; doi:10.1097/QAD.0000000000000642.
People who inject drugs (PWID) account for roughly 13% of the prevalent HIV/AIDS population outside of sub-Saharan Africa, and access to opioid substitution treatment (OST) is limited in many settings globally. OST likely facilitates access to HAART, yet sparse evidence is available to support this hypothesis. The authors' objective was to determine the causal impact of OST exposure on HAART adherence among HIV-positive PWID in a Canadian setting. They executed a retrospective cohort study using linked population-level data for British Columbia, Canada (January 1996-March 2010). We considered HIV-positive PWID after meeting HAART initiation criteria. A marginal structural model was estimated on a monthly timescale using inverse probability of treatment weights. The primary outcome was 95% HAART adherence, according to pharmacy refill compliance. Exposure to OST was defined as 95% of OST receipt, and we controlled for a range of fixed and time-varying covariates. This study included 1852 (63.3%) HIV-positive PWID with a median follow-up of 5.5 years; 34% were female and 39% had previously accessed OST. The baseline covariate-adjusted odds of HAART adherence following OST exposure was 1.96 (95% confidence interval: 1.72-2.24), although the adjusted odds estimated within the marginal structural model was 1.68 (1.48-1.92). Findings were robust to sensitivity analyses on model specification. In a setting characterized by universal healthcare and widespread access to both office-based OST and HAART, OST substantially increased the odds of HAART adherence. This underlines the need to address barriers to OST globally to reduce the disease burden of both opioid dependence and HIV/AIDS.

Compartmentalized Replication Of R5 T Cell-Tropic HIV-1 In the Central Nervous System Early In the Course Of Infection Sturdevant CB, Joseph SB, Schnell G, Price RW, Swanstrom R, Spudich S. PLoS Pathog. 2015 Mar 26;11(3):e1004720. doi: 10.1371/ journal.ppat.1004720. eCollection 2015.
Compartmentalized HIV-1 replication within the central nervous system (CNS) likely provides a foundation for neurocognitive impairment and a potentially important tissue reservoir. The timing of emergence and character of this local CNS replication has not been defined in a population of subjects. The authors examined the frequency of elevated cerebrospinal fluid (CSF) HIV-1 RNA concentration, the nature of CSF viral populations compared to the blood, and the presence of a cellular inflammatory response (with the potential to bring infected cells into the CNS) using paired CSF and blood samples obtained over the first two years of infection from 72 ART-naïve subjects. Using single genome amplification (SGA) and phylodynamics analysis of full-length env sequences, the authors compared CSF and blood viral populations in 33 of the 72 subjects. Independent HIV-1 replication in the CNS (compartmentalization) was detected in 20% of sample pairs analyzed by SGA, or 7% of all sample pairs, and was exclusively observed after four months of infection. In subjects with longitudinal sampling, 30% showed evidence of CNS viral replication or pleocytosis/inflammation in at least one time point, and in approximately 16% of subjects we observed evolving CSF/CNS compartmentalized viral replication and/or a marked CSF inflammatory response at multiple time points suggesting an ongoing or recurrent impact of the infection in the CNS. Two subjects had one of two transmitted lineages (or their recombinant) largely sequestered within the CNS shortly after transmission, indicating an additional mechanism for establishing early CNS replication. Transmitted variants were R5 T cell-tropic. Overall, examination of the relationships between CSF viral populations, blood and CSF HIV-1 RNA

concentrations, and inflammatory responses suggested four distinct states of viral population dynamics, with associated mechanisms of local viral replication and the early influx of virus into the CNS. This study considerably enhances the generalizability of the authors' results and greatly expands our knowledge of the early interactions of HIV-1 in the CNS.

Novel Genetic Locus Implicated for HIV-1 Acquisition with Putative Regulatory Links to HIV Replication and Infectivity: A Genome-Wide Association Study Johnson EO, Hancock DB, Gaddis NC, Levy JL, Page G, Novak SP, Glasheen C, Saccone NL, Rice JP, Moreau MP, Doheny KF, Romm JM, Brooks AI, Aouizerat BE, Bierut LJ, Kral AH. PLoS One. 2015 Mar 18; 10(3):e0118149. doi: 10.1371/journal.pone.0118149. eCollection 2015.

Fifty percent of variability in HIV-1 susceptibility is attributable to host genetics. Thus identifying genetic associations is essential to understanding pathogenesis of HIV-1 and important for targeting drug development. To date, however, CCR5 remains the only gene conclusively associated with HIV acquisition. To identify novel host genetic determinants of HIV-1 acquisition, the authors conducted a genome-wide association study among a high-risk sample of 3,136 injection drug users (IDUs) from the Urban Health Study (UHS). In addition to being IDUs, HIV- controls were frequency-matched to cases on environmental exposures to enhance detection of genetic effects. The authors tested independent replication in the Women's Interagency HIV Study (N=2,533). They also examined publicly available gene expression data to link SNPs associated with HIV acquisition to known mechanisms affecting HIV replication/infectivity. Analysis of the UHS nominated eight genetic regions for replication testing. SNP rs4878712 in FRMPD1 met multiple testing correction for independent replication (P=1.38x10-4), although the UHS-WIHS meta-analysis p-value did not reach genome-wide significance (P=4.47x10-7 vs. P<5.0x10-8) Gene expression analyses provided promising biological support for the protective G allele at rs4878712 lowering risk of HIV: (1) the G allele was associated with reduced expression of FBXO10 (r=-0.49, P=6.9x10-5); (2) FBXO10 is a component of the Skp1-Cul1-F-box protein E3 ubiquitin ligase complex that targets Bcl-2 protein for degradation; (3) lower FBXO10 expression was associated with higher BCL2 expression (r=-0.49, P=8x10-5); (4) higher basal levels of Bcl-2 are known to reduce HIV replication and infectivity in human and animal in vitro studies. These results suggest new potential biological pathways by which host genetics affect susceptibility to HIV upon exposure for follow-up in subsequent studies.

CD4+ T Cell-Dependent Reduction In Hepatitis C Virus-Specific Neutralizing Antibody Responses Following Coinfection With Human Immunodeficiency Virus Bailey JR, Dowd KA, Snider AE, Osburn WO, Mehta SH, Kirk GD, Thomas DL, Ray SC. J Infect Dis. 2015 Mar 9. pii: jiv139. [Epub ahead of print].

HIV infection leads to lower rates of HCV clearance after acute infection, higher HCV viremia, and accelerated progression of HCV-related fibrosis. The mechanisms underlying this acceleration of HCV progression by HIV are poorly understood, but HIV-induced dysfunction in the anti-HCV humoral immune response may play a role. To define the effect of HIV coinfection on the anti-HCV antibody response, the authors measured anti-HCV envelope (E1E2) binding antibody titers, neutralizing antibody (nAb) titers, and neutralizing antibody breadth of serum from HCV-infected subjects isolated longitudinally before and after incident HIV infection. A significant reduction in HCV envelope-specific binding antibody and neutralizing antibody titers was detected in subjects with $CD4^+$ T cell counts of <350 cells/mm^3 after HIV infection, and subjects with $CD4^+$ T cell counts of <200 cells/mm^3 also showed a reduction in nAb breadth. Subjects who maintained ≥350

$CD4^+$ T cells/mm^3 displayed little to no decline in antibody levels. Depletion of $CD4^+$ T cells by HIV infection results in a global decline in the anti-HCV envelope antibody response, including binding antibody titers, neutralizing antibody titers, and neutralizing antibody breadth.

Transactional Sex and the HIV Epidemic Among Men Who Have Sex With Men (MSM): Results From A Systematic Review and Meta-Analysis Oldenburg CE, Perez-Brumer AG, Reisner SL, Mimiaga MJ. AIDS Behav. 2015 Feb; [Epub ahead of print].
Engagement in transactional sex has been hypothesized to increase risk of HIV among MSM, however conflicting evidence exists. The authors conducted a systematic review and meta-analysis comparing HIV prevalence among MSM who engaged in transactional sex to those who did not (33 studies in 17 countries; n = 78,112 MSM). Overall, transactional sex was associated with a significant elevation in HIV prevalence (OR 1.34, 95 % CI 1.11-1.62). Latin America (OR 2.28, 95 % CI 1.87-2.78) and Sub-Saharan Africa (OR 1.72, 95 % CI 1.02-2.91) were the only regions where this elevation was noted. Further research is needed to understand factors associated with sex work and subsequent HIV risk in Latin America and Sub-Saharan Africa.

Prevalence and Predictors Of Concurrent Sexual Partnerships In A Predominantly African American Population In Jackson, Mississippi Nunn A, MacCarthy S, Barnett N, Rose J, Chan P, Yolken A, Cornwall A, Chamberlain N, Barnes A, Riggins R, Moore E, Simmons D, Parker S, Mena L. AIDS Behav. 2014 Dec; 18(12): 2457-2468.
Concurrent sexual partnerships, or sexual partnerships that overlap in time, have been associated with HIV and sexually transmitted infections (STI). How best to measure concurrency and the personal characteristics and predictors of concurrency are not yet well understood. The authors compared two frequently used concurrency definitions, including a self-reported measure based on participant response regarding overlapping sex with partners, and the UNAIDS measure based on overlapping dates of last sex and intention to have sex again. The authors performed multivariable logistic regression analyses to identify socio-demographic, behavioral, and structural predictors of concurrency among 1,542 patients at an urban STI clinic in Jackson, Mississippi. Nearly half (44 %) reported concurrency based on self-reported sex with other partners, and 26 % reported concurrency according to the UNAIDS concurrency measure. Using the self-reported concurrency measure, the strongest predictors of concurrency were perceived partner concurrency, drug use at last sex, having more than 10 lifetime partners, and being recently incarcerated. Strongest predictors of concurrency using the UNAIDS measure were lifetime number of partners and perceived partner concurrency. Concurrency is highly prevalent in this population in the Deep South and social, structural and behavioral factors were important predictors of concurrency for both measures. Future research should use time anchored data collection methods and biomarkers to assess whether both definitions of concurrency are associated with HIV outcomes.

Post-Exposure Prophylaxis Use and Recurrent Exposure To HIV Among Men Who Have Sex With Men Who Use Crystal Methamphetamine Oldenburg CE, Jain S, Mayer KH, Mimiaga MJ. Drug Alcohol Depend. 2015 Jan; 146[Epub ahead of print] 75-80.
Men who have sex with men (MSM) who use crystal methamphetamine (CM) are at increased risk for HIV infection. Post-exposure prophylaxis (PEP) is a useful HIV prevention strategy if individuals are able to identify high-risk exposures and seek timely care, however to date there has been limited data on the use of PEP by CM users. Retrospective cohort study of all PEP prescriptions (N=1130 prescriptions among 788 MSM) at Fenway Community Health in Boston,

MA was undertaken. Multivariable models were used to assess the association between CM use during exposure (7.4% used CM during exposure) and chronically (7.4% of MSM were chronic CM users) and individual-level and event-level outcomes among MSM who used PEP at least once. Compared to those who had not used CM, MSM PEP users who used CM more frequently returned for repeat PEP (aOR 5.13, 95% CI 2.82 to 9.34) and were significantly more likely to seroconvert over the follow-up period (aHR 3.61, 95% CI 1.51 to 8.60). MSM who used CM had increased odds of unprotected anal intercourse as the source of exposure (aOR 2.12, 95% CI 1.16 to 3.87) and knowing that their partner was HIV infected (aOR 2.27, 95% CI 1.42 to 3.64). While MSM who use CM may have challenges accessing ART in general, these data highlight the fact that those who were able to access PEP subsequently remained at increased risk of HIV seroconversion. Counseling and/or substance use interventions during the PEP course should be considered for CM-using MSM.

Chronic Cocaine Use and Its Association With Myocardial Steatosis Evaluated By 1H Magnetic Resonance Spectroscopy In African Americans Lai S, Gerstenblith G, Li J, Zhu H, Bluemke DA, Liu CY, Zimmerman SL, Chen S, Lai H, Treisman G. J Addict Med.; 9(1): 31-39.
Cardiac steatosis is a manifestation of ectopic fat deposition and is associated with obesity. The impact of chronic cocaine use on obesity measures and on the relationship between obesity measures and cardiac steatosis is not well-characterized. The objectives of this study were to compare obesity measures in chronic cocaine users and nonusers, and to explore which factors, in addition to obesity measures, are associated with myocardial triglyceride in African Americans, using noninvasive magnetic resonance spectroscopy. Between June 2004 and January 2014, 180 healthy African American adults without HIV infection, hypertension, and diabetes were enrolled in an observational proton magnetic resonance spectroscopy and imaging study investigating factors associated with cardiac steatosis. Among these 180 participants, 80 were chronic cocaine users and 100 were nonusers. The median age was 42 (interquartile range, 34-47) years. Obesity measures trended higher in cocaine users than in nonusers. The median myocardial triglyceride was 0.6% (interquartile range, 0.4%-1.1%). Among the factors investigated, years of cocaine use, leptin, and visceral fat were independently associated with myocardial triglyceride. Body mass index and visceral fat, which were significantly associated with myocardial triglyceride in noncocaine users, were not associated with myocardial triglyceride content in cocaine users. This study shows (1) cocaine users may have more fat than nonusers and (2) myocardial triglyceride is independently associated with duration of cocaine use, leptin, and visceral fat in all subjects, whereas leptin and high-density lipoprotein cholesterol, but not visceral fat or body mass index, in cocaine users, suggesting that chronic cocaine use may modify the relationships between obesity measures and myocardial triglyceride.

Naturally Selected Hepatitis C Virus Polymorphisms Confer Broad Neutralizing Antibody Resistance Bailey JR, Wasilewski LN, Snider AE, El-Diwany R, Osburn WO, Keck Z, Foung SK, Ray SC. J Clin Invest. 2015 Jan; 125(1): 437-447.
For hepatitis C virus (HCV) and other highly variable viruses, broadly neutralizing mAbs are an important guide for vaccine development. The development of resistance to anti-HCV mAbs is poorly understood, in part due to a lack of neutralization testing against diverse, representative panels of HCV variants. Here, the authors developed a neutralization panel expressing diverse, naturally occurring HCV envelopes (E1E2s) and used this panel to characterize neutralizing breadth and resistance mechanisms of 18 previously described broadly neutralizing anti-HCV human mAbs.

The observed mAb resistance could not be attributed to polymorphisms in E1E2 at known mAb-binding residues. Additionally, hierarchical clustering analysis of neutralization resistance patterns revealed relationships between mAbs that were not predicted by prior epitope mapping, identifying 3 distinct neutralization clusters. Using this clustering analysis and envelope sequence data, the authors identified polymorphisms in E2 that confer resistance to multiple broadly neutralizing mAbs. These polymorphisms, which are not at mAb contact residues, also conferred resistance to neutralization by plasma from HCV-infected subjects. Together, the authors' method of neutralization clustering with sequence analysis reveals that polymorphisms at noncontact residues may be a major immune evasion mechanism for HCV, facilitating viral persistence and presenting a challenge for HCV vaccine development.

SERVICES RESEARCH

Screening and Brief Intervention For Drug Use In Primary Care: The ASPIRE Randomized Clinical Trial Saitz RR, Palfai TP, Cheng DM, Alford DP, Bernstein JA, Lloyd-Travaglini CA, Meli SM, Chaisson CE, Samet JH. JAMA. 2014 Aug 6, 312(5); 5012-5013.
The United States has invested substantially in screening and brief intervention for illicit drug use and prescription drug misuse, based in part on evidence of efficacy for unhealthy alcohol use. However, it is not a recommended universal preventive service in primary care because of lack of evidence of efficacy. To test the efficacy of 2 brief counseling interventions for unhealthy drug use (any illicit drug use or prescription drug misuse)—a brief negotiated interview (BNI) and an adaptation of motivational interviewing (MOTIV)—compared with no brief intervention. This 3-group randomized trial took place at an urban hospital-based primary care internal medicine practice; 528 adult primary care patients with drug use (Alcohol, Smoking, and Substance Involvement Screening Test [ASSIST] substance-specific scores of ≥4) were identified by screening between June 2009 and January 2012 in Boston, Massachusetts. Two interventions were tested: the BNI is a 10- to 15-minute structured interview conducted by health educators; the MOTIV is a 30- to 45-minute intervention based on motivational interviewing with a 20- to 30-minute booster conducted by master's-level counselors. All study participants received a written list of substance use disorder treatment and mutual help resources. Primary outcome was number of days of use in the past 30 days of the self-identified main drug as determined by a validated calendar method at 6 months. Secondary outcomes included other self-reported measures of drug use, drug use according to hair testing, ASSIST scores (severity), drug use consequences, unsafe sex, mutual help meeting attendance, and health care utilization. At baseline, 63% of participants reported their main drug was marijuana, 19% cocaine, and 17% opioids. At 6 months, 98% completed follow-up. Mean adjusted number of days using the main drug at 6 months was 12 for no brief intervention vs 11 for the BNI group (incidence rate ratio [IRR], 0.97; 95% CI, 0.77-1.22) and 12 for the MOTIV group (IRR, 1.05; 95% CI, 0.84-1.32; $P = .81$ for both comparisons vs no brief intervention). There were also no significant effects of BNI or MOTIV on any other outcome or in analyses stratified by main drug or drug use severity. Brief intervention did not have efficacy for decreasing unhealthy drug use in primary care patients identified by screening. These results do not support widespread implementation of illicit drug use and prescription drug misuse screening and brief intervention.

Cost-effectiveness Of Rapid Hepatitis C Virus (HCV) Testing and Simultaneous Rapid HCV and HIV Testing In Substance Abuse Treatment Programs Schackman BR, Leff JA, Barter DM, DiLorenzo MA, Feaster DJ, Metsch LR, Freedberg KA, Linas BP. Addiction. 2015; 110(1): 129-143.
The objective of this study was to evaluate the cost-effectiveness of rapid hepatitis C virus (HCV) and simultaneous HCV/HIV antibody testing in substance abuse treatment programs. The authors used a decision analytic model to compare the cost-effectiveness of no HCV testing referral or offer, off-site HCV testing referral, on-site rapid HCV testing offer and on-site rapid HCV and HIV testing offer. Base case inputs included 11% undetected chronic HCV, 0.4% undetected HIV, 35% HCV co-infection among HIV-infected, 53% linked to HCV care after testing antibody-positive and 67% linked to HIV care. Disease outcomes were estimated from established computer simulation models of HCV [Hepatitis C Cost-Effectiveness (HEP-CE)] and HIV [Cost-Effectiveness of Preventing AIDS Complications (CEPAC)].Data on test acceptance and costs were from a national randomized trial of HIV testing strategies conducted at 12 substance abuse treatment programs in

the United States. Lifetime costs (2011 US$) and quality-adjusted life years (QALYs) discounted at 3% annually; incremental cost-effectiveness ratios (ICERs).On-site rapid HCV testing had an ICER of $18,300/QALY compared with no testing, and was more efficient than (dominated) off-site HCV testing referral. On-site rapid HCV and HIV testing had an ICER of $64,500/QALY compared with on-site rapid HCV testing alone. In one- and two-way sensitivity analyses, the ICER of on-site rapid HCV and HIV testing remained <$100,000/QALY, except when undetected HIV prevalence was <0.1% or when we assumed frequent HIV testing elsewhere. The ICER remained <$100,000/ QALY in 91% of probabilistic sensitivity analyses. On-site rapid hepatitis C virus and HIV testing in substance abuse treatment programs is cost-effective at a <$100,000/quality-adjusted life year threshold.

Stigma, Discrimination, Treatment Effectiveness, and Policy: Public Views about Drug Addiction and Mental Illness Barry CL, McGinty EE, Pescosolido BA, Goldman HH. Psych Serv 2014; 65: 1260-1272.
Public attitudes about drug addiction and mental illness were compared. A Web-based national survey (N=709) was conducted to compare attitudes about stigma, discrimination, treatment effectiveness, and policy support in regard to drug addiction and mental illness. Respondents held significantly more negative views toward persons with drug addiction. More respondents were unwilling to have a person with drug addiction marry into their family or work closely with them. Respondents were more willing to accept discriminatory practices against persons with drug addiction, more skeptical about the effectiveness of treatments, and more likely to oppose policies aimed at helping them. The authors conclude that drug addiction is often treated as a subcategory of mental illness, and insurance plans group them together under the rubric of "behavioral health." Given starkly different public views about drug addiction and mental illness, advocates may need to adopt differing approaches to reducing stigma and advancing public policy.

Current Practices Of Screening For Incident Hepatitis C Virus (HCV) Infection Among HIV-infected, HCV-uninfected Individuals In Primary Care Freiman JM, Huang W, White LF, Geng EH, Hurt CB, Taylor LE, Overton ET, Cachay ER, Kitahata MM, Moore RD, Rodriguez B, Mayer KH, Linas BP. Clin Infect Dis. 2014; 59(12): 1686-1693.
Human immunodeficiency virus (HIV)-infected, hepatitis C virus (HCV)-uninfected patients are at risk for incident HCV infection, but little is known about screening practices for incident HCV among HIV-infected individuals in HIV primary care clinics. The authors used data from the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) to investigate historical trends in screening for incident HCV infection among HIV-infected patients who were HCV-uninfected at enrollment in care. They used descriptive measures and Poisson regression to identify factors associated with screening for HCV infection (using HCV antibody or RNA), performed temporal analyses to assess changes in screening over time, and investigated the frequency with which elevated alanine aminotransferase (ALT) levels were followed by diagnostic HCV testing. Among 17 090 patients registered at CNICS sites between 2000 and 2011, 14 534 (85%) received HCV antibody screening within 3 months of enrolling in care, and 9077 met all of the inclusion criteria. Only 55.6% ever received additional HCV screening. HCV screening increased over time, but not uniformly at all sites. Only 26.7% of first-time ALT elevations to >100 IU/L were followed up within 12 months by HCV antibody or RNA testing. Although most HIV-infected patients were screened for prevalent HCV infection at enrollment in care, only half who were HCV uninfected were screened again. Screening varied between sites, even when controlling for demographics and

risk behaviors. Patients with new ALT elevations to >100 IU/L were seldom assessed for incident HCV infection. Guidelines are needed to help HIV providers know whom to screen, how frequently to screen, and which screening test to use.

High Prevalence Of Non-fatal Overdose Among People Who Inject Drugs In Malaysia: Correlates Of Overdose And Implications For Overdose Prevention From A Cross-sectional Study Bazazi AR, Zelenev A, Fu JJ, Yee I, Kamarulzaman A, Altice FL. Int J Drug Policy. 2014.
Overdose is the leading cause of death among opioid users, but no data are available on overdose among people who inject drugs in Malaysia. The authors present the first estimates of the prevalence and correlates of recent non-fatal overdose among people who inject drugs in Malaysia. In 2010, 460 people who inject drugs were recruited using respondent-driven sampling (RDS) in Klang Valley to assess health outcomes associated with injection drug use. Self-reported history of non-fatal overdose in the previous 6 months was the primary outcome. Socio-demographic, behavioral and structural correlates of non-fatal overdose were assessed using multivariable logistic regression. All 460 participants used opioids and nearly all (99.1%) met criteria for opioid dependence. Most injected daily (91.3%) and were male (96.3%) and ethnically Malay (90.4%). Overall, 20% of participants had overdosed in the prior 6 months, and 43.3% had ever overdosed. The RDS-adjusted estimate of the 6-month period prevalence of overdose was 12.3% (95% confidence interval [CI] 7.9-16.6%). Having injected for more years was associated with lower odds of overdose (adjusted odds ratio [AOR] 0.6 per 5 years of injection, CI: 0.5-0.7). Rushing an injection from fear of the police nearly doubled the odds of overdose (AOR 1.9, CI: 1.9-3.6). Alcohol use was associated with recent non-fatal overdose (AOR 2.1, CI: 1.1-4.2), as was methamphetamine use (AOR 2.3, CI: 1.3-4.6). When adjusting for past-month drug use, intermittent but not daily methadone use was associated with overdose (AOR 2.8, CI: 1.5-5.9).This study reveals a large, previously undocumented burden of non-fatal overdose among people who inject drugs in Malaysia and highlights the need for interventions that might reduce the risk of overdose, such as continuous opioid substitution therapy, provision of naloxone to prevent fatal overdose, treatment of poly-substance use, and working with police to improve the risk environment.

Alcohol and Drug Treatment Involvement, 12-step Attendance and Abstinence: 9-year Cross-lagged Analysis Of Adults In An Integrated Health Plan Witbrodt J, Ye Y, Bond J, Chi F, Weisner C, Mertens J. J Subst Abuse Treat. 2014; 46(4): 412-419.
This study explored causal relationships between post-treatment 12-step attendance and abstinence at multiple data waves and examined indirect paths leading from treatment initiation to abstinence 9-years later. Adults (N = 1945) seeking help for alcohol or drug use disorders from integrated healthcare organization outpatient treatment programs were followed at 1-, 5-, 7- and 9-years. Path modeling with cross-lagged partial regression coefficients was used to test causal relationships. Cross-lagged paths indicated greater 12-step attendance during years 1 and 5 and were casually related to past-30-day abstinence at years 5 and 7 respectfully, suggesting 12-step attendance leads to abstinence (but not vice versa) well into the post-treatment period. Some gender differences were found in these relationships. Three significant time-lagged, indirect paths emerged linking treatment duration to year-9 abstinence. Conclusions are discussed in the context of other studies using longitudinal designs. For outpatient clients, results reinforce the value of lengthier treatment duration and 12-step attendance in year 1.

Dynamics and Control Of Ebola Virus Transmission In Montserrado, Liberia: A Mathematical Modelling Analysis Lewnard JA, Ndeffo Mbah ML, Alfaro-Murillo JA, Altice FL, Bawo L, Nyenswah TG, Galvani AP. Lancet Infect Dis. 2014; 14(12): 1189-1195.
A substantial scale-up in public health response is needed to control the unprecedented Ebola virus disease (EVD) epidemic in West Africa. Current international commitments seek to expand intervention capacity in three areas: new EVD treatment centers, case ascertainment through contact tracing, and household protective kit allocation. The authors aimed to assess how these interventions could be applied individually and in combination to avert future EVD cases and deaths. They developed a transmission model of Ebola virus that they fitted to reported EVD cases and deaths in Montserrado County, Liberia. The authors used this model to assess the effectiveness of expanding EVD treatment centers, increasing case ascertainment, and allocating protective kits for controlling the outbreak in Montserrado. They varied the efficacy of protective kits from 10% to 50%. They compared intervention initiation on Oct 15, 2014, Oct 31, 2014, and Nov 15, 2014. The status quo intervention was defined in terms of case ascertainment and capacity of EVD treatment centers on Sept 23, 2014, and all behavior and contact patterns relevant to transmission as they were occurring at that time. The primary outcome measure was the expected number of cases averted by Dec 15, 2014. The authors estimated the basic reproductive number for EVD in Montserrado to be 2·49 (95% CI 2·38-2·60). They expect that allocating 4800 additional beds at EVD treatment centers and increasing case ascertainment five-fold in November, 2014, can avert 77 312 (95% CI 68 400-85 870) cases of EVD relative to the status quo by Dec 15, 2014. Complementing these measures with protective kit allocation raises the expectation as high as 97,940 (90,096-105,606) EVD cases. If deployed by Oct 15, 2014, equivalent interventions would have been expected to avert 137,432 (129,736-145,874) cases of EVD. vIf delayed to Nov 15, 2014, the authors expect the interventions will at best avert 53,957 (46,963-60,490) EVD cases. The number of beds at EVD treatment centers needed to effectively control EVD in Montserrado substantially exceeds the 1700 pledged by the USA to West Africa. Accelerated case ascertainment is needed to maximize effectiveness of expanding the capacity of EVD treatment centers. Distributing protective kits can further augment prevention of EVD, but it is not an adequate stand-alone measure for controlling the outbreak. These findings highlight the rapidly closing window of opportunity for controlling the outbreak and averting a catastrophic toll of EVD cases and deaths.US National Institutes of Health.

Utilization and Outcomes Of Detoxification and Maintenance Treatment For Opioid Dependence In Publicly-funded Facilities In California, USA: 1991-2012 Nosyk B, Li L, Evans E, Urada D, Huang D, Wood E, Rawson R, Hser Y-I. Drug Alcohol Depend. 2014; 143: 149-157.
California treats the largest population of opioid dependent individuals in the USA and is among a small group of states that applies regulations for opioid treatment that are more stringent than existing federal regulations. The authors aim to characterize changes in patient characteristics and treatment utilization over time, and identify determinants of successful completion of detoxification and MMT retention in repeated attempts. State-wide administrative data was obtained from California Outcome Measurement System during the period: January 1st, 1991-March 31st, 2012. Short-term detoxification treatment and long-term maintenance treatment, primarily with methadone, was available to study participants. Mixed effects regression models were used to define determinants of successful completion of the detoxification treatment protocol (as classified by treatment staff) and duration of maintenance treatment. The study sample consisted of 237,709 unique individuals and 885,971 treatment episodes; 837% were detoxification treatment episodes in 1994, dropping to 40.5% in 2010. Among individuals accessing only detoxification, the adjusted

odds of success declined with each successive attempt (vs. 1st attempt: 2nd: OR: 0.679; 95% CI (0.610, 0.755); 3rd: 0.557 (0.484, 0.641); 4th: 0.526 (0.445, 0.622); 5th: 0.407 (0.334, 0.497); ≥6th: 0.339 (0.288, 0.399). For those ever accessing maintenance treatment, later subsequent attempts were longer in duration, and those with two or more prior attempts at detoxification had marginally longer subsequent maintenance episodes (hazard ratio: 0.97; 95% CI: 0.95, 0.99). Finally, only 10.9% of all detoxification episodes were followed by admission into maintenance treatment within 14 days. This study has revealed high rates of detoxification treatment for opioid dependence in California throughout the study period, and decreasing odds of success in repeated attempts at detoxification.

How Do Recovery Definitions Distinguish Recovering Individuals? Five Typologies
Witbrodt J, Kaskutas LA, Grella CE. Drug Alcohol Depend. 2015.
Six percent of American adults say they are "in recovery" from an alcohol or drug problem yet only a scant emergent literature has begun to ask how they define "recovery" or explored whether there is heterogeneity among their definitions. Secondary analysis of the "What is Recovery?" online survey employed latent class analysis (LCA) to identify typologies of study participants based on their actual endorsement of 39 recovery elements and to compare the composition of these typologies in terms of distinguishing personal characteristics. A five-class solution provided the best fit and conceptual representation for the recovery definitions. Classes were labeled 12-step traditionalist (n=4912); 12-step enthusiast (n=2014); secular (n=980); self-reliant (n=1040); and atypical (n=382) based on patterns of endorsement of the recovery elements. Abstinence, spiritual, and social interaction elements differentiated the classes most (as did age and recovery duration but to a lesser extent). Although levels and patterns of endorsement to the elements varied by class, a rank-ordering of the top 10 elements indicated that four elements were endorsed by all five classes: being honest with myself, handling negative feelings without using, being able to enjoy life, and process of growth and development. The results of the LCA demonstrate the diversity of meanings, and varying degrees of identification with, specific elements of recovery. As others have found, multiple constituents are invested in how recovery is defined and this has ramifications for professional, personal, and cultural processes related to how strategies to promote recovery are implemented

Cigarette Smoking During Substance Use Disorder Treatment: Secondary Outcomes From A National Drug Abuse Treatment Clinical Trials Network Study McClure EA, Campbell ANC, Pavlicova M, Hu M, Winhusen T, Vandrey RG, Ruglass LM, Covey LS, Stitzer ML, Kyle TL, Nunes EV. J Subst Abuse Treat. 2014.
The majority of patients enrolled in treatment for substance use disorders (SUDs) also use tobacco. Many will continue to use tobacco even during abstinence from other drugs and alcohol, often leading to smoking-related illnesses. Despite this, little research has been conducted to assess the influence of being a smoker on SUD treatment outcomes and changes in smoking during a treatment episode .In this secondary analysis, cigarette smoking was evaluated in participants completing outpatient SUD treatment as part of a multi-site study conducted by the National Drug Abuse Treatment Clinical Trials Network. Analyses included the assessment of changes in smoking and nicotine dependence via the Fagerstrom Test for Nicotine Dependence during the 12-week study among all smokers (aim #1), specifically among those in the experimental treatment group (aim #2), and the moderating effect of being a smoker on treatment outcomes (aim #3).Participants generally did not reduce or quit smoking throughout the course of the study. Among a sub-set of participants with higher baseline nicotine dependence scores randomized to the control arm, scores

at the end of treatment were lower compared to the experimental arm, though measures of smoking quantity did not appear to decrease. Further, being a smoker was associated with poorer treatment outcomes compared to non-smokers enrolled in the trial. This study provides evidence that patients enrolled in community-based SUD treatment continue to smoke, even when abstaining from drugs and alcohol. These results add to the growing literature encouraging the implementation of targeted, evidence-based interventions to promote abstinence from tobacco among SUD treatment patients.

Release From Incarceration, Relapse To Opioid Use and the Potential For Buprenorphine Maintenance Treatment: A Qualitative Study Of The Perceptions Of Former Inmates With Opioid Use Disorder Fox AD, Maradiaga J, Weiss L, Sanchez J, Starrels JL, Cunningham CO. Addict Sci Clin Pract. 2015; 10(1): 2.
The United States has the highest rate of incarceration in the world (937 per 100,000 adults). Approximately one-third of heroin users pass through correctional facilities annually. Few receive medication assisted treatment (MAT; either methadone or buprenorphine) for opioid use disorder during incarceration, and nearly three-quarters relapse to heroin use within 3 months of release. This qualitative study investigated barriers to and facilitators of buprenorphine maintenance treatment (BMT) following release from incarceration ("re-entry"). The authors conducted 21 semi-structured interviews of former inmates with opioid use disorder recruited from addiction 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. Participants reported adverse re-entry conditions, including persistent exposure to drug use and stressful life events, which were perceived to contribute to opioid relapse and affected addiction treatment decisions during re-entry. Themes that emerged relating to BMT included: 1) reliance on willpower; 2) fear of dependency on medications; 3) variable exposure to buprenorphine; and 4) acceptability of BMT following relapse. Willpower was perceived to be more important for recovery than medications. Many participants experienced painful withdrawal from methadone during incarceration and were fearful that using MAT would lead to opioid tolerance and painful withdrawal again in the future. Participants reported both positive and negative experiences taking illicit buprenorphine, which affected interest in BMT. Overall, BMT was perceived to be a good treatment option for opioid use disorder that could reduce the risk of re-incarceration. BMT was perceived to be acceptable, but former inmates with opioid use disorder may be reluctant to utilize BMT upon re-entry. Factors limiting utilization of BMT could be mitigated though policy change or interventions. Policies of the criminal justice system (e.g., forced detoxification) may be dissuading former inmates from utilizing effective treatments for opioid use disorder. Interventions that improve education and access to BMT for former inmates with opioid use disorder could facilitate entrance into treatment. Both policy changes and interventions are urgently needed to reduce the negative consequences of opioid relapse following re-entry.

The Impact Of Prior Authorization On Buprenorphine Dose, Relapse Rates, and Cost For Massachusetts Medicaid Beneficiaries With Opioid Dependence Clark RE, Baxter JD, Barton BA, Aweh G, O'Connell E, Fisher WH. Health Serv Res. 2014; 49(6): 1964-1979.
The objective of this study was to assess the impact of a 2008 dose-based prior authorization policy for Massachusetts Medicaid beneficiaries using buprenorphine + naloxone for opioid addiction treatment. Doses higher than 16 mg required progressively more frequent authorizations. Mediciaid claims for 2007 and 2008 linked with Department of Public Health (DPH) service records. The authors conducted time series for all buprenorphine users and a longitudinal cohort analysis of

2,049 individuals who began buprenorphine treatment in 2007. Outcome measures included use of relapse-related services, health care expenditures per person, and buprenorphine expenditures. The authors used ICD-9 codes and National Drug Codes to identify individuals with opioid dependence who filled prescriptions for buprenorphine. Medicaid and DPH data were linked with individual identifiers. Individuals using doses >24 mg decreased from 16.5 to 4.1 percent. Relapses increased temporarily for some users but returned to previous levels within 3 months. Buprenorphine expenditures decreased but total expenditures did not change significantly. Prior authorization policies strategically targeted by dose level appear to successfully reduce use of higher than recommended buprenorphine doses. Savings from these policies are modest and may be accompanied by brief increases in relapse rates. Lower doses may decrease diversion of buprenorphine.

Guideline-concordant Management Of Opioid Therapy Among Human Immunodeficiency Virus (HIV)-infected and Uninfected Veterans Gaither JR, Goulet JL, Becker WC, Crystal S, Edelman EJ, Gordon K, Kerns RD, Rimland D, Skanderson M, Weisberg DF, Justice AC, Fiellin DA. J Pain. 2014; 15(11): 1130-1140.
Whether patients receive guideline-concordant opioid therapy (OT) is largely unknown and may vary based on provider and patient characteristics. The authors assessed the extent to which human immunodeficiency virus (HIV)-infected and uninfected patients initiating long-term (≥ 90 days) OT received care concordant with American Pain Society/American Academy of Pain Medicine and Department of Veterans Affairs/Department of Defense guidelines by measuring receipt of 17 indicators during the first 6 months of OT. Of 20,753 patients, HIV-infected patients (n = 6,604) were more likely than uninfected patients to receive a primary care provider visit within 1 month (52.0% vs 30.9%) and 6 months (90.7% vs 73.7%) and urine drug tests within 1 month (14.8% vs 11.5%) and 6 months (19.5% vs 15.4%; all P < .001). HIV-infected patients were also more likely to receive OT concurrent with sedatives (24.6% vs 19.6%) and a current substance use disorder (21.6% vs 17.2%). Among both patient groups, only modest changes in guideline concordance were observed over time: urine drug tests and OT concurrent with current substance use disorders increased, whereas sedative co-prescriptions decreased (all Ps for trend < .001). Over a 10-year period, on average, patients received no more than 40% of recommended care. OT guideline-concordant care is rare in primary care, varies by patient/provider characteristics, and has undergone few changes over time. The promulgation of OT clinical guidelines has not resulted in substantive changes over time in OT management, which falls well short of the standard recommended by leading medical societies. Strategies are needed to increase the provision of OT guideline-concordant care for all patients.

Violent Reinjury and Mortality Among Youth Seeking Emergency Department Care For Assault-related Injury: A 2-year Prospective Cohort Study Cunningham RM, Carter PM, Ranney M, Zimmerman MA, Blow FC, Booth BM, Goldstick J, Walton MA. JAMA Pediatr. 2015; 169(1): 63-70.
Violence is a leading cause of morbidity and mortality among youth, with more than 700,000 emergency department (ED) visits annually for assault-related injuries. The risk for violent reinjury among high-risk, assault-injured youth is poorly understood. The objective of this study was to compare recidivism for violent injury and mortality outcomes among drug-using, assault-injured youth (AI group) and drug-using, non-assault-injured control participants (non-AI group) presenting to an urban ED for care. Participants were enrolled in a prospective cohort study from December 2,

2009, through September 30, 2011, at an urban level I ED and followed up for 24 months. The authors administered validated measures of violence and substance use and mental health diagnostic interviews and reviewed medical records at baseline and at each point of follow-up (6, 12, 18, and 24 months). Follow-up over 24 months. Use of ED services for assault or mortality measured from medical record abstraction supplemented with self-report. The authors followed 349 AI and 250 non-AI youth for 24 months. Youth in the AI group had almost twice the risk for a violent injury requiring ED care within 2 years compared with the non-AI group (36.7% vs 22.4%; relative risk [RR], 1.65 [95% CI, 1.25-2.14]; P < .001). Two-year mortality was 0.8%. Poisson regression modeling identified female sex (RR, 1.30 [95% CI, 1.02-1.65]), assault-related injury (RR, 1.57 [95% CI, 1.19-2.04), diagnosis of a drug use disorder (RR, 1.29 [95% CI, 1.01-1.65]), and posttraumatic stress disorder (RR, 1.47 [95% CI, 1.09-1.97]) at the index visit as predictive of ED recidivism or death within 24 months. Parametric survival models demonstrated that assault-related injury (P < .001), diagnosis of posttraumatic stress disorder (P = .008), and diagnosis of a drug use disorder (P = .03) significantly shortened the expected waiting time until the first ED return visit for violence or death. Violent injury is a reoccurring disease, with one-third of our AI group experiencing another violent injury requiring ED care within 2 years of the index visit, almost twice the rate of a non-AI comparison group. Secondary violence prevention measures addressing substance use and mental health needs are needed to decrease subsequent morbidity and mortality due to violence in the first 6 months after an assault injury.

Burden Of Hepatitis C Virus Disease and Access To Hepatitis C Virus Services In People Who Inject Drugs In India: A Cross-sectional Study Solomon SSuhas, Mehta SH, Srikrishnan AK, Solomon S, McFall AM, Laeyendecker O, Celentano DD, Iqbal SH, Anand S, Vasudevan CK, Saravanan S, Lucas GM, Kumar MS, Sulkowski MS, Quinn TC. Lancet Infect Dis. 2015; 15(1): 36-45.
90% of individuals infected with hepatitis C virus (HCV) worldwide reside in resource-limited settings. The authors aimed to characterize the prevalence of HCV, HIV/HCV co-infection, and the HCV care continuum in people who inject drugs in India.14,481 people (including 31 seeds-individuals selected as the starting point for sampling because they were well connected in the drug using community) who inject drugs were sampled from 15 cities throughout India using respondent-driven sampling from Jan 2, 2013 to Dec 19, 2013. Data from seeds were excluded from all analyses. HCV prevalence was estimated by the presence of anti-HCV antibodies incorporating respondent-driven sampling weights. HCV care continuum outcomes were self-reported except for viral clearance in treatment-experienced participants. The median age of participants was 30 years (IQR 24-36) and 13 608 (92·4%) of 14 449 were men (data were missing for some variables). Weighted HCV prevalence was 5777 (37·2%) of 14 447; HIV/HCV co-infection prevalence was 2085 (13·2%) of 14 435. Correlates of HCV infection included high lifetime injection frequency, HIV positivity, and a high prevalence of people with HIV RNA (more than 1000 copies per mL) in the community. Of the 5777 people who inject drugs that were HCV antibody positive, 440 (5·5%) were aware of their status, 225 (3·0%) had seen a doctor for their HCV, 79 (1·4%) had taken HCV treatment, and 18 (0·4%) had undetectable HCV RNA. Of 12 128 participants who had not previously been tested for HCV, 6138 (50·5%) did not get tested because they had not heard of HCV. In the 5777 people who were HCV antibody positive, 2086 (34·4%) reported harmful or hazardous alcohol use, of whom 1082 (50·4%) were dependent, and 3821 (65·3%) reported needle sharing. Awareness of HCV positive status was significantly associated with higher education, HIV testing history, awareness of HIV positive status, and higher community antiretroviral therapy

coverage. The high burden of HCV and HIV/HCV co-infection coupled with low-access to HCV services emphasizes an urgent need to include resource-limited settings in the global HCV agenda. Although new treatments will become available worldwide in the near future, programs to improve awareness and reduce disease progression and transmission need to be scaled up without further delay. Failure to do so could result in patterns of rising mortality, undermining advances in survival attributed to widespread HIV treatment.US National Institutes of Health.

Challenges In Managing HIV In People Who Use Drugs Kamarulzaman A, Altice FL. Curr Opin Infect Dis. 2015; 28(1): 10-16.
HIV management in people who use drugs (PWUD) is typically complex and challenging due to the presence of multiple medical and psychiatric comorbidities as well as social, physical, economic and legal factors that often disrupt the HIV continuum of care. In this review, the authors describe the individual, health systems and societal barriers to HIV treatment access and care retention for PWUD. In addition, the clinical management of HIV-infected PWUD is often complicated by the presence of multiple infectious and noninfectious comorbidities. Improved HIV treatment outcomes can be enhanced through improved testing and linkage strategies along with better treatment retention and antiretroviral (ART) adherence. Improved ART adherence can be achieved through the provision of opioid substitution therapy (OST), directly administered ART (DAART) and integration of ART with OST services. Recent advances with direct-acting antivirals (DAAs) for hepatitis C virus (HCV) have shown superior outcomes than interferon-based regimes in HIV-HCV co-infected patients. Newer diagnostic technologies for tuberculosis (TB) hold promise for earlier diagnosis for PWUD co-infected with TB, and TB treatment outcomes are improved through combination with OST.HIV-infected PWUDs are a key population who frequently experience suboptimal outcomes along the HIV continuum of care. A comprehensive strategy that encompasses evidence-based prevention and treatment interventions that target the individual, family, healthcare system, legal and societal structure is required to ensure greater participation and success in HIV treatment and care.

Understanding the Service Needs Of Assault-injured, Drug-using Youth Presenting For Care In An Urban Emergency Department Bohnert KM, Walton MA, Ranney M, Bonar EE, Blow FC, Zimmerman MA, Booth BM, Cunningham RM. Addict Behav. 2015; 41: 97-105.
Violence is a leading cause of injury among youth 15-24years and is frequently associated with drug use. To inform optimal violence interventions, it is critical to understand the baseline characteristics and intent to retaliate of drug-using, assault-injured (AI) youth in the Emergency Department (ED) setting, where care for violent injury commonly occurs. At an urban ED, AI youth ages 14-24 endorsing any past six-month substance use (n=350), and a proportionally-sampled substance-using comparison group (CG) presenting for non-assault-related care (n=250), were recruited and completed a baseline assessment (82% participation). Medical chart review was also conducted. Conditional logistic regression was performed to examine correlates associated with AI. Over half (57%) of all youth met the criteria for drug and/or alcohol use disorder, with only 9% receiving prior treatment. Among the AI group, 1 in 4 intended to retaliate, of which 49% had firearm access. From bivariate analyses, AI youth had poorer mental health, greater substance use, and were more likely to report prior ED visits for assault or psychiatric evaluation. Based on multivariable modeling, AI youth had greater odds of being on probation/parole (AOR=2.26; CI=1.28, 3.90) and having PTSD (AOR=1.88; CI=1.01, 3.50) than the CG.AI youth may have unmet needs for substance use and mental health treatment, including PTSD. These characteristics

along with the risk of retaliation, increased ED service utilization, low utilization of other health care venues, and firearm access highlight the need for interventions that initiate at the time of ED visit.

Heroin Use and HIV Disease Progression: Results From A Pilot Study Of A Russian Cohort
Edelman EJ, Cheng DM, Krupitsky EM, Bridden C, Quinn E, Walley AY, Lioznov DA, Blokhina E, Zvartau E, Samet JH. AIDS Behav. 2014.
Opioids have immunosuppressive properties, yet their impact on HIV disease progression remains unclear. Using longitudinal data from HIV-infected antiretroviral therapy-naïve Russian individuals (n = 77), the authors conducted a pilot study to estimate the effect of heroin use on HIV disease progression. Heroin use was categorized based on past 30 days self-reported use at baseline, 6 and 12 months as none, intermittent or persistent. The authors estimated the effect of heroin use on HIV disease progression, measured as change in CD4 count from baseline to 12 months, using multivariable linear regression. Those with intermittent (n = 21) and no heroin use (n = 39) experienced mean decreases in CD4 count from baseline to 12 months (-103 and -10 cells/mm^3, respectively; adjusted mean difference (AMD) -93; 95 % CI -245, 58). Those with persistent use (n = 17) showed a mean increase of 53 cells/mm^3 (AMD 63; 95 % CI -95, 220). Future studies exploring the effects of heroin withdrawal on HIV disease progression are warranted.

Survey Of US Correctional Institutions For Routine HCV Testing Beckwith CG, Kurth AE, Bazerman L, Solomon L, Patry E, Rich JD, Kuo I. Am J Public Health. 2015; 105(1): 68-71.
To ascertain HCV testing practices among US prisons and jails, the authors conducted a survey study in 2012, consisting of medical directors of all US state prisons and 40 of the largest US jails, that demonstrated a minority of US prisons and jails conduct routine HCV testing. Routine voluntary HCV testing in correctional facilities is urgently needed to increase diagnosis, enable risk-reduction counseling and preventive health care, and facilitate evaluation for antiviral treatment.

Program Capacity To Eliminate Outcome Disparities In Addiction Health Services
Guerrero EG, Aarons GA, Grella CE, Garner BR, Cook B, Vega WA. Adm Policy Ment Health. 2014.
The authors evaluated program capacity factors associated with client outcomes in publicly funded substance abuse treatment organizations in one of the most populous and diverse regions of the United States. Using multilevel cross-sectional analyses of program data (n=97) merged with client data from 2010 to 2011 for adults (n=8,599), the authors examined the relationships between program capacity (leadership, readiness for change, and Medi-Cal payment acceptance) and client wait time and treatment duration. Acceptance of Medi-Cal was associated with shorter wait times, whereas organizational readiness for change was positively related to treatment duration. Staff attributes were negatively related to treatment duration. Overall, compared to low program capacity, high program capacity was negatively associated with wait time and positively related to treatment duration. In conclusion, program capacity, an organizational indicator of performance, plays a significant role in access to and duration of treatment. Implications for health care reform implementation in relation to expansion of public health insurance and capacity building to promote health equities are discussed.

Relationship Between Low-Income Patient Census and Substance Use Disorder Treatment Programs' Availability Of Tobacco Cessation Services Muilenburg JL, Laschober TC, Eby LT. J Drug Issues. 2015; 45(1): 69-79.
Low income adults with substance use disorders (SUDs) have a high prevalence of tobacco use and often limited access to tobacco cessation treatment. This study examines the relationship between low-income SUD patient census (i.e., percentage of patients whose treatment costs are covered by Medicaid and Federal block grants) and SUD programs' availability of three evidence-based tobacco cessation services: behavioral treatments, system-level support, and pharmacotherapy. Data were collected from a random sample of 1,006 program administrators in 2010. Mixed-effects models results show that the percentage of low-income patients is significantly positively associated with the availability of behavioral treatments and system-level support but not pharmacotherapy. Thus, low-income patients may have similar access to tobacco cessation pharmacotherapy but greater access to behavioral treatments and system-level support. However, the availability of tobacco cessation services is not widespread overall, which may hamper access to extensive services to address low-income SUD patients' high smoking rates.

Gender Abuse and Major Depression Among Transgender Women: A Prospective Study Of Vulnerability and Resilience Nuttbrock L, Bockting W, Rosenblum A, Hwahng S, Mason M, Macri M, Becker J. Am J Public Health. 2014; 104(11): 2191-2198.
The authors examined the social and interpersonal context of gender abuse and its effects on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition major depression among transgender women. They conducted a 3-year prospective study (2004-2007) among 230 transgender women aged 19 to 59 years from the New York City Metropolitan Area. Statistical techniques included generalized estimating equations (logistic regression). They observed significant associations of psychological and physical gender abuse with major depression during follow-up. New or persistent experiences of both types of abuse were associated with 4- to 7-fold increases in the likelihood of incident major depression. Employment, transgender presentation, sex work, and hormone therapy correlated across time with psychological abuse; the latter 2 variables correlated with physical abuse. The association of psychological abuse with depression was stronger among younger than among older transgender women. Psychological and physical gender abuse is endemic in this population and may result from occupational success and attempts to affirm gender identity. Both types of abuse have serious mental health consequences in the form of major depression. Older transgender women have apparently developed some degree of resilience to psychological gender abuse.

Gender Abuse, Depressive Symptoms, and And Substance Use Among Transgender Women: A 3-year Prospective Study Nuttbrock L, Bockting W, Rosenblum A, Hwahng S, Mason M, Macri M, Becker J. Am J Public Health. 2014; 104(11): 2199-2206.
The authors examined the effects of gender abuse (enacted stigma), depressive symptoms, and demographic, economic, and lifestyle factors on substance use among transgender women. They conducted a 3-year prospective study (December 2004 to September 2007) of 230 transgender women aged 19 to 59 years from the New York Metropolitan Area. Statistical techniques included generalized estimating equations with logistic and linear regression links. Six-month prevalence of any substance use at baseline was 76.2%. Across assessment points, gender abuse was associated with alcohol, cannabis, cocaine, or any substance use during the previous 6 months, the number of days these substances were used during the previous month, and the number of substances used.

Additional modeling associated changes in gender abuse with changes in substance use across time. Associations of gender abuse and substance use were mediated 55% by depressive symptoms. Positive associations of employment income, sex work, transgender identity, and hormone therapy with substance use were mediated 19% to 42% by gender abuse. Gender abuse, in conjunction with depressive symptoms, is a pervasive and moderately strong risk factor for substance use among transgender women. Improved substance abuse treatment is sorely needed for this population.

Randomized Trial Of Family Therapy Versus Nonfamily Treatment For Adolescent Behavior Problems In Usual Care Hogue A, Dauber S, Henderson CE, Bobek M, Johnson C, Lichvar E, Morgenstern J. J Clin Child Adolesc Psychol. 2014; 1-16.
A major focus of implementation science is discovering whether evidence-based approaches can be delivered with fidelity and potency in routine practice. This randomized trial compared usual care family therapy (UC-FT), implemented without a treatment manual or extramural support as the standard-of-care approach in a community clinic, to nonfamily treatment (UC-Other) for adolescent conduct and substance use disorders. The study recruited 205 adolescents (M age = 15.7 years; 52% male; 59% Hispanic American, 21% African American) from a community referral network, enrolling 63% for primary mental health problems and 37% for primary substance use problems. Clients were randomly assigned to either the UC-FT site or one of five UC-Other sites. Implementation data confirmed that UC-FT showed adherence to the family therapy approach and differentiation from UC-Other. Follow-ups were completed at 3, 6, and 12 months post-baseline. There was no between-group difference in treatment attendance. Both conditions demonstrated improvements in externalizing, internalizing, and delinquency symptoms. However, UC-FT produced greater reductions in youth-reported externalizing and internalizing among the whole sample, in delinquency among substance-using youth, and in alcohol and drug use among substance-using youth. The degree to which UC-FT outperformed UC-Other was consistent with effect sizes from controlled trials of manualized family therapy models. Nonmanualized family therapy can be effective for adolescent behavior problems within diverse populations in usual care, and it may be superior to nonfamily alternatives.

The Space Of Common Psychiatric Disorders In Adolescents: Comorbidity Structure and Individual Latent Liabilities Blanco C, Wall MM, He J-P, Krueger RF, Olfson M, Jin CJ, Burstein M, Merikangas KR. J Am Acad Child Adolesc Psychiatry. 2015; 54(1): 45-52.
The objectives of this study were to construct a virtual space of common adolescent psychiatric disorders, spanned by factors reflecting major psychopathological dimensions; and to locate psychiatric disorders in that space, examine whether the major psychopathological dimensions can be hierarchically organized, and determine the distribution of the latent scores of individuals in the space spanned by those dimensions. Exploratory factor analyses of data from the National Comorbidity Survey Adolescent Supplement (NCS-A) using the psychiatric diagnoses as indicators were used to identify the latent major psychopathological dimensions. The loadings of the disorders on those dimensions were used as coordinates to calculate the distance among disorders. The distribution of individuals in the space was based on the latent scores on the factors reflecting the major psychopathological conditions. A model with 3 correlated factors provided an excellent fit (Comparative Fit Index [CFI] = 0.97, Tucker-Lewis Index [TLI] = 0.95, the root mean squared error of approximation [RMSEA] = 0.008) for the structure of disorders and a 4-factor model could be hierarchically organized, ultimately yielding a general psychopathology factor. Distances between disorders ranged from 0.079 (between social phobia and generalized anxiety disorder [GAD]) and

1.173 (between specific phobia and conduct disorder [CD]). At the individual level, there were 546 distinct liabilities observed (22% of all 2,455 potential liabilities). A novel way of understanding psychiatric disorders in adolescents is as existing in a space with a limited number of dimensions with no disorder aligning along 1 single dimension. These dimensions are hierarchically organized, allowing analyses at different levels of organization. Furthermore, individuals with psychiatric disorders present with a broad range of liabilities, reflecting the diversity of their clinical presentations.

Supply Of Buprenorphine Waivered Physicians: The Influence Of State Policies Stein BD, Gordon AJ, Dick AW, Burns RM, Pacula RL, Farmer CM, Leslie DL, Sorbero M. J Subst Abuse Treat. 2015; 48(1): 104-111.
Buprenorphine, an effective opioid use disorder treatment, can be prescribed only by buprenorphine-waivered physicians. The authors calculated the number of buprenorphine-waivered physicians/100,000 county residents using 2008-11 Buprenorphine Waiver Notification System data, and used multivariate regression models to predict number of buprenorphine-waivered physicians/100,000 residents in a county as a function of county characteristics, state policies and efforts to promote buprenorphine use. In 2011, 43% of US counties had no buprenorphine-waivered physicians and 7% had 20 or more waivered physicians. Medicaid funding, opioid overdose deaths, and specific state guidance for office-based buprenorphine use were associated with more buprenorphine-waivered physicians, while encouraging methadone programs to promote buprenorphine use had no impact. These findings provide important empirical information to individuals seeking to identify effective approaches to increase the number of physicians able to prescribe buprenorphine.

Dynamics In the Costs Of Criminality Among Opioid Dependent Individuals Krebs E, Kerr T, Montaner J, Wood E, Nosyk B. Drug Alcohol Depend. 2014; 144: 193-200.
Research into the avoided crime-related costs associated with methadone maintenance treatment (MMT) is sparse. The authors' objective was to characterize the dynamics in crime-related costs associated with MMT effectiveness among opioid dependent individuals in Vancouver, Canada. They considered individuals enrolled in a prospective study between December, 2011 and May, 2013. Monthly crime-related costs (2013 CAD) were derived from self-reported criminal activity. On the basis of MMT receipt and illicit opioid use, individuals were classified in mutually exclusive health states: (i) MMT high effectiveness; (ii) MMT low effectiveness; (iii) opioid abstinence; or (iv) relapse. The authors classified individuals as daily, non-daily or non-stimulant users and controlled for demographic and socio-economic characteristics. A two-part multiple regression model was constructed; the first part modeled non-zero cost probability, the second estimated the level of costs. Avoided costs were estimated for each health state and stratified by stimulant use intensity. This study included 982 individuals (median age 47, 38% female) for 2232 observations. Individuals on MMT with high effectiveness incurred lower monthly costs of criminality (avoided costs of $6298; 95% C.I. ($1578, $11,017)), as did opioid abstinent individuals ($6563 ($1564, $11,561)). Avoided costs for daily stimulant users were greater than for non-daily users, both for individuals on MMT with high effectiveness ($12,975 vs. $4125) and opioid abstinent ($12,640 vs. $4814). Using longitudinal data on individuals with a history of MMT, the authors found substantially lower costs of criminality associated with high effect to MMT. Avoided costs were highest among daily stimulant users that were on MMT with high effectiveness or those opioid abstinent.

Efficacy Of A Process Improvement Intervention On Delivery Of HIV Services To Offenders: A Multisite Trial Pearson FS, Shafer MS, Dembo R, Del Mar Vega-Debie G, Pankow J, Duvall JL, Belenko S, Frisman LK, Visher CA, Pich M, Patterson Y. Am J Public Health. 2014; 104(12): 2385-2391.
The authors tested a modified Network for the Improvement of Addiction Treatment (NIATx) process improvement model to implement improved HIV services (prevention, testing, and linkage to treatment) for offenders under correctional supervision. As part of the Criminal Justice Drug Abuse Treatment Studies, Phase 2, the HIV Services and Treatment Implementation in Corrections study conducted 14 cluster-randomized trials in 2011 to 2013 at 9 US sites, where one correctional facility received training in HIV services and coaching in a modified NIATx model and the other received only HIV training. The outcome measure was the odds of successful delivery of an HIV service. The results were significant at the .05 level, and the point estimate for the odds ratio was 2.14. Although overall the results were heterogeneous, the experiments that focused on implementing HIV prevention interventions had a 95% confidence interval that exceeded the no-difference point. The results demonstrate that a modified NIATx process improvement model can effectively implement improved rates of delivery of some types of HIV services in correctional environments.

Effects Of An Organizational Linkage Intervention On Inter-Organizational Service Coordination Between Probation/Parole Agencies and Community Treatment Providers Welsh WN, Knudsen HK, Knight K, Ducharme L, Pankow J, Urbine T, Lindsey A, Abdel-Salam S, Wood J, Monico L, Link N, Albizu-Garcia C, Friedmann PD. Adm Policy Ment Health. 2015.
Weak coordination between community correctional agencies and community-based treatment providers is a major barrier to diffusion of medication-assisted treatment (MAT)-the inclusion of medications (e.g., methadone and buprenorphine) in combination with traditional counseling and behavioral therapies to treat substance use disorders. In a multisite cluster randomized trial, experimental sites (j = 10) received a 3-h MAT training plus a 12-month linkage intervention; control sites (j = 10) received the 3-h training alone. Hierarchical linear models showed that the intervention resulted in significant improvements in perceptions of interagency coordination among treatment providers, but not probation/parole agents. Implications for policy and practice are discussed.

Impact Of Community-Based Programs On Incarceration Outcomes Among Gay and Bisexual Stimulant-Using Homeless Adults Nyamathi AM, Reback CJ, Shoptaw S, Salem BE, Zhang S, Farabee D, Khalilifard F. Community Ment Health J. 2015.
This study was part of a randomized controlled trial designed to improve hepatitis knowledge and health promoting behaviors and subsequently decrease stimulant use and incarceration with 422 (G/B) homeless men between 18 and 46 years of age. Findings revealed that no significant program differences on incarceration in the 4 months following the intervention. However, younger participants (p = .010), and those with prior incarceration (p = .001) were at greater risk for incarceration at 4 months. An additional factor associated with incarceration at 4 months included living on the street for at least 1 week (p = .049).

Are Symptom Features Of Depression During Pregnancy, the Postpartum Period and Outside the Peripartum Period Distinct? Results From A Nationally Representative Sample Using Item Response Theory (IRT) Hoertel N, Lopez S, Peyre H, Wall MM, Gonzalez-Pinto A, Limosin F, Blanco C. Depress Anxiety. 2015; 32(2): 129-140.
Whether there are systematic differences in depression symptom expression during pregnancy, the postpartum period and outside these periods (i.e., outside the peripartum period) remains debated. The aim of this study was to use methods based on item response theory (IRT) to examine, after equating for depression severity, differences in the likelihood of reporting DSM-IV symptoms of major depressive episode (MDE) in women of childbearing age (i.e., aged 18-50) during pregnancy, the postpartum period and outside the peripartum period. The authors conducted these analyses using a large, nationally representative sample of women of childbearing age from the United States (n = 11,256) who participated in the second wave of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).The overall 12-month prevalence of all depressive criteria (except for worthlessness/guilt) was significantly lower in pregnant women than in women of childbearing age outside the peripartum period, whereas the prevalence of all symptoms (except for "psychomotor symptoms") was not significantly different between the postpartum and the nonperipartum group. There were no clinically significant differences in the endorsement rates of symptoms of MDE by pregnancy status when equating for levels of depression severity. This study suggests that the clinical presentation of depressive symptoms in women of childbearing age does not differ during pregnancy, the postpartum period and outside the peripartum period. These findings do not provide psychometric support for the inclusion of the peripartum onset specifier for major depressive disorder in the DSM-5.

An Exploratory Qualitative Assessment Of Self-reported Treatment Outcomes and Satisfaction Among Patients Accessing An Innovative Voluntary Drug Treatment Centre In Malaysia Ghani MA, Brown S-E, Khan F, Wickersham JA, Lim SH, Dhaliwal SK, Kamarulzaman A, Altice FL. Int J Drug Policy. 2015; 26(2): 175-182.
In Malaysia, compulsory drug detention centers (CDDCs) hold suspected drug users for two years without adjudication. Acute detoxification without healthcare access has been documented. CDDCs are criticized globally due to ineffectiveness in treating addiction and human rights violations. In response, the Malaysian government began transitioning these facilities into voluntary drug treatment centers known as "Cure and Care" (C&C) center that embrace a holistic treatment-based approach to drug addiction rehabilitation. An explorative qualitative study was undertaken to explore patient perspectives and satisfaction regarding treatment and services at the new Cure and Care center in Kota Bharu, Malaysia. A convenience sample of 20 patients was recruited to participate in semi-structured in-depth interviews. Content analysis was used to identify the salient themes. Patients identified methadone treatment, psychosocial programs, religious instruction, and recreational activities as important factors contributing to treatment success for addressing both health and addiction needs. Though many had previously been in a CDDC, adherence to treatment in the C&C center was perceived to be facilitated by the degree of social support, the voluntary nature and the array of new programs available for selection. C&Cs represents a dramatic shift in the Malaysian government’s approach to drug addiction. These findings demonstrate positive patient experiences associated with the holistic treatment-based approach of these centers. This exploratory study provides additional evidence to document this ongoing policy transition and may guide continued expansion of new holistic drug treatment programs across the country.

Examining Sex Differences In DSM-IV Borderline Personality Disorder Symptom Expression Using Item Response Theory (IRT) Hoertel N, Peyre H, Wall MM, Limosin F, Blanco C. J Psychiatr Res. 2014; 59: 213-219.
Limited literature suggests that there may be differences in how women and men experience borderline personality disorder (BPD) symptoms. The aim of the current study was to use methods based on item response theory (IRT) to examine whether, when equating for levels of BPD symptom severity, there are sex differences in the likelihood of reporting DSM-IV BPD symptoms. The authors conducted these analyses using a large, nationally representative sample from the USA (n = 34,653), the second wave of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Data from women and men were compared. There were statistically and clinically significant sex differences for 3 out of the 9 DSM-IV BPD symptoms. The authors found that women were more likely to experience suicidal/self-mutilation behavior, affective instability and chronic feelings of emptiness and tended to be less likely to endorse impulsivity at lower levels of borderline personality disorder severity than men, while affective instability and chronic feelings of emptiness appeared to be significantly less discriminant in terms of severity in men than in women. There were no significant differences between women and men on the remaining DSM-IV symptoms. Overall, these findings indicate substantial sex differences in borderline personality disorder symptom expression. Although these results may reflect sex-bias in diagnostic criteria, they are in keeping with recent arguments suggesting that BPD could be understood as a clinical phenomenon that may partially differ in men and women.

Criminal Investigations In Child Protective Services Cases: An Empirical Analysis Cross TP, Chuang E, Helton JJ, Lux EA. Child Maltreat. 2014.
This study analyzed the frequency and correlates of criminal investigation of child maltreatment in cases investigated by child protective service (CPS), using national probability data from the National Survey of Child and Adolescent Well-Being. Criminal investigations were conducted in slightly more than 25% of cases. Communities varied substantially in percentage criminally investigated. Sexual abuse was the most frequent type of maltreatment criminally investigated followed by physical abuse. Logistic regression results indicated that criminal investigations were more likely when caseworkers perceived greater harm and more evidence; when CPS conducted an investigation rather than an assessment; when a parent or a legal guardian reported the maltreatment; and when cases were located in communities in which CPS and police had a memorandum of understanding (MOU) governing coordination. Most variation between communities in criminal investigation remained unexplained. The findings suggest the potential of MOUs for communities wanting to increase criminal investigation.

The Validity Of Self-reported Medication Adherence As An Outcome In Clinical Trials Of Adherence-promotion Interventions: Findings From the MACH14 Study Simoni JM, Huh D, Wang Y, Wilson IB, Reynolds NR, Remien RH, Goggin K, Gross R, Rosen MI, Schneiderman N, Arnsten J, Golin CE, Erlen JA, Bangsberg DR, Liu H. AIDS Behav. 2014; 18(12): 2285-2290.
In medication adherence-promotion trials, participants in the intervention arm are often cognizant of the researcher's aim to improve adherence; this may lead to their inflating reports of their own adherence compared to control arm participants. Using data from 1,247 HIV-positive participants across eight U.S. Studies in the Multi-site Adherence Collaboration on HIV (MACH14) collaboration, the authors evaluated the validity of self-reported adherence by examining whether its association with two more objective outcomes [1], electronically monitored adherence and [2] viral

load, varied by study arm. After adjusting for potential confounders, there was no evidence of greater overestimation of self-reported adherence among intervention arm participants, supporting its potential as a trial outcome indicator.

Treatment Outcomes For Prescription Drug Misusers: The Negative Effect Of Geographic Discordance Oser CB, Harp KLH. J Subst Abuse Treat. 2015; 48(1): 77-84.
This is the first known study to examine geographic discordance (traveling from one's home residence to a county with a different socio-cultural context to receive substance abuse treatment) as a predictor of clinical and social functioning treatment outcomes (i.e., relapse, self-help attendance, anxiety, and incarceration) among a sample of prescription drug misusers. Treatment entry and 12-month follow-up client-level survey data were collected from 187 clients who misused prescription drugs, and center-level survey data were collected from the supervisors at treatment centers attended by the clients. Multivariate models reveal that geographic discordance significantly increased the odds that prescription drug misusers would report relapse to prescription opioid misuse, anxiety, and any incarceration at follow-up. Moreover, geographically discordant clients were significantly less likely to have attended a self-help group, net of the effect of other individual- and center-level factors. Implications for clinical practice and substance abuse treatment policy are provided.

Integrating Antiretroviral Therapy In Methadone Maintenance Therapy Clinics: Service Provider Perceptions Lin C, Cao X, Li L. Int J Drug Policy. 2014; 25(6): 1066-1070.
Using methadone maintenance therapy (MMT) clinics to deliver antiretroviral therapy (ART) is an effective strategy to promote treatment initiation and adherence for HIV-positive drug users. This paper describes the implementation barriers perceived by service providers for an intervention pilot designed to integrate ART services in MMT clinics. The study was conducted in six MMT clinics in Sichuan province, China. Two service providers selected from each of the six clinics underwent training in administering ART. The trained providers delivered ART-related services in their clinics. A focus group was conducted among the service providers to assess their experiences and perceived challenges in delivering integrated services. Barriers at policy, institutional, provider, and client levels were identified. Policy level barriers included household registration restrictions and a lack of insurance coverage for testing expenses. Inefficient coordination between treatment sites and MMT clinics was an obstacle at the institutional level. Insufficient training and added workload were barriers at the provider level. Finally, conflict with daily dosing habits was identified as the primary reason that clients did not accept ART. Although integrating ART into MMT clinics is beneficial, multilevel barriers to implementation need to be addressed. This study documents the need for treatment transferability and insurance coverage, protection of client confidentiality, proper provider training, coordination with treatment sites, and individualized ART service for MMT clients.

Rural/Urban Residence, Access, and Perceived Need For Treatment Among African American Cocaine Users Borders TF, Booth BM, Stewart KE, Cheney AM, Curran GM. J Rural Health. 2015; 31(1): 98-107.
Thr objective of this study was to examine how rural/urban residence, perceived access, and other factors impede or facilitate perceived need for drug use treatment, a concept closely linked to treatment utilization. Two hundred rural and 200 urban African American cocaine users who were not receiving treatment were recruited via Respondent-Driven Sampling and completed a structured

in-person interview. Bivariate and multivariate analyses were conducted to test the associations between perceived need and rural/urban residence, perceived access, and other predisposing (e.g,, demographics), enabling (e.g., insurance), and health factors (eg, psychiatric distress). In bivariate analyses, rural relative to urban cocaine users reported lower perceived treatment need (37% vs 48%), availability, affordability, overall ease of access, and effectiveness, as well as lower perceived acceptability of residential, outpatient, self-help, and hospital-based services. In multivariate analyses, there was a significant interaction between rural/urban residence and the acceptability of religious counseling. At the highest level of acceptability, rural users had lower odds of perceived need (OR = 0.21); at the lowest level, rural users had higher odds of perceived need (OR = 3.97) than urban users. Among rural users, the acceptability of religious counseling was negatively associated with perceived need (OR = 0.65). Ease of access was negatively associated (OR = 0.71) whereas local treatment effectiveness (OR = 1.47) and the acceptability of hospital-based treatment (OR = 1.29) were positively associated with perceived need among all users. These findings suggest rural/urban disparities in perceived need and access to drug use treatment. Among rural and urban cocaine users, improving perceptions of treatment effectiveness and expanding hospital-based services could promote treatment seeking.

Prevalence Of and Risk Factors For Methicillin-resistant Staphylococcus Aureus Colonization In HIV Infection: A Meta-analysis Zervou FN, Zacharioudakis IM, Ziakas PD, Rich JD, Mylonakis E. Clin Infect Dis. 2014; 59(9): 1302-1311.
Human immunodeficiency virus (HIV)-infected individuals who are colonized with methicillin-resistant Staphylococcus aureus (MRSA) have increased risk for MRSA infection. The authors conducted a meta-analysis of published studies to estimate the prevalence of MRSA colonization in this population. They performed a systematic literature review and meta-analysis. The PubMed and Embase databases were searched and studies reporting prevalence of MRSA colonization among HIV-infected individuals were included. Among 7940 citations, 32 studies reporting data on 6558 HIV-infected individuals were considered eligible for our meta-analysis. The authors found that 6.9% (95% confidence interval [CI], 4.8-9.3) of individuals with HIV infection are MRSA carriers, with the corresponding figure across North American studies being 8.8% (95% CI, 6.0-12.2). History of hospitalization during the previous 12 months was associated with a 3.1 times higher risk of MRSA colonization (risk ratio [RR], 3.11 [95% CI, 1.62-5.98]). Previous or current incarceration was also associated with a higher risk for carriage (RR, 1.77 [95% CI, 1.26-2.48]). Current antiretroviral therapy or use of trimethoprim-sulfamethoxazole did not impact the risk of MRSA carriage (RR, 1.02 [95% CI, .64-1.63] and 1.45 [95% CI, .69-3.03], respectively). Extranasal screening increased the detection of MRSA colonization by at least 31.6% (95% CI, 15.8-50.0). The added yield from groin screening was 19.3% (95% CI, 11.5-28.5), from perirectal screening 18.5% (95% CI, 7.4-33.2), and from throat cultures 17.5% (95% CI, 12.0-24).Individuals with HIV infection constitute a highly vulnerable population for MRSA colonization, and prior exposure to hospital or incarceration are significant factors. Nasal screening alone will underestimate the rate of colonization by at least one-third.

Achieving Ecological Validity Of Occupation-Based Interventions For Healthy Aging Orellano-Colon EM, Varas-Diaz N, Bernal G, Mountain GA. Phys Occup Ther Geriatr. 2014; 32(4): 368-380.
The objective of this study was to develop a culturally sensitive occupation-based health promotion intervention for older Hispanic adults who live alone. The authors used a mixed method design for

the content validation of the intervention and the Ecological Validity Model (EVM) to culturally center the intervention. In the quantitative phase, aging experts as well as community members from two activity centers for the elderly in Puerto Rico completed a content validity ratio exercise. In the qualitative phase, the authors conducted three focus groups with these participants. Data analysis included content validity ratio and a directed content analysis. This resulted in a working version of the intervention protocol addressing the eight dimensions of the EVM. The EVM can be used to culturally center preventive interventions to other ethnic minority groups to augment the external validity and cultural competence of interventions. Future research must test the feasibility of this new intervention.

Memory Banking: A Life Story Intervention For Aging Preparation and Mental Health Promotion Zanjani F, Downer BG, Hosier AF, Watkins JD. J Aging Health. 2015; 27(2): 355-376.
The aim of this study is to examine the feasibility of Memory Banking (MB), a life story development intervention within the context of aging preparation. Individuals participate in MB to strategically document and share their life story, including mapping out future dreams, aspirations, plans, and decisions. Data (2010-2012) from eight MB workshops were examined to determine the impact of the intervention on mental health, social support, and quality of life. Recruitment efforts resulted in n = 72 participants, primarily female (72%), White/Caucasian (93%), average age of 70 years. Data indicated intervention effects showing improvements in depression (p = .041), mood disturbance (p = .0067), and cognitive performance (p = .0045). MB outcomes indicate that the intervention is promising and supports continued investigation and development in the area of life story development for aging preparation and improving late life mental health distress in a community setting. Future research is needed to examine the versatility and long-term effects of the MB intervention.

Pain and Emotional Distress Among Substance-use Patients Beginning Treatment Relative To A Representative Comparison Group Wiest KL, Colditz JB, Carr K, Asphaug VJ, McCarty D, Pilkonis PA. J Addict Med. 2014; 8(6): 407-414.
A secondary analysis assessed health-related quality-of-life (HRQOL) characteristics (i.e., anxiety, depression, fatigue, and types of pain) among patients entering substance-use treatment and identified characteristics specific to treatment modalities relative to a representative comparison group. As part of a larger alcohol bank assessment, substance-use patients (n = 406) beginning methadone treatment (n = 170) or other outpatient treatment (n = 236) and a comparison group representative of the general population (n = 1000) completed a survey measuring anxiety, depression, fatigue, pain interference, and pain in the last 7 days. Previous studies lacked comparable and concurrent assessments across these 3 groups. Patients entering substance-use treatment had relatively high levels of emotional distress and poorer HRQOL relative to the general population. Among treatment modalities, patients beginning methadone treatment reported the highest levels of pain interference and pain behavior and the poorest physical functioning. Before the potentially modifying effects of methadone maintenance, patients beginning agonist therapy reported the greatest levels of compromised quality of life. These data present the magnitude of differences in HRQOL characteristics between treatment and comparison groups using the same assessment rubric and may help inform the design and timing of treatment modalities, thereby enhancing treatment efficacy for patients.

Race/Ethnic Disparities In the Utilization Of Treatment For Drug Dependent Inmates In U.S. State Correctional Facilities Nowotny KM. Addict Behav. 2015; 40: 148-153.
Research has documented racial and ethnic disparities in utilization, access, continuity, and quality of care for psychiatric disorders including treatment for substance use disorders among those with similar need in the general community. Currently, the extent of racial and ethnic disparities in treatment within U.S. correctional facilities is unknown. This study examines race/ethnic disparities in treatment for drug dependent inmates using the 2004 Survey of Inmates in State Correctional Facilities. Fixed effects logistic regression is used to analyze treatment outcomes for 5180 inmates housed within 286 prisons. The analysis accounts for differences in background characteristics (i.e., age, gender, marital status, foreign born status, veteran status), socioeconomic characteristics (i.e., education, employment prior to incarceration), mental health (i.e., diagnosis with a serious mental illness), and incarceration experiences (i.e., current conviction, previous incarceration episodes, time served, additional sentencing requirements, external social support, disciplinary violations). The findings identify a remarkable unmet need among drug dependent inmates in that less than one-half of drug dependent inmates had received any type of treatment in prison at the time of the interview with the most common treatment type being self-help groups. Compared to whites, drug dependent Latino inmates have significantly lower odds of utilizing treatment, yet there are no significant black--white disparities found. The current study suggests that treatment for drug dependent inmates needs to be expanded to include clinically or medically based treatment since the failure to address addictions in the criminal legal system has been identified as the single most significant reason for re-arrest and recidivism once released.

Adapting and Implementing An Evidence-based Treatment With Justice-involved Adolescents: The Example Of Multidimensional Family Therapy Liddle HA. Fam Process. 2014; 53(3): 516-528.
For over four decades family therapy research and family centered evidence-based therapies for justice-involved youths have played influential roles in changing policies and services for these young people and their families. But research always reveals challenges as well as advances. To be sure, demonstration that an evidence-based therapy yields better outcomes than comparison treatments or services as usual is an accomplishment. But the extraordinary complexity embedded in that assertion feels tiny relative to what we are now learning about the so-called transfer of evidence-based treatments to real world practice settings. Today's family therapy studies continue to assess outcome with diverse samples and presenting problems, but research and funding priorities also include studying particular treatments in non-research settings. Does an evidence-based intervention work as well in a community clinic, with clinic personnel? How much of a treatment has to change to be accepted and implemented in a community clinic? Perhaps it is the setting and existing procedures that have to change? And, in those cases, do accommodations to the context compromise outcomes? Thankfully, technology transfer notions gave way to more systemic, dynamic, and frankly, more family therapy-like conceptions of the needed process. Implementation science became the more sensible, as well as the theoretically and empirically stronger overarching framework within which the evidence-based family based therapies now operate. Using the example of Multidimensional Family Therapy, this article discusses treatment development, refinement, and implementation of that adapted approach in a particular clinical context-a sector of the juvenile justice system-juvenile detention.

From Risk Assessment To Risk Management: Matching Interventions To Adolescent Offenders' Strengths and Vulnerabilities Singh JP, Desmarais SL, Sellers BG, Hylton T, Tirotti M, Van Dorn RA. Child Youth Serv Rev. 2014; 47(Pt 1): 1-9.
Though considerable research has examined the validity of risk assessment tools in predicting adverse outcomes in justice-involved adolescents, the extent to which risk assessments are translated into risk management strategies and, importantly, the association between this link and adverse outcomes has gone largely unexamined. To address these shortcomings, the Risk-Need-Responsivity (RNR) model was used to examine associations between identified strengths and vulnerabilities, interventions, and institutional outcomes for justice-involved youth. Data were collected from risk assessments completed using the Short-Term Assessment of Risk and Treatability: Adolescent Version (START:AV) for 120 adolescent offenders (96 boys and 24 girls). Interventions and outcomes were extracted from institutional records. Mixed evidence of adherence to RNR principles was found. Accordant to the risk principle, adolescent offenders judged to have more strengths had more strength-based interventions in their service plans, though adolescent offenders with more vulnerabilities did not have more interventions targeting their vulnerabilities. With respect to the need and responsivity principles, vulnerabilities and strengths identified as particularly relevant to the individual youth's risk of adverse outcomes were addressed in the service plans about half and a quarter of the time, respectively. Greater adherence to the risk and need principles was found to predict significantly the likelihood of externalizing outcomes. Findings suggest some gaps between risk assessment and risk management and highlight the potential usefulness of strength-based approaches to intervention.

An Experimental Trial Of Adaptive Programming In Drug Court: Outcomes At 6, 12 and 18 Months Marlowe DB, Festinger DS, Dugosh KL, Benasutti KM, Fox G, Harron A. J Exp Criminol. 2014; 10(2): 129-149.
The objective of this study was to test whether an adaptive program improves outcomes in drug court by adjusting the schedule of court hearings and clinical case-management sessions pursuant to a priori performance criteria. Consenting participants in a misdemeanor drug court were randomly assigned to the adaptive program ($n = 62$) or to a baseline-matching condition ($n = 63$) in which they attended court hearings based on the results of a criminal risk assessment. Outcome measures were re-arrest rates at 18 months post-entry to the drug court and urine drug test results and structured interview results at 6 and 12 months post-entry. Although previously published analyses revealed significantly fewer positive drug tests for participants in the adaptive condition during the first 18 weeks of drug court, current analyses indicate the effects converged during the ensuing year. Between-group differences in new arrest rates, urine drug test results and self-reported psychosocial problems were small and non-statistically significant at 6, 12 and 18 months post-entry. A non-significant trend ($p = .10$) suggests there may have been a small residual impact (Cramer's $\nu = .15$) on new misdemeanor arrests after 18 months. Adaptive programming shows promise for enhancing short-term outcomes in drug courts; however, additional efforts are needed to extend the effects beyond the first 4 to 6 months of enrollment.

The Setting Is the Service: How The Architecture Of Sober Living Residences Supports Community Based Recovery Wittman F, Jee B, Polcin DL, Henderson D. Int J Self Help Self Care. 2014; 8(2): 189-225.
The architecture of residential recovery settings is an important silent partner in the alcohol/drug recovery field. The settings significantly support or hinder recovery experiences of residents, and

shape community reactions to the presence of sober living houses (SLH) in ordinary neighborhoods. Grounded in the principles of Alcoholics Anonymous, the SLH provides residents with settings designed to support peer based recovery; further, these settings operate in a community context that insists on sobriety and strongly encourages attendance at 12-step meetings. Little formal research has been conducted to show how architectural features of the recovery setting - building appearance, spatial layouts, furnishings and finishes, policies for use of the facilities, physical care and maintenance of the property, neighborhood features, aspects of location in the city - function to promote (or retard) recovery, and to build (or detract from) community support. This paper uses a case-study approach to analyze the architecture of a community-based residential recovery service that has demonstrated successful recovery outcomes for its residents, is popular in its community, and has achieved state-wide recognition. The Environmental Pattern Language (Alexander, Ishikawa, & Silverstein, 1977) is used to analyze its architecture in a format that can be tested, critiqued, and adapted for use by similar programs in many communities, providing a model for replication and further research.

Comparative Effectiveness Of California's Proposition 36 and Drug Court Programs Before and After Propensity Score Matching Evans E, Li L, Urada D, Anglin MD. Crime Delinq. 2014; 60(6): 909-938.
California's voter-initiated Proposition 36 (Prop 36) program is often unfavorably compared to drug courts, but little is empirically known about the comparative effectiveness of the two approaches. Using statewide administrative data, analyses were conducted on all Prop 36 and drug court offenders with official records of arrest and drug treatment. Propensity score matching was used to create equivalent groups, enabling comparisons of success at treatment discharge, recidivism over 12 months' post-treatment entry, and magnitude of behavioral changes. Significant behavioral improvements occurred for both Prop 36 and drug court offenders, but while more Prop 36 offenders were successful at discharge, more recidivated over 12 months. Core programmatic differences likely contributed to differences in outcomes. Policy implications are discussed.

Maximizing Social Model Principles In Residential Recovery Settings Polcin D, Mericle A, Howell J, Sheridan D, Christensen J. J Psychoactive Drugs. 2014; 46(5): 436-43.
Peer support is integral to a variety of approaches to alcohol and drug problems. However, there is limited information about the best ways to facilitate it. The "social model" approach developed in California offers useful suggestions for facilitating peer support in residential recovery settings. Key principles include using 12-step or other mutual-help group strategies to create and facilitate a recovery environment, involving program participants in decision making and facility governance, using personal recovery experience as a way to help others, and emphasizing recovery as an interaction between the individual and their environment. Although limited in number, studies have shown favorable outcomes for social model programs. Knowledge about social model recovery and how to use it to facilitate peer support in residential recovery homes varies among providers. This article presents specific, practical suggestions for enhancing social model principles in ways that facilitate peer support in a range of recovery residences.

Patient Perspectives On Buprenorphine/naloxone: A Qualitative Study Of Retention During the Starting Treatment With Agonist Replacement Therapies (START) Study Teruya C, Schwartz RP, Mitchell SG, Hasson AL, Thomas C, Buoncristiani SH, Hser Y-I, Wiest K, Cohen AJ, Glick N, Jacobs P, McLaughlin P, Ling W. J Psychoactive Drugs. 2014; 46(5): 412-426.
This study examines the barriers and facilitators of retention among patients receiving buprenorphine/naloxone at eight community-based opioid treatment programs across the United States. Participants (n = 105) were recruited up to three and a half years after having participated in a randomized clinical trial comparing the effect of buprenorphine/naloxone and methadone on liver function. Semi-structured interviews were conducted with 67 patients provided with buprenorphine/naloxone who had terminated early and 38 patients who had completed at least 24 weeks of the trial. Qualitative data were analyzed using the constant comparison method. Barriers to buprenorphine/naloxone retention that emerged included factors associated with: (1) the design of the clinical trial; (2) negative medication or treatment experience; and (3) personal circumstances. The facilitators comprised: (1) positive experience with the medication; (2) personal determination and commitment to complete; and (3) staff encouragement and support. The themes drawn from interviews highlight the importance of considering patient's; prior experience with buprenorphine/naloxone and methadone, medication preference, personal circumstances, and motivation to abstain from illicit use or misuse of opioids, as these may influence retention. Ongoing education of patients and staff regarding buprenorphine/naloxone, especially in comparison to methadone, and support from staff and peers are essential.

Emergency Department Use Among HIV-Infected Released Jail Detainees Boyd AT, Song DL, Meyer JP, Altice FL. J Urban Health. 2014.
Release from short-term jail detention is highly destabilizing, associated with relapse to substance use, recidivism, and disrupted health care continuity. Little is known about emergency department (ED) use, potentially a surrogate for medical, psychiatric, or social instability, by people living with HIV/AIDS (PLWHA) leaving jails. All ED visits were reviewed from medical records for a cohort of 109 PLHWA in the year following release from county jail in Connecticut, between January 1, 2008 and December 31, 2010. Primary outcomes were frequency and timing of ED visits, modeled using multivariate negative binomial regression and Cox proportional hazards regression, respectively. Demographic, substance use, and psychiatric disorder severity factors were evaluated as potential covariates. Overall, 71 (65.1%) of the 109 participants made 300 unique ED visits (2.75 visits/person-year) in the year following jail-release. Frequency of ED use was positively associated with female sex (incidence rate ratios, IRR 2.40 [1.36-4.35]), homelessness (IRR 2.22 [1.15-4.41]), and recent substance use (IRR 2.47 [1.33-4.64]), and inversely associated with lifetime drug severity (IRR 0.01 [0-0.10]), and being retained in HIV primary care (IRR 0.80 [0.65-0.99]). Those in late or sustained HIV care used the ED sooner than those not retained in HIV primary care (median for late retention 16.3 days, median for sustained retention 24.9 days, median for no retention not reached at 12 months, p value 0.004). Using multivariate modeling, those who used the ED earliest upon release were more likely to be homeless (HR 1.98 [1.02-3.84]), to be retained in HIV care (HR 1.30 [1.04-1.61]), and to have recently used drugs (HR 2.51 [1.30-4.87]), yet had a low lifetime drug severity (HR 0.01 [0.00-0.14]). Among PLWHA released from jail, frequency of ED use is high, often soon after release, and is associated with social and drug-related destabilizing factors. Future interventions for this specific population should focus on addressing these resource gaps, ensuring housing, and establishing immediate linkage to HIV primary care after release from jail.

Risk Profile and Treatment Needs Of Women In Jail With Co-occurring Serious Mental Illness and Substance Use Disorders Nowotny KM, Belknap J, Lynch S, DeHart D. Women Health. 2014; 54(8): 781-795.
Recent research has documented the unusually high rates of incarcerated women's serious mental illness (SMI) and substance use disorders (SUD). Complicating these high rates is the high comorbidity of SMI with SUD and trauma histories. Yet, incarcerated women have significantly less access to treatment and health services while incarcerated than men. The authors used data from a multi-site, multi-method project funded by the Bureau of Justice Assistance (2011-2012) to determine the risk profile of women in jail (n = 491) with a current co-occurring SMI (i.e., major depressive disorder, bipolar disorder, schizophrenia spectrum disorder) and SUD (i.e., abuse, dependence). The study spanned multiple geographic regions, and structured diagnostic interviews were used to understand better the women that comprised this vulnerable population. One-in-five of the women had a current co-occurring disorder (CCOD). The findings revealed that significantly more women with a CCOD had been exposed to violence and were exposed to drugs at a younger age. Further, about one-third of women with a CCOD had received no treatment from a health care professional in the past year, demonstrating a substantial unmet need. The authors conclude that investing in mental and behavioral health care in jails is critical to the health and safety of women as well as the communities to which they return.

Continuous-Time System Identification Of A Smoking Cessation Intervention Timms KP, Rivera DE, Collins LM, Piper ME. Int J Control. 2014; 87(7): 1423-1437.
Cigarette smoking is a major global public health issue and the leading cause of preventable death in the United States. Toward a goal of designing better smoking cessation treatments, system identification techniques are applied to intervention data to describe smoking cessation as a process of behavior change. System identification problems that draw from two modeling paradigms in quantitative psychology (statistical mediation and self-regulation) are considered, consisting of a series of continuous-time estimation problems. A continuous-time dynamic modeling approach is employed to describe the response of craving and smoking rates during a quit attempt, as captured in data from a smoking cessation clinical trial. The use of continuous-time models provide benefits of parsimony, ease of interpretation, and the opportunity to work with uneven or missing data.

A Hybrid Model Predictive Control Strategy For Optimizing A Smoking Cessation Intervention Timms KP, Rivera DE, Piper ME, Collins LM. Proc Am Control Conf. 2014; 2014: 2389-2394.
The chronic, relapsing nature of tobacco use represents a major challenge in smoking cessation treatment. Recently, novel intervention paradigms have emerged that seek to adjust treatments over time in order to meet a patient's changing needs. This article demonstrates that Hybrid Model Predictive Control (HMPC) offers an appealing framework for designing these optimized, time-varying smoking cessation interventions. HMPC is a particularly appropriate approach as it recognizes that intervention doses must be assigned in predetermined, discrete units while retaining receding-horizon, constraint-handling, and combined feedback and feedforward capabilities. Specifically, an intervention algorithm is developed here in which counseling and two pharmacotherapies are manipulated to reduce daily smoking and craving levels. The potential usefulness of such an intervention is illustrated through simulated treatment of a quit attempt in a hypothetical patient, which highlights that prioritizing reduction in craving over total daily smoking levels significantly reduces craving levels, suppresses relapse, and successfully rejects time-varying

disturbances such as stress, all while adhering to several practical operational constraints and resource use considerations.

HIV In People Reincarcerated In Connecticut Prisons and Jails: An Observational Cohort Study Meyer JP, Cepeda J, Springer SA, Wu J, Trestman RL, Altice FL. Lancet HIV. 2014; 1(2): e77-e84.
Re-incarceration in prison or jail correlates with non-sustained HIV viral suppression, but HIV treatment outcomes in released prisoners who are re-incarcerated have not recently been systematically assessed despite advances in antiretroviral treatment (ART) potency, simplicity, and tolerability. In a retrospective cohort of re-incarcerated inmates with HIV in Connecticut (2005-12), the authors used longitudinally linked demographic, pharmacy, and laboratory databases to examine correlates of viral suppression. The primary outcome was viral suppression on re-incarceration, defined as viral load lower than 400 RNA copies per mL. Of 497 prisoners and jail detainees with HIV, with 934 re-incarcerations, individuals were mostly unmarried, uninsured, and black men prescribed a protease-inhibitor-based ART regimen. During the median 329 days (IQR 179-621) between prison release and re-incarceration, the proportion of incarceration periods with viral suppression decreased significantly from 52% to 31% (mean HIV-RNA increased by $0{\cdot}4\ \log_{10}$; $p<0{\cdot}0001$), lower than Connecticut's HIV-infected prison population and those prescribed ART nationally. 158 (51%) of 307 individuals with viral suppression on release had viral suppression on re-incarceration. Viral suppression on re-incarceration was associated with increasing age (adjusted odds ratio [OR] 1·04, 95% CI 1·01-1.07), being prescribed non-nucleoside reverse transcriptase inhibitor-based regimens (1.63, 1.14-2.34), and having higher levels of medical or psychiatric comorbidity (1.16, 1.03-1.30). Identification of individuals most at risk for recidivism and loss of viral suppression might mitigate the risk that repeated re-incarceration poses to systems of public health and safety. Bristol-Myers Squibb Virology, Patterson Trust, and National Institute on Drug Abuse.

The Evolution Of Peer Run Sober Housing As A Recovery Resource For California Communities Wittman FD, Polcin D. Int J Self Help Self Care. 2014; 8(2): 157-187.
Sober living houses (SLHs) are alcohol- and drug-free living environments that offer social support to persons attempting to abstain from alcohol and drugs. They use a peer-oriented, social model approach that emphasizes mutual support, financial self-sufficiency, and resident involvement in decision making and management of the facility. Although they represent an important response to the increasing call for more services that help sustain abstinence from drugs and alcohol over time, they are an under recognized and underutilized recovery resource. The purpose of this paper is to trace the evolution of sober living houses in California from the early influences of Alcoholics Anonymous (AA) in the 1930s to the establishment of current SLH associations, such as the Sober Living Network in Southern California. The paper describes key events and policies that influenced SLHs. Although initial research on outcomes of SLH residents has been very encouraging, there is a need for more research to guide improvement of structure and operations. The paper concludes with a discussion of implications for the growth of recovery services and for community housing policy.

Psychiatric Severity and HIV-Risk Sexual Behaviors Among Persons With Substance Use Disorders Majer JM, Komer AC, Jason LA. J Dual Diagn. 2015; 11(1): 3-11.
The relationship between mental illness and human-immunodeficiency virus (HIV)-risk sexual behavior among persons with substance use disorders is not well-established because of differences in assessing psychiatric factors (types, symptoms, severity), substance use (diagnosis, survey responses, past substance use), and HIV-risk sexual behaviors (individual measures, combination of sex/drug use risk behaviors) across studies. This study utilized a more global and dimensional aspect of psychiatric issues (problem severity) to examine the relationship with HIV-risk sexual behaviors and substance use among persons with substance use disorders. Participants included 224 men and 46 women, with a mean age of 40.4ýýyears (SD = 9.5). The most common substances were heroin/opiates, with 41.4% reporting use of these substances (n = 110), while 27.8% reported using cocaine (n = 74) and 12.8% reported using alcohol (n = 34). Of all participants, 39 (14.4%) were identified as having high psychiatric severity (defined using the psychiatric severity score from the Addiction Severity Index), which was used as an indication of probable comorbid psychiatric and substance use disorders. Among these participants likely to have comorbid disorders, hierarchical linear regression was conducted to examine HIV-risk sexual behaviors (number of partners and unprotected sexual behaviors in the past 30ýýdays) in relation to psychiatric severity, substance use, and gender. Gender (women) and psychiatric severity (higher) were significantly related to greater HIV-risk sexual behaviors. After entering gender and substance use into the regression model, psychiatric severity accounted for another 21.9% of the variance in number of partners and 14.1% of the variance in unprotected sexual behaviors. Overall, the models accounted for 55.5% and 15.6% of the variance, respectively. A significant interaction was found for number of partners (but not frequency of unprotected behavior), such that those higher in psychiatric severity and higher in substance use had a greater number of sexual partners. The model including this interaction term accounted for 63.4% of the variance in number of partners. Findings suggest psychiatric severity is an underlying risk factor for HIV-risk sexual behavior among persons with substance use disorders who have various psychiatric comorbidities.

Correlates Of Heroin and Methamphetamine Use Among Homeless Male Ex-Jail And Prison Offenders Nyamathi A, Salem BE, Farabee D, Hall E, Zhang S, Marfisee M, Khalilifard F, Musto S, Leake B. Addict Res Theory. 2014; 22(6): 463-473.
Homeless men exiting California State jails and prisons are a heterogeneous community with varied childhood, incarceration and drug use histories. This cross-sectional study assessed whether homeless men who were discharged from either jail or prison into a residential substance abuse treatment program, differed in terms of methamphetamine and heroin use. This study utilized baseline data collected on 540 recently paroled men randomized to one of three programs that assessed the impact of a peer coaching intervention on subsequent drug use and re-incarceration. The authors found that younger ex-offenders exiting prisons and jails were more likely to have used methamphetamine alone, whereas African American ex-offenders were less likely to have used methamphetamine alone when compared to other ethnic groups. Further, ex-offenders exiting jails and self-reporting use of heroin only at baseline were significantly more likely than their counterparts to have been removed from home before age 18. For men exiting jails, there was an association between lower self-esteem and having used methamphetamine but not heroin. However, having used both heroin and methamphetamine was associated with both violent crime and cognitive problems in both jail and prison samples. These findings showcase the need to understand unique correlates of both heroin and methamphetamine as they relate to jail and prison populations.

Clinical Practice Guideline For the Management Of Chronic Kidney Disease In Patients Infected With HIV: 2014 Update By the HIV Medicine Association Of the Infectious Diseases Society Of America Lucas GM, Ross MJ, Stock PG, Shlipak MG, Wyatt CM, Gupta SK, Atta MG, Wools-Kaloustian KK, Pham PA, Bruggeman LA, Lennox JL, Ray PE, Kalayjian RC. Clin Infect Dis. 2014; 59(9): e96-138.
It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Preferences For Professional Versus Informal Care At End Of Life Amongst African-American Drug Users With HIV/AIDS Mitchell MM, Robinson AC, Nguyen TQ, Smith TJ, Knowlton AR. AIDS Care. 2015; 27(2): 218-122.
With the advent of antiretroviral therapies, persons living with HIV/AIDS (PLHIVs) are living longer but with increased impairment and care needs. The purpose of this study was to assess whether a vulnerable population of PLHIVs preferred informal versus professional care when unable to care for themselves, and individual and support network factors associated with preference for informal care. The findings have potential implications for facilitating the population's informal care at end of life. Data were from the BEACON study, which examined social factors associated with health outcomes among former or current drug-using PLHIVs in Baltimore, MD. Structural equation modeling was used to identify individual and support network characteristics associated with PLHIV's preference for informal (family or friends) compared to professional care. The structural equation model indicated preference for informal care was associated with female sex, greater informal care receipt, reporting one's main partner (i.e., boy/girlfriend or spouse) as the primary source of informal care, and a support network comprised greater numbers of female kin and persons supportive of the participant's HIV treatment adherence. Not asking for needed help to avoid owing favors was associated with preferring professional care. Findings suggest that interventions to promote informal end of life care should bolster supportive others'; resources and skills for care provision and treatment adherence support, and should address perceived norms of reciprocity. Such intervention will help ensure community caregiving in a population with high needs for long-term care.

End-Stage Renal Disease Among HIV-Infected Adults In North America Abraham AG, Althoff KN, Jing Y, Estrella MM, Kitahata MM, Wester CW, Bosch RJ, Crane H, Eron J, Gill MJ, Horberg MA, Justice AC, Klein M, Mayor AM, Moore RD, Palella FJ, Parikh CR, Silverberg MJ, Golub ET, Jacobson LP, Napravnik S, Lucas GM; for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of the International Epidemiologic Databases to Evaluate AIDS (IeDEA). Clin Infect Dis. 2014.
Human immunodeficiency virus (HIV)-infected adults, particularly those of black race, are at high-risk for end-stage renal disease (ESRD), but contributing factors are evolving. The authors hypothesized that improvements in HIV treatment have led to declines in risk of ESRD, particularly among HIV-infected blacks. Using data from the North American AIDS Cohort Collaboration for Research and Design from January 2000 to December 2009, we validated 286 incident ESRD cases using abstracted medical evidence of dialysis (lasting >6 months) or renal transplant. A total of 38 354 HIV-infected adults aged 18-80 years contributed 159 825 person-years (PYs). Age- and sex-

standardized incidence ratios (SIRs) were estimated by race. Poisson regression was used to identify predictors of ESRD. HIV-infected ESRD cases were more likely to be of black race, have diabetes mellitus or hypertension, inject drugs, and/or have a prior AIDS-defining illness. The overall SIR was 3.2 (95% confidence interval [CI], 2.8-3.6) but was significantly higher among black patients (4.5 [95% CI, 3.9-5.2]). ESRD incidence declined from 532 to 303 per 100 000 PYs and 138 to 34 per 100 000 PYs over the time period for blacks and non-blacks, respectively, coincident with notable increases in both the prevalence of viral suppression and the prevalence of ESRD risk factors including diabetes mellitus, hypertension, and hepatitis C virus co-infection. The risk of ESRD remains high among HIV-infected individuals in care but is declining with improvements in virologic suppression. HIV-infected black persons continue to comprise the majority of cases, as a result of higher viral loads, comorbidities, and genetic susceptibility.

Characteristics Of Students Participating In Collegiate Recovery Programs: A National Survey Laudet AB, Harris K, Kimball T, Winters KC, Moberg DP. J Subst Abuse Treat. 2014.
Relapse rates are high among individuals with substance use disorders (SUD), and for young people pursuing a college education, the high rates of substance use on campus can jeopardize recovery. Collegiate Recovery Programs (CRPs) are an innovative campus-based model of recovery support that is gaining popularity but remains under-investigated. This study reports on the first nationwide survey of CRP-enrolled students (N=486 from 29 different CRPs). Using an online survey, the authors collected information on background, SUD and recovery history, and current functioning. Most students (43% females, mean age=26) had used multiple substances, had high levels of SUD severity, high rates of treatment and 12-step participation. Fully 40% smoke. Many reported criminal justice involvement and periods of homelessness. Notably, many reported being in recovery from, and currently engaging in multiple behavioral addictions-e.g., eating disorders, and sex and love addiction. Findings highlight the high rates of co-occurring addictions in this under-examined population and underline the need for treatment, recovery support programs and college health services to provide integrated support for mental health and behavioral addictions to SUD-affected young people.

Technology Use In Linking Criminal Justice Reentrants To HIV Care In The Community: A Qualitative Formative Research Study Peterson J, Cota M, Gray H, Bazerman L, Kuo I, Kurth A, Beckwith C. J Health Commun. 2014; 1-7.
Innovative interventions increasing linkage, adherence, and retention in care among HIV-infected persons in the criminal justice system are needed. The authors conducted a qualitative study to investigate technology-based tools to facilitate linkage to community-based care and viral suppression for HIV-infected jail detainees on antiretroviral medications being released to the community. The authors conducted 24 qualitative interviews-12 in Rhode Island and 12 in Washington, DC-among recently incarcerated HIV-infected persons to elicit their perceptions on the use of technology tools to support linkage to HIV care among criminal justice populations. This article discusses participants' perceptions of the acceptability of technological tools such as (a) a computer-based counseling and (b) text messaging interventions. The participants reported positive experiences when previewing the technology-based tools to facilitate linkage to HIV care and adherence to HIV medications. Successful linkage to care has been shown to improve HIV-associated and non-HIV-associated health outcomes, as well as prevent criminal recidivism and facilitate reentrant's; successful and meaningful transition. These findings can be used to inform the

implementation of interventions aimed at promoting adherence to antiretroviral medications and linkage to care for HIV-infected persons being released from the correctional setting.

Reciprocal Responsibility and Social Support among Women in Substance Use Recovery
Brereton KL, Alvarez J, Jason LA, Stevens EB, Dyson VB, McNeilly C, Ferrari JR. Int J Self Help Self Care. 2014; 8(2): 239-257.
This study sought to identify individual- and house-level predictors of women's employment, education, and retention in self-run recovery homes. Data from a national study of 292 women in Oxford House, an international organization of recovery homes grounded on self-help/mutual aid and 12-step principles were analyzed. Results indicated that the houses' Reciprocal Responsibility predicted number of days of paid work. Individual and house variables did not predict participation in education. The presence of recovery home members in personal social networks was statistically significant in predicting retention in the recovery home. Lastly, results indicated that number of days of paid work were not predictive of likelihood of substance use in the next 12 months. The findings of this study indicate that the ability to develop social networks and Reciprocal Responsibility in recovery homes can contribute to positive outcomes for women.

Does Gender Matter? Exploring Mental Health Recovery Court Legal and Health Outcomes
Kothari CL, Butkiewicz R, Williams ER, Jacobson C, Morse DS, Cerulli C. Health Justice. 2014; 2(1): 12.
Based upon therapeutic justice principles, mental health courts use legal leverage to improve access and compliance to treatment for defendants who are mentally ill. Justice-involved women have a higher prevalence of mental illness than men, and it plays a greater role in their criminal behavior. Despite this, studies examining whether women respond differently than men to mental health courts are lacking. Study goals were to examine gender-related differences in mental health court participation, and in criminal justice, psychiatric and health-related outcomes. This study utilized a quasi-experimental pre-posttest design without a control group. The data were abstracted from administrative records of Kalamazoo Community Mental Health and Substance Abuse agency, the county jail and both county hospitals, 2008 through 2011. Generalized estimating equation regression was used to assess gender-differences in pre-post program outcomes (jail days, psychiatric and medical hospitalization days, emergency department visits) for the 30 women and 63 men with a final mental health court disposition. Program-eligible females were more likely than males to become enrolled in mental health court. Otherwise they were similar on all measured program-participation characteristics: treatment compliance, WRAP participation and graduation rate. All participants showed significant reductions in emergency department visits, but women-completers had significantly steeper drops than males: from 6.7 emergency department visits to 1.3 for women, and from 4.1 to 2.4 for men. A similar gender pattern emerged with medical-hospitalization-days: from 2.2 medical hospital days down to 0.1 for women, and from 0.9 days up to 1.8 for men. While women had fewer psychiatric hospitalization days than men regardless of program involvement (2.5 and 4.6, respectively), both genders experienced fewer days after MHRC compared to before. Women and men showed equal gains from successful program completion in reduced jail days. Despite similar participation characteristics, findings point to greater health gains by female compared to male participants, and to lower overall psychiatric acuity. Mental-health-court participation was associated with decreased psychiatric hospitalization days and emergency department visits. Successful program completion correlated to fewer jail days for both women and men.

Exploring Intentions To Discriminate Against Patients Living With HIV/AIDS Among Future Healthcare Providers In Malaysia Earnshaw VA, Jin H, Wickersham J, Kamarulzaman A, John J, Altice FL. Trop Med Int Health. 2014; 19(6): 672-679.
Stigma towards people living with HIV/AIDS (PLWHA) is strong in Malaysia. Although stigma has been understudied, it may be a barrier to treating the approximately 81,000 Malaysian PLWHA. The current study explores correlates of intentions to discriminate against PLWHA among medical and dental students, the future healthcare providers of Malaysia. An online, cross-sectional survey of 1296 medical and dental students was conducted in 2012 at seven Malaysian universities; 1165 (89.9%) completed the survey and were analyzed. Socio-demographic characteristics, stigma-related constructs and intentions to discriminate against PLWHA were measured. Linear mixed models were conducted, controlling for clustering by university. The final multivariate model demonstrated that students who intended to discriminate more against PLWHA were female, less advanced in their training, and studying dentistry. They further endorsed more negative attitudes towards PLWHA, internalized greater HIV-related shame, reported more HIV-related fear and disagreed more strongly that PLWHA deserve good care. The final model accounted for 38% of the variance in discrimination intent, with 10% accounted for by socio-demographic characteristics and 28% accounted for by stigma-related constructs. It is critical to reduce stigma among medical and dental students to eliminate intentions to discriminate and achieve equitable care for Malaysian PLWHA. Stigma-reduction interventions should be multipronged, addressing attitudes, internalized shame, fear and perceptions of deservingness of care.

The Relationship Between Drug Use, Drug-related Arrests, and Chronic Pain Among Adults On Probation Reingle Gonzalez JM, Walters ST, Lerch J, Taxman FS. J Subst Abuse Treat. 2014.
The intersection between chronic health conditions, drug use, and treatment seeking behavior among adults in the criminal justice system has been largely understudied. This study examined whether chronic pain was associated with opiate use, other illicit drug use, and drug-related arrests in a sample of substance-using probationers. The authors expected that probationers with chronic pain-related diagnoses would report more opiate use and drug-related arrests. This study used baseline data from 250 adults on probation in Baltimore, Maryland and Dallas, Texas who were participating in a larger clinical trial. Eighteen percent of probationers in this sample reported suffering from chronic pain. In bivariate analyses, probationers with chronic pain reported more drug-related arrests ($t=-1.81$; $p<0.05$) than those without chronic pain. Multivariate analyses support the hypothesis that probationers who reported chronic pain were marginally more likely to use opiates (OR=2.37; 95% CI .89-1.05) and non-opiate illicit drugs (OR=3.11; 95% CI 1.03-9.39) compared to offenders without chronic pain. In summary, these findings suggest that adults under probation supervision who suffer from chronic pain may be involved in criminal activity (specifically, drug-related criminal activity) in an effort to self-medicate their physical health condition(s). Screening probationers for chronic pain in the probation setting and referring these adults to pain management treatment may be an important step in advancing public safety.

Leveraging Intensive Longitudinal Data To Better Understand Health Behaviors Timms KP, Martin CA, Rivera DE, Hekler EB, Riley W. Conf Proc IEEE Eng Med Biol Soc. 2014; 2014: 6888-6891.
Behavioral scientists have historically relied on static modeling methodologies. The rise in mobile and wearable sensors has made intensive longitudinal data (ILD) - behavioral data measured frequently over time - increasingly available. Consequently, analytical frameworks are emerging

that seek to reliably quantify dynamics reflected in these data. Employing an input-output perspective, dynamical systems models from engineering can characterize time-varying behaviors as processes of change. Specifically, ILD and parameter estimation routines from system identification can be leveraged together to offer parsimonious and quantitative descriptions of dynamic behavioral constructs. The utility of this approach for facilitating a better understanding of health behaviors is illustrated with two examples. In the first example, dynamical systems models are developed for Social Cognitive Theory (SCT), a prominent concept in behavioral science that considers interrelationships between personal factors, the environment, and behaviors. Estimated models are then obtained that explore the role of SCT in a physical activity intervention. The second example uses ILD to model day-to-day changes in smoking levels as a craving-mediated process of behavior change.

The Importance Of Behavior Theory In Control System Modeling Of Physical Activity Sensor Data Riley WT, Martin CA, Rivera DE. Conf Proc IEEE Eng Med Biol Soc. 2014; 2014: 6880-6883.
Among health behaviors, physical activity has the most extensive record of research using passive sensors. Control systems and other system dynamic approaches have long been considered applicable for understanding human behavior, but only recently has the technology provided the precise and intensive longitudinal data required for these analytic approaches. Although sensors provide intensive data on the patterns and variations of physical activity over time, the influences of these variations are often unmeasured. Health behavior theories provide an explanatory framework of the putative mediators of physical activity changes. Incorporating the intensive longitudinal measurement of these theoretical constructs is critical to improving the fit of control system model of physical activity and for advancing behavioral theory. Theory-based control models also provide guidance on the nature of the controllers which serve as the basis for just-in-time adaptive interventions based on these control system models.

Evaluating Alternative Aftercare Models For Ex-Offenders Jason LA, Olson BD, Harvey R. J Drug Issues. 2015; 45(1): 53-68.
This study examined the role played by aftercare following (mainly) inpatient community-based treatment in the outcomes of criminal ex-offenders with substance use disorders. Two hundred and seventy individuals who had been released from the criminal justice system were randomly assigned to either a Therapeutic Community (TC), recovery homes called Oxford Houses (OHs), or usual care settings (UA). The OHs and TCs are residential settings that emphasized socialization and abstinence from drugs and alcohol, but OHs do not include the formal therapeutic change interventions common to TCs, nor did they include any on-site access to drug abuse or health care professionals. UA involved what occurred naturally after completing treatment, which included staying with friends or family members, their own house or apartment, homeless shelters, or other settings. Longer lengths of stay in either the TCs or OHs were associated with increased employment, and reduced alcohol and drug use. Those assigned to the OH condition received more money from employment, worked more days, achieved higher continuous alcohol sobriety rates, and had more favorable cost-benefit ratios.

Multiple Comparisons For Survival Data With Propensity Score Adjustment Zhu H, Lu B. Comput Stat Data Anal. 2015; 86(): 42-51.
This article considers the practical problem in clinical and observational studies where multiple treatment or prognostic groups are compared and the observed survival data are subject to right censoring. Two possible formulations of multiple comparisons are suggested. Multiple Comparisons with a Control (MCC) compare every other group to a control group with respect to survival outcomes, for determining which groups are associated with lower risk than the control. Multiple Comparisons with the Best (MCB) compare each group to the truly minimum risk group and identify the groups that are either with the minimum risk or the practically minimum risk. To make a causal statement, potential confounding effects need to be adjusted in the comparisons. Propensity score based adjustment is popular in causal inference and can effectively reduce the confounding bias. Based on a propensity-score-stratified Cox proportional hazards model, the approaches of MCC test and MCB simultaneous confidence intervals for general linear models with normal error outcome are extended to survival outcome. This paper specifies the assumptions for causal inference on survival outcomes within a potential outcome framework, develops testing procedures for multiple comparisons and provides simultaneous confidence intervals. The proposed methods are applied to two real data sets from cancer studies for illustration, and a simulation study is also presented.

An Examination Of The First Oxford House In The UK: A Preliminary Investigation Majer JM, Beers K, Jason LA. Drugs (Abingdon Engl). 2014; 21(5): 347-356.
An exploratory investigation was conducted to examine the implementation of the first self-run, communal-living setting based on the Oxford House model, in the United Kingdom (UK). A cross-sectional, mixed methods design was used to examine the Oxford House models' total abstinence approach to recovery from substance use disorders among residents (n = 7) living in the first Oxford House established in the UK. Several measures commonly used in addiction research and personal narratives were used to assess residents' response to Oxford House living. Findings suggest that the Oxford House model is a post-treatment intervention that meets the needs of individuals seeking an abstinence-based recovery from alcohol and/or drug dependence in the UK.

CLINICAL TRIALS NETWORK-RELATED RESEARCH

Long-term Outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study Weiss RD, Potter JS, Griffin ML, Provost SE, Fitzmaurice GM, McDermott KA, Srisarajivakul EN, Dodd DR, Dreifuss JA, McHugh RK, Carroll KM. Drug Alcohol Depend. 2015 Mar 6. [Epub ahead of print].
Despite the growing prevalence of prescription opioid dependence, longitudinal studies have not examined long-term treatment response. The current study examined outcomes over 42 months in the Prescription Opioid Addiction Treatment Study (POATS). POATS was a multi-site clinical trial lasting up to 9 months, examining different durations of buprenorphine-naloxone plus standard medical management for prescription opioid dependence, with participants randomized to receive or not receive additional opioid drug counseling. A subset of participants (N=375 of 653) enrolled in a follow-up study. Telephone interviews were administered approximately 18, 30, and 42 months after main-trial enrollment. Comparison of baseline characteristics by follow-up participation suggested few differences. At Month 42, much improvement was seen: 31.7% were abstinent from opioids and not on agonist therapy; 29.4% were receiving opioid agonist therapy, but met no symptom criteria for current opioid dependence; 7.5% were using illicit opioids while on agonist therapy; and the remaining 31.4% were using opioids without agonist therapy. Participants reporting a lifetime history of heroin use at baseline were more likely to meet DSM-IV criteria for opioid dependence at Month 42 (OR=4.56, 95% CI=1.29-16.04, $p<.05$). Engagement in agonist therapy was associated with a greater likelihood of illicit-opioid abstinence. Eight percent (n=27/338) used heroin for the first time during follow-up; 10.1% reported first-time injection heroin use. The authors conclude that long-term outcomes for those dependent on prescription opioids demonstrated clear improvement from baseline. However, a subset exhibited a worsening course, by initiating heroin use and/or injection opioid use.

An Electronic Screen for Triaging Adolescent Substance Use by Risk Levels Levy S, Weiss R, Sherritt L, Ziemnik R, Spalding A, Van Hook S, Shrier LA. JAMA Pediatr. 2014 Sep; 168(9): 822-828.
Screening adolescents for substance use and intervening immediately can reduce the burden of addiction and substance-related morbidity. Several screening tools have been developed to identify problem substance use for adolescents, but none have been calibrated to triage adolescents into clinically relevant risk categories to guide interventions. The objective of this study was to describe the psychometric properties of an electronic screen and brief assessment tool that triages adolescents into 4 actionable categories regarding their experience with nontobacco substance use. Adolescent patients (age range, 12-17 years) arriving for routine medical care at 2 outpatient primary care centers and 1 outpatient center for substance use treatment at a pediatric hospital completed an electronic screening tool from June 1, 2012, through March 31, 2013, that consisted of a question on the frequency of using 8 types of drugs in the past year (Screening to Brief Intervention). Additional questions assessed severity of any past-year substance use. Patients completed a structured diagnostic interview (Composite International Diagnostic Interview-Substance Abuse Module), yielding Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) substance use diagnoses. For the entire screen and the Screening to Brief Intervention, sensitivity and specificity for identifying nontobacco substance use, substance use disorders, severe substance use disorders, and tobacco dependence were calculated using the Composite International Diagnostic Interview-Substance Abuse Module as the criterion standard. Of 340 patients invited to

participate, 216 (63.5%) enrolled in the study. Sensitivity and specificity were 100% and 84% (95% CI, 76%-89%) for identifying nontobacco substance use, 90% (95% CI, 77%-96%) and 94% (95% CI, 89%-96%) for substance use disorders, 100% and 94% (95% CI, 90%-96%) for severe substance use disorders, and 75% (95% CI, 52%-89%) and 98% (95% CI, 95%-100%) for nicotine dependence. No significant differences were found in sensitivity or specificity between the full tool and the Screening to Brief Intervention. The authors concluded that a single screening question assessing past-year frequency use for 8 commonly misused categories of substances appears to be a valid method for discriminating among clinically relevant risk categories of adolescent substance use.

Initial Response as a Predictor of 12-week Buprenorphine-Naloxone Treatment Response in a Prescription Opioid-Dependent Population McDermott KA, Griffin ML, Connery HS, Hilario EY, Fiellin DA, Fitzmaurice GM, Weiss RD. J Clin Psychiatry. 2015 Feb; 76(2): 189-194.
Initial medication response has been shown to predict treatment outcome across a variety of substance use disorders, but no studies have examined the predictive power of initial response to buprenorphine-naloxone in the treatment of prescription opioid dependence. The authors therefore conducted a secondary analysis of data from the Prescription Opioid Addiction Treatment Study to determine whether initial response to buprenorphine-naloxone predicted 12-week treatment outcome in a prescription opioid-dependent population. Using data from a multisite, randomized controlled trial of buprenorphine-naloxone plus counseling for DSM-IV prescription opioid dependence (June 2006-July 2009), the authors conducted a secondary analysis to investigate the relationship between initial medication response and 12-week treatment outcome to establish how soon the efficacy of buprenorphine-naloxone could be predicted (N = 360). Outcomes were determined from the Substance Use Report, a self-report measure of substance use, and confirmatory urinalysis. Predictive values were calculated to determine the importance of abstinence versus use at various time points within the first month of treatment (week 1, weeks 1-2, 1-3, or 1-4) in predicting successful versus unsuccessful treatment outcome (based on abstinence or near-abstinence from opioids) in the last 4 weeks of buprenorphine-naloxone treatment (weeks 9-12). Outcome was best predicted by medication response after 2 weeks of treatment. Two weeks of initial abstinence was moderately predictive of treatment success (positive predictive value = 71%), while opioid use in both of the first 2 weeks was strongly predictive of unsuccessful treatment outcome (negative predictive value [NPV] = 84%), especially when successful outcome was defined as total abstinence from opioids in weeks 9-12 (NPV = 94%). The authors conclude that evaluating prescription opioid-dependent patients after 2 weeks of buprenorphine-naloxone treatment may help determine the likelihood of successful outcome at completion of the current treatment regimen. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT00316277.

Using Behavioral Economics to Predict Opioid Use during Prescription Opioid Dependence Treatment Worley MJ, Shoptaw SJ, Bickel WK, Ling W. Drug Alcohol Depend. 2015 Mar 1; 148: 62-68. Epub 2014 Dec 30.
Research grounded in behavioral economics has previously linked addictive behavior to disrupted decision-making and reward-processing, but these principles have not been examined in prescription opioid addiction, which is currently a major public health problem. This study examined whether pre-treatment drug reinforcement value predicted opioid use during outpatient treatment of prescription opioid addiction. Secondary analyses examined participants with prescription opioid dependence who received 12 weeks of buprenorphine-naloxone and counseling

in a multi-site clinical trial (N=353). Baseline measures assessed opioid source and indices of drug reinforcement value, including the total amount and proportion of income spent on drugs. Weekly urine drug screens measured opioid use. Obtaining opioids from doctors was associated with lower pre-treatment drug spending, while obtaining opioids from dealers/patients was associated with greater spending. Controlling for demographics, opioid use history, and opioid source frequency, patients who spent a greater total amount (OR=1.30, p<.001) and a greater proportion of their income on drugs (OR=1.31, p<.001) were more likely to use opioids during treatment. The authors conclude that individual differences in drug reinforcement value, as indicated by pre-treatment allocation of economic resources to drugs, reflects propensity for continued opioid use during treatment among individuals with prescription opioid addiction. Future studies should examine disrupted decision-making and reward-processing in prescription opioid users more directly and test whether reinforcer pathology can be remediated in this population.

NIDA Clinical Trials Network Common Data Elements Initiative: Advancing Big-Data Addictive-Disorders Research Ghitza UE, Gore-Langton RE, Lindblad R, Tai B.
Front Psychiatry. 2015 Mar 3; 6: 33. eCollection 2015.
The Clinical Trials Network (CTN) of the National Institute on Drug Abuse (NIDA) recently launched a public portal (http://cde.drugabuse.gov), which provides a single-source repository for CTN-recommended common data elements (CDEs) for substance use disorders (SUD) for use in electronic health record systems (EHRs) and clinical research. A CDE in this context is a data element consisting of a question and enumerated set of possible values for responses precisely defined by standardized metadata descriptors. CDEs consisting of individual question/answer pairs can be combined into more complex questionnaires and case report forms or used when gathering medical information in the context of providing clinical care. Thus, CDEs describe semantic characteristics for a discrete piece of data, which will be collected, stored, or exchanged during the course of a study or health examination. This will facilitate exchange of standardized data because of the use of CDEs. In this manner, NIDA CDEs can be commonly applied to multiple data collection systems whether in research or clinical care and across different institutions, such that their intentional commonality with use of common data standards can improve data quality, facilitate data re-purposing, and promote data sharing. This paper describes objectives and importance of the CTN CDEs initiative and portal to translational psychiatric research: To support harmonized use of EHR-compatible common data elements to enable exchange and integration of data to answer clinically meaningful questions of broad interest to SUD treatment research, thereby facilitating big-data biomedical science crossing boundaries between research and clinical care.

Web-based Treatment for Substance Use Disorders: Differential Effects by Primary Substance Cochran G, Stitzer M, Campbell AN, Hu MC, Vandrey R, Nunes EV. Addict Behav. 2015 Jun; 45: 191-194. Epub 2015 Feb 8.
This secondary analysis of data from a large, multi-site effectiveness trial (NCT01104805) sought to determine whether effects of a web-based behavioral treatment (Therapeutic Education System [TES]) differed by participants' self-identified primary drug of abuse. The all-comers sample of individuals entering outpatient psychosocial counseling treatment for substance abuse (N=497) cited cannabis (22.9%; n=114), stimulants (34.4%, n=171), opioids (21.7%, n=108), or alcohol (20.9%, n=104) as their primary substance of abuse. Participants were randomly assigned to receive treatment-as-usual (TAU) with or without TES substituted for approximately 2h of usual counseling. Multivariate analyses of abstinence outcomes examined interactions of treatment effects

with primary substance. Adjusted odds ratios (AORs) demonstrated that primary stimulant users receiving TES were more likely to be abstinent in the final four weeks of treatment compared to stimulant users receiving TAU (AOR=3.59, 95% CI=1.25-10.27). Adjusted odds ratios for alcohol (AOR=3.15, 95% CI=0.85-11.65) and cannabis (AOR=2.64, 95% CI=0.73-9.52) also were of similar magnitude to stimulants but did not reach significance. Abstinence among primary opioid users was not improved by the TES intervention (AOR=0.35, 95% CI=0.09-1.47). This study supports the TES web-delivered treatment as a viable intervention for the majority of substance users entering outpatient counseling treatment, with demonstrated effectiveness among stimulant users and promising effects in alcohol and cannabis users but little or no effect in primary opioid users. Web-delivered treatments hold promise for expanding the availability of effective behavioral interventions for the majority of substance use disorders.

Implementation of Integrated Therapies for Comorbid Post-Traumatic Stress Disorder and Substance Use Disorders in Community Substance Abuse Treatment Programs Killeen TK, Back SE, Brady KT. Drug Alcohol Rev 2015 Mar 4. [Epub ahead of print].
The high prevalence of trauma and post-traumatic stress disorder (PTSD) in individuals with substance use disorders (SUDs) presents a number of treatment challenges for community treatment providers and programs in the USA. Although several evidence-based, integrated therapies for the treatment of comorbid PTSD/SUD have been developed, rates of utilisation of such practices remain low in community treatment programs. The goal of this article was to review the extant literature on common barriers that prevent adoption and implementation of integrated treatments for PTSD/SUD among substance abuse community treatment programs. Organisational, provider-level and patient-level factors that drive practice decisions were discussed, including organizational philosophy of care policies, funding and resources, as well as provider and patient knowledge and attitudes related to implementation of new integrated treatments for comorbid PTSD and SUD. Understanding and addressing these community treatment challenges may facilitate use of evidence-based integrated treatments for comorbid PTSD and SUD.

Pathways to Change: Use Trajectories Following Trauma-Informed Treatment of Women with Co-occurring Post-Traumatic Stress Disorder and Substance Use Disorders López-Castro T, Hu MC, Papini S, Ruglass LM, Hien DA. Drug Alcohol Rev. 2015 Mar 4. [Epub ahead of print].
Despite advances towards integration of care for women with co-occurring substance use disorder (SUD) and post-traumatic stress disorder (PTSD), low abstinence rates following SUD/PTSD treatment remain the norm. The utility of investigating distinct substance use trajectories is a critical innovation in the detection and refining of effective interventions for this clinical population.
The present study reanalysed data from the largest randomised clinical trial to date for co-occurring SUD and PTSD in women (National Drug Abuse Treatment Clinical Trials Network; Women and Trauma Study). Randomized participants (n = 353) received one of two interventions in addition to treatment as usual for SUD: (i) trauma-informed integrative treatment for PTSD/SUD; or (ii) an active control psychoeducation course on women's health. The present study utilised latent growth mixture models (LGMM) with multiple groups to estimate women's substance use patterns during the 12-month follow-up period. Findings provided support for three different trajectories of substance use in the post-treatment year: (i) consistently low likelihood and use frequency; (ii) consistently high likelihood and use frequency; and (iii) high likelihood and moderate use frequency. Covariate analyses revealed improvement in PTSD severity was associated with membership in a specific substance use trajectory, although receiving trauma-informed treatment

was not. Additionally, SUD severity, age and after-care efforts were shown to be related to trajectory membership. Findings highlight the necessity of accounting for heterogeneity in post-treatment substance use, relevance of trauma-informed care in SUD recovery and benefits of incorporating methodologies like LGMM when evaluating SUD treatment outcomes.

Opioid Addicted Buprenorphine Injectors: Drug Use During and After 12-weeks of Buprenorphine-Naloxone or Methadone in the Republic of Georgia Piralishvili G, Otiashvili D, Sikharulidze Z, Kamkamidze G, Poole S, Woody GE. J Subst Abuse Treat. 2015 Mar; 50: 32-37. Epub 2014 Oct 22.
The aim of this study is to assess the prevalence of non-opioid drug use among opioid-addicted, buprenorphine injecting individuals in Georgia, during and after a 12-week course of buprenorphine-naloxone (Suboxone®) or methadone. This was a randomized controlled trial with daily observed Suboxone® or methadone and weekly counseling, urine tests and timeline followback (TLFB) in weeks 0-12 and 20, and the Addiction Severity Index (ASI) at weeks 0, 4, 8, 12, 20. Of the 80 patients (40/group, 4 women), 68 (85%) completed the 12-weeks of study treatment and 66 (82.5%) completed the 20-week follow-up. At baseline, injecting more than one drug in the last 30 days was reported by 68.4% of patients in the methadone and 72.5% in the Suboxone® groups. Drug use was markedly reduced in both treatment conditions but there were significant differences in the prevalence of specific drugs with more opioid (1.5 vs. 0.2%; $p=0.03$), less amphetamine (0.2 vs. 2.8%; $p<0.001$) and less marijuana (1.7 vs. 10.2%; $p<0.001$) positive urine tests in the methadone vs. Suboxone® groups. At the 20-week follow-up, TLFB results on the 34 that continued methadone or the 3 on Suboxone® showed less opioid (5.6 vs. 27.6%; $p<0.001$), illicit buprenorphine (2.7 vs. 13.8%; $p=0.005$), benzodiazepine (13.5 vs. 34.5%; $p<0.001$), and marijuana (2.8 vs. 20.7%; $p<0.001$) use than the 29 who did not continue opioid substitution therapy. Despite small but significant differences in opioid and other drug use, both treatments were highly effective in reducing opioid and non-opioid drug use.

Comorbidities and Race/Ethnicity among Adults with Stimulant Use Disorders in Residential Treatment Sanchez K, Chartier KG, Greer TL, Walker R, Carmody T, Rethorst CD, Ring KM, Dela Cruz AM, Trivedi MH. J Ethn Subst Abuse. 2015; 14(1): 79-95. Epub 2015 Jan 12.
Comorbid physical and mental health problems are associated with poorer substance abuse treatment outcomes; however, little is known about these conditions among stimulant abusers at treatment entry. This study compared racial and ethnic groups on baseline measures of drug use patterns, comorbid physical and mental health disorders, quality of life, and daily functioning among cocaine and stimulant abusing/dependent patients. Baseline data from a multi-site randomized clinical trial of vigorous exercise as a treatment strategy for a diverse population of stimulant abusers (N = 290) were analyzed. Significant differences between groups were found on drug use characteristics, stimulant use disorders, and comorbid mental and physical health conditions. Findings highlight the importance of integrating health and mental health services into substance abuse treatment and could help identify potential areas for intervention to improve treatment outcomes for racial and ethnic minority groups.

Alcohol Screening among Opioid Agonist Patients in a Primary Care Clinic and an Opioid Treatment Program Klimas J, Muench J, Wiest K, Croff R, Rieckman T, McCarty D. J Psychoactive Drugs. 2015 Jan-Mar; 47(1): 65-70.
Problem alcohol use is associated with adverse health and economic outcomes, especially among people in opioid agonist treatment. Screening, brief intervention, and referral to treatment (SBIRT) are effective in reducing alcohol use; however, issues involved in SBIRT implementation among opioid agonist patients are unknown. To assess identification and treatment of alcohol use disorders, the authors reviewed clinical records of opioid agonist patients screened for an alcohol use disorder in a primary care clinic (n = 208) and in an opioid treatment program (n = 204) over a two-year period. In the primary care clinic, 193 (93%) buprenorphine patients completed an annual alcohol screening and six (3%) had elevated AUDIT scores. In the opioid treatment program, an alcohol abuse or dependence diagnosis was recorded for 54 (27%) methadone patients. Practitioner focus groups were completed in the primary care (n = 4 physicians) and the opioid treatment program (n = 11 counselors) to assess experience with and attitudes towards screening opioid agonist patients for alcohol use disorders. Focus groups suggested that organizational, structural, provider, patient, and community variables hindered or fostered alcohol screening. Alcohol screening is feasible among opioid agonist patients. Effective implementation, however, requires physician training and systematic changes in workflow.

Men and Women from the STRIDE Clinical Trial: An Assessment of Stimulant Abstinence Symptom Severity at Residential Treatment Entry Chartier KG, Sanchez K, Killeen TK, Burrow A, Carmody T, Greer TL, Trivedi MH. Am J Addict. 2015 Feb 17. [Epub ahead of print].
Gender-specific factors associated with stimulant abstinence severity were examined in a stimulant abusing or dependent residential treatment sample (N = 302). Bivariate statistics tested gender differences in stimulant abstinence symptoms, measured by participant-reported experiences of early withdrawal. Multivariate linear regression examined gender and other predictors of stimulant abstinence symptom severity. Women compared to men reported greater stimulant abstinence symptom severity. Anxiety disorders and individual anxiety-related abstinence symptoms accounted for this difference. African American race/ethnicity was predictive of lower stimulant abstinence severity. Women were more sensitive to anxiety-related stimulant withdrawal symptoms. Clinics that address anxiety-related abstinence symptoms, which more commonly occur in women, may improve treatment outcome.

The Use of Technology in Participant Tracking and Study Retention: Lessons Learned from a Clinical Trials Network Study Mitchell SG, Schwartz RP, Alvanzo AA, Weisman MS, Kyle TL, Turrigiano EM, Gibson ML, Perez L, McClure EA, Clingerman S, Froias A, Shandera DR, Walker R, Babcock DL, Bailey GL, Miele GM, Kunkel LE, Norton M, Stitzer ML. Subst Abus. 2015 Feb 11:0. [Epub ahead of print].
The growing use of newer communication and internet technologies, even among low income and transient populations, require research staff to update their outreach strategies to ensure high follow-up and participant retention rates. This paper presents the views of research assistants on the use of cell phones and the internet to track participants in a multi-site randomized trial of substance use disorder treatment. Pre-interview questionnaires exploring tracking and other study-related activities were collected from 21 research staff across the 10 participating US sites. Data were then used to construct a semi-structured interview guide which, in turn, was used to interview 12 of the same staff members. The questionnaires and interview data were entered in Atlas.ti and analyzed

for emergent themes related to the use of technology for participant tracking purposes. Study staff reported that most participants had cell phones, despite having unstable physical addresses and landlines. The incoming call feature of most cell phones was useful for participants and research staff alike, and texting proved to have additional benefits. However, reliance on participants' cell phones also proved problematic. Even homeless participants were found to have access to the internet through public libraries and could respond to study staff e-mails. Some study sites opened generic social media accounts, through which study staff sent private messages to participants. However, the Institutional Review Board (IRB) approval process for tracking participants using social media at some sites was prohibitively lengthy. Internet searches through Google, national paid databases, obituaries, and judiciary websites were also helpful tools. Research staff perceive that cell phones, internet searches, and social networking sites were effective tools to achieve high follow-up rates in drug abuse research. Studies should incorporate cell phone, texting, and social network website information on locator forms; obtain IRB approval for contacting participants using social networking websites; and include web searches, texting, and the use of social media in staff training as standard operating procedures.

Delivery of Behavioral HIV Prevention Services in New York City Outpatient Substance Abuse Treatment Clinics: Providers' Perspectives on Opportunities and Challenges Spector AY, Remien RH. AIDS Educ Prev. 2015 Feb; 27(1): 1-14.
Providers (e.g., counselors, physicians) of substance abuse treatment have an opportunity to address HIV. This study identified: (1) providers' HIV prevention practices, (2) barriers, and (3) promoters to offering HIV prevention in substance abuse treatment. Semistructured qualitative interviews with one director, one medical provider, and four counselors, from each of six outpatient clinics (N = 36) were transcribed and coded according to thematic content analysis. Providers' practices included: (1) recommending condoms, (2) explaining HIV transmission, (3) HIV testing, and (4) assessing risk. Barriers included: (1) believing that clients know enough about HIV, (2) believing that clients are not at risk, (3) lacking information, (4) outdated training (i.e., > 5 years ago), (5) HIV stigma, and (6) avoidance. While some providers recommended condoms and HIV testing, many avoided discussing HIV. These results suggest a need for training to improve understanding of HIV transmission, effective counseling practices, and to build capacity for HIV testing or linkages with HIV service agencies.

Toward Personalized Smoking-Cessation Treatment: Using a Predictive Modeling Approach to Guide Decisions Regarding Stimulant Medication Treatment of Attention-Deficit/ Hyperactivity Disorder (ADHD) in Smokers. Luo SX, Cvey LS, Hu MC, Levin FR, Nunes EV, Winhusen TM. Am J Addict. 2015 Feb 6. [Epub ahead of print].
Osmotic-release oral system methylphenidate (OROS-MPH) did not show overall benefit as an adjunct smoking cessation treatment for adult smokers with ADHD in a randomized, placebo-controlled, multicenter clinical trial. A secondary analysis revealed a significant interaction between ADHD symptom severity and treatment-response to OROS-MPH, but did not account for other baseline covariates or estimate the magnitude of improvement in outcome if treatment were optimized. This present study addressed the gaps in how this relationship should inform clinical practice. Using data from the Adult Smokers with ADHD Trial (N = 255, six sites in five US States), the authors build predictive models to calculate the probability of achieving prolonged abstinence, verified by self-report, and expired carbon monoxide measurement. They evaluate the potential improvement in achieving prolonged abstinence with and without stratification on baseline

ADHD severity. Predictive modeling demonstrates that the interaction between baseline ADHD severity and treatment group is not affected by adjusting for other baseline covariates. A clinical trial simulation shows that giving OROS-MPH to patients with baseline Adult ADHD Symptom Rating Scale (ADHD-RS) >35 and placebo to those with ADHD-RS ≤35 would significantly improve the prolonged abstinence rate ($52 \pm 8\%$ vs. $42 \pm 5\%$, $p < .001$). In smokers with ADHD, utilization of a simple decision rule that stratifies patients based on baseline ADHD severity can enhance overall achievement of prolonged smoking abstinence. Similar analysis methods should be considered for future clinical trials for other substance use disorders.

Substance Abuse Treatment Response in a Latino Sample: The Influence of Family Conflict Fish JN, Maier CA, Priest JB. J Subst Abuse Treat. 2015 Feb;v49:v27-34. Epub 2014 Aug 4.
Latino Americans report underutilization of treatment and poor treatment response for substance use and abuse compared to other racial/ethnic groups; thus, it is important to assess factors that contribute to these disparities. The current study objective was to assess the influence of family conflict on substance abuse treatment response in a sample of Latino Americans using two different yet complementary analyses. First, ordinary least squares regression was used to assess the association between overall family conflict and pre- and post-treatment substance use. Second, repeated measures latent class analysis was used to identify groups based on family member conflict and timing of conflict during treatment. Findings indicated that family conflict contributed unique variance to concurrent substance use; however pre-treatment family conflict was not related to post-treatment outcomes. Results also identified three distinct family conflict groups: no/low conflict, pre-treatment conflict, and post-treatment conflict who differed in pre- and post-treatment substance use. Post hoc investigation revealed that those who experienced pre-treatment conflict but low post-treatment conflict showed the greatest decrease in substance use. Findings highlight the importance of considering family conflict during all stages of treatment for Latino American substance users.

Community Perspectives on Drug/Alcohol Use, Concerns, Needs, and Resources in Four Washington State Tribal Communities Radin SM, Kutz SH, La Marr J, Vendiola D, Vendiola M, Wilbur B, Thomas LR, Donovan DM. J Ethn Subst Abuse. 2015; 14(1): 29-58. Epub 2015 Jan 3.
Community-university teams investigated substance use, abuse, and dependence (SUAD) and related concerns, needs, strengths, and resources in four Washington State Tribal communities. A total of 153 key community members shared their perspectives through 43 semi-structured interviews and 19 semi-structured focus groups. Qualitative data analysis revealed robust themes: prescription medications and alcohol were perceived as most prevalent and concerning; family and peer influences and emotional distress were prominent perceived risk factors; and SUAD intervention resources varied across communities. Findings may guide future research and the development of much needed strength-based, culturally appropriate, and effective SUAD interventions for American Indians, Alaska Natives, and their communities.

A Clustering Method to Identify Who Benefits Most from the Treatment Group in Clinical Trials Lee BS, Sen PK, Park NS, Boothroyd RA, Peters RH, Chiriboga DA. Health Psychol Behav Med. 2015 Jan 1; 2(1): 723-734. Epub 2014 Jul 10.
In randomized controlled trials (RCTs), the most compelling need is to determine whether the treatment condition was more effective than control. However, it is generally recognized that not all participants in the treatment group of most clinical trials benefit equally. While subgroup analyses

are often used to compare treatment effectiveness across pre-determined subgroups categorized by patient characteristics, methods to empirically identify naturally occurring clusters of persons who benefit most from the treatment group have rarely been implemented. This article provides a modeling framework to accomplish this important task. Utilizing information about individuals from the treatment group who had poor outcomes, the present study proposes an a priori clustering strategy that classifies the individuals with initially good outcomes in the treatment group into: (a) group GE (good outcome, effective), the latent subgroup of individuals for whom the treatment is likely to be effective and (b) group GI (good outcome, ineffective), the latent subgroup of individuals for whom the treatment is not likely to be effective. The method is illustrated through a re-analysis of a publically available data set from the National Institute on Drug Abuse. The RCT examines the effectiveness of motivational enhancement therapy from 461 outpatients with substance abuse problems. The proposed method identified latent subgroups GE and GI, and the comparison between the two groups revealed several significantly different and informative characteristics even though both subgroups had good outcomes during the immediate post-therapy period. As a diagnostic means utilizing out-of-sample forecasting performance, the present study compared the relapse rates during the long-term follow-up period for the two subgroups. As expected, group GI, composed of individuals for whom the treatment was hypothesized to be ineffective, had a significantly higher relapse rate than group GE (63% vs. 27%; $\chi^2 = 9.99$, p-value = .002).

<u>The "S" Allele of the Serotonin Transporter Is Not Associated with Major Depression in a Sample of Veterans</u> Cornelius JR, Haas GL, Goldstein G, Hanusa B, Walker JD, Fox LJ, Ferrell J. Adv Genet Res. 2014;12:1-10.

The results of some studies suggest that the serotonin transporter-linked polymorphic region (5-HTTLPR) short (S) allele, relative to the long (L) allele, is associated with risk for Major Depressive Disorder (MDD), and thus serves as a biomarker for MDD, while results from other studies do not support that conclusion. Persons with an S allele demonstrate a 2- to 2.5 fold decrease in serotonin transcription rate compared to the L-allele, which may increase their risk for MDD. Differences in study populations may help explain the differences in findings between those meta-analyses. To date, there have been no published reports which have addressed the possible association between the S allele and MDD among military veterans. This manuscript describes a first study to assess the possible association of the S allele with MDD among a study population of veterans in treatment for a substance use disorder. The authors hypothesized that the S allele would be associated with MDD in our study sample. Subjects signing informed consent were 101 Veterans recruited from VA behavioral health and substance use treatment clinics in the VA Pittsburgh Healthcare System, and 91 of those subjects were genotyped for 5-HTTLPR polymorphisms. The study sample from whom genetic material was collected included 82 males and 9 females, of whom 53 were white, 38 were black, and one was "other". Fifty-four members of the study sample (59%) met DSM-IV criteria for an MDD on the SCID. Forty-five of the subjects demonstrated one or two S alleles, while 46 did not do so. The presence of the S allele of the serotonin transporter was not found to be significantly associated with the diagnosis of major depressive disorder in our sample (Chi-square=0.1.63, df=1, p=0.199). That finding, in combination with other recent negative findings from other researchers involving non-veterans, raises questions regarding the clinical utility of utilizing genetics tests involving the assessment of the alleles of the serotonin transporter as a possible biomarker for MDD.

Gender-Based Outcomes and Acceptability Of A Computer-Assisted Psychosocial Intervention For Substance Use Disorders Campbell AN, Nunes EV, Pavlicova M, Hatch-Maillette M, Hu MC, Bailey GL, Sugarman DE, Miele GM, Rieckmann T, Shores-Wilson K, Turrigiano E, Greenfield SF. J Subst Abuse Treat. 2014 Dec 30. [Epub ahead of print].
Digital technologies show promise for increasing treatment accessibility and improving quality of care, but little is known about gender differences. This secondary analysis uses data from a multi-site effectiveness trial of a computer-assisted behavioral intervention, conducted within NIDA's National Drug Abuse Clinical Trials Network, to explore gender differences in intervention acceptability and treatment outcomes. Men (n=314) and women (n=192) were randomly assigned to 12-weeks of treatment-as-usual (TAU) or modified TAU+Therapeutic Education System (TES), whereby TES substituted for 2hours of TAU per week. TES is composed of 62 Web-delivered, multimedia modules, covering skills for achieving and maintaining abstinence plus prize-based incentives contingent on abstinence and treatment adherence. Outcomes were: (1) abstinence from drugs and heavy drinking in the last 4weeks of treatment, (2) retention, (3) social functioning, and (4) drug and alcohol craving. Acceptability was the mean score across five indicators (i.e., interesting, useful, novel, easy to understand, and satisfaction). Gender did not moderate the effect of treatment on any outcome. Women reported higher acceptability scores at week 4 (p=.02), but no gender differences were detected at weeks 8 or 12. Acceptability was positively associated with abstinence, but only among women (p=.01). Findings suggest that men and women derive similar benefits from participating in a computer-assisted intervention, a promising outcome as technology-based treatments expand. Acceptability was associated with abstinence outcomes among women. Future research should explore characteristics of women who report less satisfaction with this modality of treatment and ways to improve overall acceptability.

Cigarette Smoking During Substance Use Disorder Treatment: Secondary Outcomes from a National Drug Abuse Treatment Clinical Trials Network Study McClure EA, Campbell AN, Pavlicova M, Hu M, Winhusen T, Vandrey RG, Ruglass LM, Covey LS, Stitzer ML, Kyle TL, Nunes EV. J Subst Abuse Treat. 2014 Dec 30. [Epub ahead of print].
The majority of patients enrolled in treatment for substance use disorders (SUDs) also use tobacco. Many will continue to use tobacco even during abstinence from other drugs and alcohol, often leading to smoking-related illnesses. Despite this, little research has been conducted to assess the influence of being a smoker on SUD treatment outcomes and changes in smoking during a treatment episode. In this secondary analysis, cigarette smoking was evaluated in participants completing outpatient SUD treatment as part of a multi-site study conducted by the National Drug Abuse Treatment Clinical Trials Network. Analyses included the assessment of changes in smoking and nicotine dependence via the Fagerström Test for Nicotine Dependence during the 12-week study among all smokers (aim #1), specifically among those in the experimental treatment group (aim #2), and the moderating effect of being a smoker on treatment outcomes (aim #3). Participants generally did not reduce or quit smoking throughout the course of the study. Among a sub-set of participants with higher baseline nicotine dependence scores randomized to the control arm, scores at the end of treatment were lower compared to the experimental arm, though measures of smoking quantity did not appear to decrease. Further, being a smoker was associated with poorer treatment outcomes compared to non-smokers enrolled in the trial. This study provides evidence that patients enrolled in community-based SUD treatment continue to smoke, even when abstaining from drugs and alcohol. These results add to the growing literature encouraging the implementation of targeted, evidence-based interventions to promote abstinence from tobacco among SUD treatment patients.

Training Addiction Professionals in Empirically Supported Treatments: Perspectives from the Treatment Community Hartzler B, Rabun C. Subst Abus. 2014; 35(1): 30-36.
Large-scale dissemination efforts seek to expand opportunities for the addiction treatment community to receive training in empirically supported treatments (ESTs). Prospective consumers of such training are valuable sources of input about content of interest, preferences for how training events are structured, and obstacles that deter receipt of training. In this mixed-method study, data were collected in 64 semistructured individual interviews with personnel during site visits to 16 community opioid treatment programs (OTPs). At each OTP, interviews were completed with the executive director, a clinical supervisor, and 2 direct-service clinicians. Topical interests were analyzed qualitatively in a cultural domain analysis. Likert ratings of training event preferences were analyzed via generalized linear mixed models (GLMMs), and unstructured interviewee comments were analyzed via narrative analysis. Obstacles to training receipt were analyzed qualitatively with both content coding and narrative analysis. Based on topics of reported interest, cultural domain analysis suggests as ESTs of note: Multidimensional Family Therapy, Motivational Enhancement Therapy, Relapse Prevention Therapy, "Seeking Safety," and broad addiction-focused pharmacotherapy. Regarding training event preferences, GLMMs and narrative analysis revealed clear preferences for time-distributed trainings and use of participatory activities (e.g., trainer demonstrations, role plays, small group exercises). Content coding identified cost as the primary obstacle to receipt of EST trainings, followed by lack of time, logistical challenges, and disinterest, and narrative analysis elaborated on contextual issues underlying these obstacles. As primary consumers of EST technologies, the treatment community has valuable input to offer. Dissemination efforts may be enhanced by greater consideration of their preferences for training content and event structure, as well as practical obstacles that challenge their receipt of training.

Characteristics of a Treatment-Seeking Population in Outpatient Addiction Treatment Centers in Mexico Marín-Navarrete R, Templos-Nuñez L, Eliosa-Hernández A, Villalobos-Gallegos L, Fernández-Mondragón J, Pérez-López A, Galván-Sosa D, Verdeja RE, Alonso E, Feaster DJ, Horigian VE. Subst Use Misuse. 2014 Nov; 49(13): 1784-1794. Epub 2014 Jul 11.
Baseline patients' characteristics are critical for treatment planning, as these can be moderators of treatment effects. In Mexico, information on treatment seekers with substance use disorders is scarce and limited to demographic characteristics. This paper presents and analyses demographic characteristics, substance use related problems, clinical features, and addiction severity in a sample of treatment seekers from the first multi-site randomized clinical trial implemented in the Mexican Clinical Trials Network on Addiction and Mental Health. A total of 120 participants were assessed prior randomization. Chi square or F-tests were used to compare sites across variables. Spearman correlation was used to associate negative consequences of substance use and motivation to change. The majority of participants were men, and the most prevalent substances reported were alcohol, marijuana, and cocaine. Participants were predominantly on the contemplation or action stage of change, and this was correlated with the perception of the negative consequences associated with substance use. Participants reported a high prevalence of substance use related problems. Substance use related problems, clinical features, and addiction severity reported by treatment seekers are important characteristics to take into account when planning treatment as they facilitate tailoring treatment to meet patients' needs.

Does Seeking Safety Reduce PTSD Symptoms in Women Receiving Physical Disability Compensation? Anderson ML, Najavits LM. Rehabil Psychol. 2014 Aug; 59(3): 349-353. Epub 2014 Jun 30.

This secondary analysis investigated the impact of 12 sessions of Seeking Safety (SS) on reducing posttraumatic stress disorder (PTSD) symptoms in a sample of dually diagnosed women with physical disabilities versus nondisabled (ND) women. SS is an evidence-based and widely implemented manualized therapy for PTSD and/or substance use disorder. It is a present-focused model that promotes coping skills and psychoeducation. As part of the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN), 353 participants with current PTSD and substance use disorder (SUD) were randomly assigned to partial-dose SS or Women's Health Education (WHE) group therapy conducted in community-based substance abuse treatment programs. The women were categorized as participants with disabilities (PWD; n = 20) or ND (n = 333) based on the question, "Do you receive a pension for a physical disability?" PTSD was assessed on the Clinician-Administered PTSD Scale (CAPS) at baseline and follow-ups after treatment (1 week, 3 months, 6 months, and 12 months). PWD experienced sustained reductions in PTSD symptoms when treated with SS but not WHE. Indeed, PTSD symptoms of PWD in WHE returned to baseline levels of severity by 12-month follow-up. This pattern of results was not observed among ND women, who sustained improvements on PTSD in both treatment conditions. These results suggest strong potential for using SS to treat PTSD among women with physical disabilities, and speak to the genuine need to address trauma and PTSD more directly with PWD. These results are also consistent with other findings from the NIDA CTN trial, in which virtually all significant results evidenced SS outperforming WHE.

WOMEN AND GENDER DIFFERENCES-RELATED RESEARCH

Increasing Progesterone Levels are Associated with Smoking Abstinence among Free-cycling Women Smokers who Receive Brief Pharmacotherapy Saladin ME, McClure EA, Baker NL, Carpenter MJ, Ramakrishnan V, Hartwell KJ, Gray KM. Nicotine Tob Res. 2015 Apr; 17(4): 398-406.

Preclinical and human laboratory research suggests that (a) progesterone may decrease drug reward, craving, and smoking behavior, and (b) estradiol may enhance drug reward and smoking behavior. A modest majority of treatment research examining the relationship between menstrual cycle phase and outcomes suggests that the luteal menstrual phase, with its uniquely higher progesterone levels, is associated with better cessation outcomes. However, no studies to date have examined the effects of naturally occurring variation in progesterone and estradiol levels on medication-assisted smoking cessation. The present study sought to fill this notable gap in the treatment literature. Weekly plasma progesterone and estradiol levels were obtained from nicotine-dependent female smokers enrolled in a 4-week cessation trial. Participants (N = 108) were randomized to receive a 4-week course of either varenicline (VAR) tablets and placebo patches or placebo tablets and nicotine patches. Plasma samples were obtained 1 week before their cessation attempt and weekly during medication administration. Abstinence was assessed weekly. Weekly hormone data replicated commonly observed menstrual cycle patterns of progesterone and estradiol levels. Importantly, increases in progesterone level were associated with a 23% increase in the odds for being abstinent within each week of treatment. This effect was driven primarily by nicotine patch-treated versus VAR-treated females. This study was the first to identify an association between progesterone level (increasing) and abstinence outcomes in free-cycling women smokers who participated in a medication-based treatment. Furthermore, the potential benefits of progesterone may vary across different pharmacotherapies. Implications of these findings for smoking cessation intervention are discussed.

An Exploratory Short-term Double-blind Randomized Trial of Varenicline versus Nicotine Patch for Smoking Cessation in Women Gray KM, McClure EA, Baker NL, Hartwell KJ, Carpenter MJ, Saladin ME. Addiction. 2015 Mar 1. [Epub ahead of print].

Within a parent study examining ovarian hormone effects on smoking cessation in women, the authors conducted an exploratory short-term trial of varenicline versus transdermal nicotine patch. This was a double-blind double-dummy randomized trial conducted at a single-site outpatient research clinic in the United States. Participants were female smokers, ages 18-45 and averaging ≥10 cigarettes per day for at least 6 months (N = 140). Participants were randomized to receive a four-week course of (a) varenicline tablets and placebo patches (n = 67), or (b) placebo tablets and nicotine patches (n = 73). Two brief cessation counseling sessions were provided for all participants. The outcome of primary clinical interest was two-week end-of-treatment abstinence. Secondary outcomes included one- and four-week end-of treatment abstinence and abstinence at a post-treatment follow-up visit occurring four weeks after treatment conclusion. Breath carbon monoxide (≤10 parts per million) was used to confirm biochemically self-reported abstinence. Two-week end-of-treatment abstinence was achieved by 37.3% (25/67) of varenicline participants and by 17.8% (13/73) of nicotine patch participants (odds ratio [OR] (95% confidence interval [CI]) 2.7 (1.3-6.0), p = 0.011). One-week (44.8% vs 20.6%, OR 3.1 (1.5-6.6), p = 0.003) and four-week (22.4% vs 9.6%, OR 2.7 (1.0-7.2), p = 0.043) end-of-treatment abstinence similarly favored varenicline, though post-treatment follow-up Russell Standard abstinence was not significantly different

between groups (23.9% vs 13.7%, OR 2.0 (0.8-4.7), p = 0.126). In an exploratory four-week head-to-head trial in female smokers, varenicline, compared with nicotine patch, more than doubled the odds of end-of-treatment abstinence, although this diminished somewhat at post-treatment follow-up.

Gender Differences in Responses to Cues Presented in the Natural Environment of Cigarette Smokers Wray JM, Gray KM, McClure EA, Carpenter MJ, Tiffany ST, Saladin ME. Nicotine Tob Res. 2015 Apr;17(4):438-442.
Introduction: Although the evidence is mixed, female smokers appear to have more difficulty quitting smoking than male smokers. Craving, stress, and negative affect have been hypothesized as potential factors underlying gender differences in quit rates. In the current study, the cue-reactivity paradigm was used to assess craving, stress, and negative affect in response to cues presented in the natural environment of cigarette smokers using ecological momentary assessment. Seventy-six daily smokers (42% female) responded to photographs (smoking, stress, and neutral) presented 4 times per day on an iPhone over the course of 2 weeks. Both smoking and stress cues elicited stronger cigarette craving and stress responses compared to neutral cues. Compared with males, females reported higher levels of post-stress cue craving, stress, and negative affect, but response to smoking cues did not differ by gender. Findings from this project were largely consistent with results from laboratory-based research and extend previous work by measuring response to cues in the natural environment of cigarette smokers. This study extends previous cue reactivity ecological momentary assessment research by using a new platform and by measuring response to stress cues outside of the laboratory. Findings from this project highlight the importance of addressing coping in response to stress cues in clinical settings, especially when working with female smokers.

The Effect of Combination Oral Contraceptives on Smoking-related Symptomatology during Short-term Smoking Abstinence Hinderaker K, Allen AM, Tosun N, al'Absi M, Hatsukami D, Allen SS. Addict Behav. 2015 Feb; 41:148-151.
Although an estimated 25% of premenopausal smokers report using oral contraceptives (OC), little is known about how OC use may influence smoking cessation. The purpose of this study was to examine the difference in smoking-related symptomatology during acute smoking abstinence between women on a standardized combination OC (Tri-Sprintec™) compared to women not on OCs (no-OC). Participants were women aged 18–40 who smoked ≥ 5 cigarettes/day and reported regular menstrual cycles. Using a controlled cross-over design, participants completed two six-day testing weeks: Low Progesterone Week (LPW; Follicular (F) phase in no-OC or 1st week of pills in OC) and High Progesterone Week (HPW; Luteal (L) phase in no-OC or 3rd week of pills in OC). Each testing week included daily assessment of symptomatology and biochemical confirmation of smoking status. During smoking abstinence, the OC group (n = 14) reported significantly lower levels of positive affect (21.56 ± 7.12 vs. 24.57 ± 6.46; $\beta = 3.63$, $p = 0.0323$) than the no-OC group (n = 28). Further significant interactions between group and testing week were observed as follows: Smoking satisfaction was higher during LPW in the OC group (LPW: 4.29 ± 1.30 vs. HPW: 4.10 ± 1.37) but higher during HPW in the no-OC group (LPW: 3.91 ± 1.30 vs. HPW: 4.23 ± 1.30; $\beta = -0.5499$, $p < 0.0001$). Similar interactions were noted in negative affect and psychological reward of smoking. These results suggest that women on OCs may have different patterns of smoking-related symptomatology during short-term smoking abstinence as compared to women not on OCs. Additional work is needed to examine how this may affect smoking cessation efforts.

Subjective Response to Nicotine by Menstrual Phase Allen AM, Lunos S, Heishman SJ, al'Absi M, Hatsukami D, Allen SS. Addictive Behaviors. 2015; 43, 50-53.
The luteal menstrual phase might be a favorable time for smoking cessation when non-nicotine interventions (e.g. counseling, bupropion) are used, whereas the follicular menstrual phase appears favorable when nicotine interventions are used. Thus, there may be an interaction between menstrual phase and response to nicotine. The authors sought to examine the role of menstrual phase on response to nicotine during acute smoking abstinence. In this controlled cross-over trial, women completed two identical experimental sessions (follicular [F] vs. luteal [L] phase) after four days of biochemically-verified smoking abstinence. During the sessions, nicotine nasal spray was administered, and participants provided a series of subjective assessments. Participants (n=140) were 29.7±6.6years old and smoked 12.6±5.8 cigarettes per day. Compared to the F phase, the L phase was associated with a greater increase in stimulation (7.2±2.2 vs. 14.4±2.3, p=0.01, respectively) and greater decrease in urge to smoke (-13.6±2.3 vs. -21.1±2.5, p=0.02, respectively) after the first dose of nicotine. No other significant differences were observed. Out of 13 total measures examined at two different time points, the authors observed only two significant menstrual phase differences in the subjective response to nicotine. Therefore, these data do not provide strong evidence for a menstrual phase difference in the subjective response to nicotine. Additional research is needed to confirm this relationship and explore how non-nicotine smoking reinforcements (such as sensory sensations) may vary by menstrual phase.

Systematic and Meta-Analytic Review of Research Examining the Impact of Menstrual Cycle Phase and Ovarian Hormones on Smoking and Cessation Weinberger AH, Smith PH, Allen SS, Cosgrove KP, Saladin ME, Gray KM, Mazure CM, Wetherington CL, McKee SA. Nicotine Tob Res. 2015 Apr; 17(4):407-421.
To determine the effect of ovarian hormones on smoking, the authors conducted a systematic review of menstrual cycle effects on smoking (i.e., ad lib smoking, smoking topography, and subjective effects) and cessation-related behaviors (i.e., cessation, withdrawal, tonic craving, and cue-induced craving). Thirty-six papers were identified on MEDLINE that included a menstrual-related search term (e.g., menstrual cycle, ovarian hormones), a smoking-related search term (e.g., smoking, nicotine), and met all inclusion criteria. Thirty-two studies examined menstrual phase, 1 study measured hormone levels, and 3 studies administered progesterone. Sufficient data were available to conduct meta-analyses for only 2 of the 7 variables: withdrawal and tonic craving. Women reported greater withdrawal during the luteal phase than during the follicular phase, and there was a nonsignificant trend for greater tonic craving in the luteal phase. Progesterone administration was associated with decreased positive and increased negative subjective effects of nicotine. Studies of menstrual phase effects on the other outcome variables were either small in number or yielded mixed outcomes. The impact of menstrual cycle phase on smoking behavior and cessation is complicated, and insufficient research is available upon which to conduct meta-analyses on most smoking outcomes. Future progress will require collecting ovarian hormone levels to more precisely quantify the impact of dynamic changes in hormone levels through the cycle on smoking behavior. Clarifying the relationship between hormones and smoking-particularly related to quitting, relapse, and medication response-could determine the best type and timing of interventions to improve quit rates for women.

Effects of Endogenous and Exogenous Progesterone on Emotional Intelligence in Cocaine-dependent Men and Women who also Abuse Alcohol Milivojevic V, Sinha R, Morgan PT, Sofuoglu M, Fox HC. Hum Psychopharmacol. 2014 Nov; 29(6):589-598.
As sex differences in substance dependence may impinge upon the perception and regulation of emotion, the authors assess emotional intelligence (EI) as a function of gender, menstrual cycle (MC) phase and hormonal changes in early abstinent cocaine-dependent individuals who abuse alcohol (CDA). Study 1: The Mayer, Salovey, and Caruso Emotional Intelligence Test (MSCEIT) was administered to 98 CDA (55 M/43 F) and 56 healthy (28 M/28 F) individuals. Performance in women was also assessed by MC phase. Study 2: The MSCEIT was administered to 28 CDA (19 M/9 F) who received exogenous progesterone (400 mg/day) versus placebo for 7 days (study 2). Study 1: Healthy females were better than healthy males at facilitating thought and managing emotions. This gender discrepancy was not observed in the CDA group. Additionally, all women in the high compared with the low progesterone phase of their MC were better at managing their emotions. Study 2: Exogenous progesterone improved ability to facilitate thought in both males and females. The authors conclude that CDA women may be vulnerable to difficulties managing and regulating emotions. Gonadal hormones may contribute to this gender effect, as increases in both endogenous and exogenous progesterone improved selective aspects of EI.

Yohimbine Administration and Cue-reactivity in Cocaine-dependent Individuals Moran-Santa Maria MM, McRae-Clark A, Baker NL, Ramakrishnan V, Brady KT. Psychopharmacology (Berl). 2014 Oct; 231(21): 4157-4165.
Preclinical studies suggest that stress potentiates cue-induced cocaine seeking and that this effect is more pronounced in females. These findings have not been characterized in clinical populations. The objectives of this study were to examine the impact a pharmacological stressor, alpha-2 adrenergic receptor antagonist yohimbine, on the subjective, endocrine, and physiologic responses to drug-paired cues cocaine-dependent men and women. In a double-blind placebo-controlled cross-over study, cocaine-dependent men ($n = 32$), cocaine-dependent women ($n = 30$), control men ($n = 32$), and control women ($n = 25$) received either yohimbine or placebo prior to two cocaine cue exposure sessions. Yohimbine increased ratings of anxiety both before ($p < 0.001$) and after ($p = 0.035$) cues, and the post-cue increase in anxiety was more pronounced in women ($p = 0.001$). Yohimbine also significantly increased craving, compared with placebo ($p < 0.05$), following the cue presentation, and this effect was greater in women than men (gender by treatment interaction; $p = 0.006$). Yohimbine also increased salivary cortisol ($p < 0.001$) and dehydroepiandrosterone ($p = 0.003$) levels, regardless of diagnostic group. Women had a significantly greater heart rate response following yohimbine as compared with men ($p < 0.001$). The authors conclude that stress may increase the salience of cocaine cues for cocaine-dependent women as compared with men. This suggests gender differences in vulnerability to craving and relapse under stressful conditions.

Prenatal Cocaine Exposure Differentially Affects Stress Responses in Girls and Boys: Associations with Future Substance Use Chaplin TM, Visconti KJ, Molfese PJ, Susman EJ, Klein LC, Sinha R, Mayes LC. Dev Psychopathol. 2015 Feb; 27(1):163-180.
Prenatal cocaine exposure may affect developing stress response systems in youth, potentially creating risk for substance use in adolescence. Further, pathways from prenatal risk to future substance use may differ for girls versus boys. The present longitudinal study examined multiple biobehavioral measures, including heart rate, blood pressure, emotion, and salivary cortisol and salivary alpha amylase (sAA), in response to a stressor in 193 low-income 14- to 17-year-olds, half

of whom were prenatally cocaine exposed (PCE). Youth's lifetime substance use was assessed with self-report, interview, and urine toxicology/breathalyzer at Time 1 and at Time 2 (6-12 months later). PCE × Gender interactions were found predicting anxiety, anger, and sadness responses to the stressor, with PCE girls showing heightened responses as compared to PCE boys on these indicators. Stress Response × Gender interactions were found predicting Time 2 substance use in youth (controlling for Time 1 use) for sAA and sadness; for girls, heightened sadness responses predicted substance use, but for boys, dampened sAA responses predicted substance use. Findings suggest distinct biobehavioral stress response risk profiles for boys and girls, with heightened arousal for girls and blunted arousal for boys associated with prenatal risk and future substance use outcomes.

A Gender-informed Model to Train Community Health Workers in Maternal Mental Health
Smith MV, Kruse-Austin A. Evaluation and Program Planning, Dec 10, 2014. [Epub ahead of print].
The New Haven **M**ental Health **O**utreach for **M**other**S** (**MOMS**) Partnership is a community-academic partnership that works to develop public health approaches to ensure that pregnant and parenting women living in the City of New Haven achieve the highest possible level of mental health. The MOMS Partnership developed a training model for community health workers specializing in maternal mental health. Six community health workers (termed Community Mental Health Ambassadors or **CMHAs**) were trained on key topics in this gender-informed maternal mental health curriculum. Pre- and post-test questionnaires assessed changes in attitudes, perceived self-efficacy and control using standardized scales. The results indicated preliminary acceptability of the training curriculum in transforming knowledge and attitudes about maternal mental health among community health workers.

Role of Orexin/Hypocretin in Conditioned Sucrose-seeking in Female Rats Cason AM, Aston-Jones G. Neuropharmacology. 2014 Nov; 86:97-102.
The orexin/hypocretin system has recently been implicated in reward-seeking, especially for highly salient food and drug rewards. Given that eating disorders affect women more than men, the authors reasoned that the orexin system may be strongly engaged in female rats, and during periods of food restriction as they recently reported in male rats. Therefore, the present study examined the involvement of the orexin system in operant responding for sucrose, and in cue-induced reinstatement of extinguished sucrose-seeking, in ad libitum fed vs. food-restricted female subjects. Female Sprague Dawley rats were trained to self-administer sucrose pellets, and we determined the effects of pretreatment with the OxR1 receptor antagonist SB 334867 (SB; 10-30 mg/kg) on fixed ratio (FR) sucrose self-administration, and on cue-induced reinstatement of extinguished sucrose-seeking. SB decreased sucrose self-administration in food-restricted but not in ad libitum-fed females. SB did not alter active lever responding during cue-induced reinstatement of sucrose-seeking in either feeding group. These results confirm the authors' previous results in male rats that signaling at the OxR1 receptor is involved in the sucrose reinforcement and self-administration in food-restricted subjects. However, the finding that SB is ineffective at attenuating cue-induced reinstatement in females, but was effective in food-restricted males, leads them to conclude that food seeking induced by conditioned stimuli engages the orexin system differentially in males and females.

Discrepant Effects of Acute Cocaine on Impulsive Choice (Delay Discounting) in Female Rats during an Increasing- and Adjusting-delay Procedure Smethells JR, Carroll ME. Psychopharmacology (Berl). 2015 Feb 28. [Epub ahead of print].

The relationship between impulsive choice and cocaine use in humans has been well established, although the causal role between these variables is complex. To disentangle this relationship, studies using rats have focused on how acute or chronic cocaine alters impulsive choice. A predominance of studies has focused on chronic cocaine regimens, but few have assessed acute cocaine's effects on impulsive choice. The current study assessed if acute cocaine administrations alter delay discounting of rats in two common impulsive choice procedures. Baseline delay discounting rates were determined in female rats using both an increasing- and adjusting-delay procedure. Once stable, a range of acute cocaine injections (2, 5, and 15 mg/kg i.p.) was administered prior to both procedures. Baseline delay discounting rates were positively correlated between the increasing- and adjusting-delay procedures. Acute administrations of cocaine produced a dose-dependent decrease in preference for the large alternative in the increasing-delay procedure but had no effect in the adjusting-delay procedure. The concordance of delay discounting rates across the two choice procedures suggests that both quantify the same underlying components of impulsive choice. However, manipulations that disrupt large alternative preference may not be readily detected under the adjusting-delay procedure unless control conditions are employed.

INTRAMURAL RESEARCH

Molecular Targets and Medications Discovery Research Branch

Medicinal Chemistry Section

Investigation Of the Binding and Functional Properties Of Extended Length D3 Dopamine Receptor-Selective Antagonists Furman CA, Roof RA, Moritz AE, Miller BN, Doyle TB, Free B, Banala AK, Paul NM, Kumar V, Sibley CD, Newman AH, Sibley DR. Eur. Neuropsychopharmacology Nov 29. pii: S0924-977X(14)00324-1. doi: 10.1016/j.euroneuro.2014.11.013.
The D3 dopamine receptor represents an important target in drug addiction in that reducing receptor activity may attenuate the self-administration of drugs and/or disrupt drug or cue-induced relapse. Medicinal chemistry efforts have led to the development of D3 preferring antagonists and partial agonists that are >100-fold selective vs. the closely related D2 receptor, as best exemplified by extended-length 4-phenylpiperazine derivatives. Based on the D3 receptor crystal structure, these molecules are known to dock to two sites on the receptor where the 4-phenylpiperazine moiety binds to the orthosteric site and an extended aryl amide moiety docks to a secondary binding pocket. The bivalent nature of the receptor binding of these compounds is believed to contribute to their D3 selectivity. In this study, the authors examined if such compounds might also be "bitopic" such that their aryl amide moieties act as allosteric modulators to further enhance the affinities of the full-length molecules for the receptor. Firstly, they deconstructed several D3-selective ligands into fragments, termed "synthons", representing either orthosteric or secondary aryl amide pharmacophores and investigated their effects on D3 receptor binding and function. The orthosteric synthons were found to inhibit radioligand binding and to antagonize dopamine activation of the D3 receptor, albeit with lower affinities than the full-length compounds. Notably, the aryl amide-based synthons had no effect on the affinities or potencies of the orthosteric synthons, nor did they have any effect on receptor activation by dopamine. Additionally, pharmacological investigation of the full-length D3-selective antagonists revealed that these compounds interacted with the D3 receptor in a purely competitive manner. These data further support that the 4-phenylpiperazine D3-selective antagonists are bivalent and that their enhanced affinity for the D3 receptor is due to binding at both the orthosteric site as well as a secondary binding pocket. Importantly, however, their interactions at the secondary site do not allosterically modulate their binding to the orthosteric site.

Differential Effects Of the Dopamine D3 Receptor Antagonist PG01037 On Cocaine and Methamphetamine Self-Administration In Rhesus Monkeys John WS, Newman AH, Nader MA. Neuropharmacology 2015; 92: 34-43.
The dopamine D3 receptor (D3R) has been shown to mediate many of the behavioral effects of psychostimulants associated with high abuse potential. This study extended the assessment of the highly selective D3R antagonist PG01037 on cocaine and methamphetamine (MA) self-administration to include a food-drug choice procedure. Eight male rhesus monkeys (n= 4/group) served as subjects in which complete cocaine and MA dose response curves were determined daily in each session. When choice was stable, monkeys received acute and five-day treatment of PG01037 (1.0-5.6 mg/kg, i.v.). Acute administration of PG01037 was effective in reallocating choice from cocaine to food and decreasing cocaine intake, however, tolerance developed by day 5 of treatment. Up to doses that disrupted responding, MA choice and intake were not affected by PG01037 treatment. PG01037 decreased total reinforcers earned per session and the behavioral

potency was significantly greater on MA-food choice compared to cocaine-food choice. Furthermore, the acute efficacy of PG01037 was correlated with the sensitivity of the D3/D2R agonist quinpirole to elicit yawning. These data suggest (1) that efficacy of D3R compounds in decreasing drug choice is greater in subjects with lower D3R, perhaps suggesting that it is percent occupancy that is the critical variable in determining efficacy and (2) differences in D3R activity in chronic cocaine vs. MA users. Although tolerance developed to the effects of PG01037 treatment on cocaine choice, tolerance did not develop to the disruptive effects on food-maintained responding. These findings suggest that combination treatments that decrease cocaine-induced elevations in DA may enhance the efficacy of D3R antagonists on cocaine self-administration.

R-Modafinil Attenuates Nicotine-Taking and Nicotine-Seeking Behavior In Rats Wang X-F, Bi G-H, He Y, Yang H-J, Gao J-T, Okunola-Bakare OM, Slack RD, Gardner EL, Xi Z-X, Newman AH. Neuropsychopharmacology 2015, advance online publication, 11 February 2015; doi:10.1038/npp.2015.24
(±)-Modafinil (MOD) is used clinically for the treatment of sleep disorders and has been investigated as a potential medication for the treatment of psychostimulant addiction. However, the therapeutic efficacy of (±)-MOD for addiction is inconclusive. Herein the authors used animal models of self-administration and in vivo microdialysis to study the pharmacological actions of R-modafinil (R-MOD) and S-modafinil (S-MOD) on nicotine-taking and nicotine-seeking behavior, and mechanisms underlying such actions. They found that R-MOD is more potent and effective than S-MOD in attenuating nicotine self-administration in Long–Evans rats. As Long Evans rats did not show a robust reinstatement response to nicotine, we used alcohol-preferring rats (P-rats) that display much higher reinstatement responses to nicotine than Long–Evans rats. The authors found that R-MOD significantly inhibited intravenous nicotine self-administration, nicotine-induced reinstatement, and nicotine-associated cue-induced drug-seeking behavior in P-rats. R-MOD alone neither sustained self-administration in P-rats previously self-administering nicotine nor reinstated extinguished nicotine-seeking behavior. The in vivo brain microdialysis assays demonstrated that R-MOD alone produced a slow-onset moderate increase in extracellular DA. Pretreatment with R-MOD dose-dependently blocked nicotine-induced dopamine (DA) release in the nucleus accumbens (NAc) in both naive and nicotine self-administrating rats, suggesting a DA-dependent mechanism underlying mitigation of nicotine's effects. In conclusion, the present findings support further investigation of R-MOD for treatment of nicotine dependence in humans.

What Can Crystal Structures Of Aminergic Receptors Tell Us About Designing Subtype-Selective Ligands? Michino M, Beuming T, Donthamsetti P, Newman AH, Javitch JA, Shi L. Pharmacol Rev. 2015; 67(1): 198-213. doi: 10.1124/pr.114.009944.
G protein-coupled receptors (GPCRs) are integral membrane proteins that represent an important class of drug targets. In particular, aminergic GPCRs interact with a significant portion of drugs currently on the market. However, most drugs that target these receptors are associated with undesirable side effects, which are due in part to promiscuous interactions with close homologs of the intended target receptors. Here, based on a systematic analysis of all 37 of the currently available high-resolution crystal structures of aminergic GPCRs, the authors review structural elements that contribute to and can be exploited for designing subtype-selective compounds. They describe the roles of secondary binding pockets (SBPs), as well as differences in ligand entry pathways to the orthosteric binding site, in determining selectivity. In addition, using the available crystal structures, the authors have identified conformational changes in the SBPs that are

associated with receptor activation and explore the implications of these changes for the rational development of selective ligands with tailored efficacy.

Designer Drug Research Unit

Stereochemistry Of Mephedrone Neuropharmacology: Enantiomer-Specific Behavioural and Neurochemical Effects In Rats Gregg RA, Baumann MH, Partilla JS, Bonano JS, Vouga A, Talarida CS, Velvadapu V, Smith GR, Peet MM, Reitz AB, Negus SS, Rawls SM. Br J Pharmacol 2015; 172(3): 883-894.
Synthetic cathinones, commonly referred to as 'bath salts', are a group of amphetamine-like drugs gaining popularity worldwide. 4-Methylmethcathinone (mephedrone, MEPH) is the most commonly abused synthetic cathinone in the UK, and exerts its effects by acting as a substrate-type releaser at monoamine transporters. Similar to other cathinone-related compounds, MEPH has a chiral centre and exists stably as two enantiomers: R-mephedrone (R-MEPH) and S-mephedrone (S-MEPH). Here, the authors provide the first investigation into the neurochemical and behavioural effects of R-MEPH and S-MEPH. They analysed both enantiomers in rat brain synaptosome neurotransmitter release assays and also investigated their effects on locomotor activity (e.g. ambulatory activity and repetitive movements), behavioural sensitization and reward. Both enantiomers displayed similar potency as substrates (i.e. releasers) at dopamine transporters, but R-MEPH was much less potent than S-MEPH as a substrate at 5-HT transporters. Locomotor activity was evaluated in acute and repeated administration paradigms, with R-MEPH producing greater repetitive movements than S-MEPH across multiple doses. After repeated drug exposure, only R-MEPH produced sensitization of repetitive movements. R-MEPH produced a conditioned place preference whereas S-MEPH did not. Lastly, R-MEPH and S-MEPH produced biphasic profiles in an assay of intracranial self-stimulation (ICSS), but R-MEPH produced greater ICSS facilitation than S-MEPH. These data are the first to demonstrate stereospecific effects of MEPH enantiomers and suggest that the predominant dopaminergic actions of R-MEPH (i.e. the lack of serotonergic actions) render this stereoisomer more stimulant-like when compared with S-MEPH. This hypothesis warrants further study.

Raphe Serotonin Neuron-Specific Oxytocin Receptor Knockout Reduces Aggression Without Affecting Anxiety-Like Behavior In Male Mice Only Pagani JH, Williams Avram SK, Cui Z, Song J, Mezey É, Senerth JM, Baumann MH, Young WS. Genes Brain Behav. 2015; 14: 167-176.
Serotonin and oxytocin influence aggressive and anxiety-like behaviors, though it is unclear how the two may interact. That the oxytocin receptor is expressed in the serotonergic raphe nuclei suggests a mechanism by which the two neurotransmitters may cooperatively influence behavior. The authors hypothesized that oxytocin acts on raphe neurons to influence serotonergically mediated anxiety-like, aggressive and parental care behaviors. They eliminated expression of the oxytocin receptor in raphe neurons by crossing mice expressing Cre recombinase under control of the serotonin transporter promoter (Slc6a4) with their conditional oxytocin receptor knockout line. The knockout mice generated by this cross are normal across a range of behavioral measures: there are no effects for either sex on locomotion in an open-field, olfactory habituation/dishabituation or, surprisingly, anxiety-like behaviors in the elevated O and plus mazes. There was a profound deficit in male aggression: only one of 11 raphe oxytocin receptor knockouts showed any aggressive behavior, compared to 8 of 11 wildtypes. In contrast, female knockouts displayed no deficits in

maternal behavior or aggression. These results show that oxytocin, via its effects on raphe neurons, is a key regulator of resident-intruder aggression in males but not maternal aggression. Furthermore, this reduction in male aggression is quite different from the effects reported previously after forebrain or total elimination of oxytocin receptors. Finally, the authors conclude that when constitutively eliminated, oxytocin receptors expressed by serotonin cells do not contribute to baseline anxiety-like behaviors or maternal care.

Medication Development Program, Neurochemistry & Voltammetry Laboratories

Cocaine-Induced Endocannabinoid Release Modulates Behavioral and Neurochemical Sensitization In Mice Mereu M, Tronci V, Chun LE, Thomas AM, Green JL, Katz JL, Tanda G. Addict Biol. 2015 Jan; 20(1): 91-103.
The endocannabinoid system has been implicated in the development of synaptic plasticity induced by several drugs abused by humans, including cocaine. However, there remains some debate about the involvement of cannabinoid receptors/ligands in cocaine-induced plasticity and corresponding behavioral actions. Here, the authors show that a single cocaine injection in Swiss-Webster mice produces behavioral and neurochemical alterations that are under the control of the endocannabinoid system. This plasticity may be the initial basis for changes in brain processes leading from recreational use of cocaine to its abuse and ultimately to dependence. Locomotor activity was monitored with photobeam cell detectors, and accumbens shell/core microdialysate dopamine levels were monitored by high-performance liquid chromatography with electrochemical detection. Development of single-trial cocaine-induced behavioral sensitization, measured as increased distance traveled in sensitized mice compared to control mice, was paralleled by a larger stimulation of extracellular dopamine levels in the core but not the shell of the nucleus accumbens. Both the behavioral and neurochemical effects were reversed by CB1 receptor blockade produced by rimonabant pre-treatments. Further, both behavioral and neurochemical cocaine sensitization were facilitated by pharmacological blockade of endocannabinoid metabolism, achieved by inhibiting the fatty acid amide hydrolase enzyme. In conclusion, these results suggest that a single unconditioned exposure to cocaine produces sensitization through neuronal alterations that require regionally specific release of endocannabinoids. Further, the present results suggest that endocannabinoids play a primary role from the earliest stage of cocaine use, mediating the inception of long-term brain-adaptive responses, shaping central pathways and likely increasing vulnerability to stimulant abuse disorders.

Preference For Distinct Functional Conformations Of the Dopamine Transporter Alters the Relationship Between Subjective Effects Of Cocaine and Stimulation Of Mesolimbic Dopamine Kohut SJ, Hiranita T, Hong S-K, Ebbs AL, Tronci V, Green J, Garcés-Ramírez L, Chun LE, Mereu M, Newman AH, Katz JL, Tanda G. *Biological* Psychiatry 2014; 76(10): 802-809.
Subjective effects of cocaine are mediated primarily by dopamine (DA) transporter (DAT) blockade. The present study assessed the hypothesis that different DAT conformational equilibria regulate differences in cocaine-like subjective effects and extracellular DA induced by diverse DA-uptake inhibitors (DUIs). The relationship between cocaine-like subjective effects and stimulation of mesolimbic DA levels by standard DUIs (cocaine, methylphenidate, WIN35,428) and atypical DUIs (benztropine analogs: AHN1-055, AHN2-005, JHW007) was investigated using cocaine discrimination and DA microdialysis procedures in rats. All drugs stimulated DA levels with

different maxima and time courses. Standard DUIs, which preferentially bind outward-facing DAT conformations, fully substituted for cocaine, consistently producing cocaine-like subjective effects at DA levels of 100–125% over basal values, regardless of dose or pretreatment time. The atypical DUIs, with DAT binding minimally affected by DAT conformation, produced inconsistent cocaine-like subjective effects. Full effects were obtained, if at all, only at a few doses and pretreatment times and at DA levels 600–700% greater than basal values. Importantly, the linear, time-independent, relationship between cocaine-like subjective effects and DA stimulation obtained with standard DUIs was not obtained with the atypical DUIs. These results suggest a time-related desensitization process underlying the reduced cocaine subjective effects of atypical DUIs that may be differentially induced by the binding modalities identified using molecular approaches. Since the DAT is the target of several drugs for treating neuropsychiatric disorders, such as attention-deficit/hyperactivity disorder, these results help to identify safe and effective medications with minimal cocaine-like subjective effects that contribute to abuse liability.

A Systematic Microdialysis Study Of Dopamine Transmission In the Accumbens Shell/Core and Prefrontal Cortex After Acute Antipsychotics Tanda G, Valentini V, De Luca MA, Perra V, Serra GP, Di Chiara G. Psychopharmacology. 2014 Oct 28. [Epub ahead of print].
The only systematic in vivo studies comparing antipsychotic (AP) effects on nucleus accumbens (NAc) shell and core dopamine (DA) transmission are voltammetric studies performed in pargyline-pretreated, halothane-anaesthetized rats. Studies in freely moving rats not pretreated with pargyline are not available. This study was intended to fill this gap by the use of in vivo microdialysis in freely moving rats. Male Sprague-Dawley rats were implanted with microdialysis probes in the NAc shell and core and medial prefrontal cortex (PFCX). The next day, rats were administered intravenously with two or three doses of APs, and dialysate DA was monitored in 10-min samples. Some rats were pretreated with pargyline (75 mg/kg i.p.) and after 1 h were given clozapine or risperidone. Clozapine, risperidone, quetiapine, raclopride, sulpiride and amisulpride increased DA preferentially in the NAc shell. Such preferential effect on shell DA was not observed after haloperidol, chlorpromazine and olanzapine. In contrast to voltammetric studies, a preferential effect on NAc core DA was not observed after any dose of AP. Pargyline pretreatment did not reduce but actually amplified the preferential effect of clozapine and risperidone on NAc shell DA. Apart from raclopride and olanzapine, the APs with lower extrapyramidal effects could be distinguished from typical APs on the basis of their ability to preferentially stimulate DA transmission in the NAc shell. There was no relationship between stimulation of PFCX DA and atypical APs profile. The differences between this study and voltammetry studies were not attributable to pargyline pretreatment.

Neuropsychopharmacology Section

Species Differences In Cannabinoid Receptor 2 and Receptor Responses To Cocaine Self-Administration In Mice and Rats Zhang H-Y, Bi G-H, Li X, Li J, Qu H, Zhang S-J, Li C-Y, Onaivi ES, Gardner EL, Xi Z-X, Liu Q-R. Neuropsychopharmacology 2015; 40: 1037-1041.
The discovery of functional cannabinoid receptors 2 (CB2Rs) in brain suggests a potential new therapeutic target for neurological and psychiatric disorders. However, recent findings in experimental animals appear controversial. Here the authors report that there are significant species differences in CB2R mRNA splicing and expression, protein sequences, and receptor responses to

CB2R ligands in mice and rats. Systemic administration of JWH133, a highly selective CB2R agonist, significantly and dose-dependently inhibited intravenous cocaine self-administration under a fixed ratio (FR) schedule of reinforcement in mice, but not in rats. However, under a progressive ratio (PR) schedule of reinforcement, JWH133 significantly increased breakpoint for cocaine self-administration in rats, but decreased it in mice. To explore the possible reasons for these conflicting findings, the authors examined CB2R gene expression and receptor structure in the brain. They found novel rat-specific CB2C and CB2D mRNA isoforms in addition to CB2A and CB2B mRNA isoforms. In situ hybridization RNAscope assays found higher levels of CB2R mRNA in different brain regions and cell types in mice than in rats. By comparing CB2R-encoding regions, the authors observed a premature stop codon in the mouse CB2R gene that truncated 13 amino-acid residues including a functional autophosphorylation site in the intracellular C-terminus. These findings suggest that species differences in the splicing and expression of CB2R genes and receptor structures may in part explain the different effects of CB2R-selective ligands on cocaine self-administration in mice and rats.

Clinical Pharmacology and Therapeutics Branch

Treatment Section

Clonidine Maintenance Prolongs Opioid Abstinence and Decouples Stress From Craving In Daily Life: A Randomized Controlled Trial With Ecological Momentary Assessment

Kowalczyk WJ, Phillips KA, Jobes ML, Kennedy AP, Ghitza UE, Agage DA, Schmittner JP, Epstein DH, Preston KL. Am J Psychiatry. 2015 Mar 17:appiajp201414081014. [Epub ahead of print].

The authors tested whether clonidine blocks stress-induced seeking of heroin and cocaine. The study was also intended to confirm translational findings from a rat model of drug relapse by using ecological momentary assessment of patients' stress to test hypotheses about clonidine's behavioral mechanism of action. The authors conducted a randomized double-blind placebo-controlled clinical trial with 208 opioid-dependent patients at an outpatient buprenorphine clinic. The 118 participants (57%) who maintained abstinence during weeks 5–6 were continued on buprenorphine and randomly assigned to receive clonidine (N=61) or placebo (N=57) for 14 weeks. Urine was tested thrice weekly. Lapse was defined as any opioid- positive or missed urine test, and relapse as two or more consecutive lapses. Time to lapse and relapse were examined with Cox regressions; longest period of abstinence was examined with a t test, and ecological momentary assessment data were examined with generalized linear mixed models. In an intent-to-treat analysis, clonidine produced the longest duration (in consecutive days) of abstinence from opioids during the intervention phase (34.8 days [SD=3.7] compared with 25.5 days [SD=2.7]; Cohen's d=0.38). There was no group difference in time to relapse, but the clonidine group took longer to lapse (hazard ratio=0.67, 95% CI=0.45–1.00). Ecological momentary assessment showed that daily-life stress was partly decoupled from opioid craving in the clonidine group, supporting the authors' hypothesized mechanism for clonidine's benefits. Clonidine, a readily available medication, is useful in opioid dependence not just for reduction of withdrawal signs, but also as an adjunctive maintenance treatment that increases duration of abstinence. Even in the absence of physical withdrawal, it decouples stress from craving in everyday life.

Are We There Yet? Feasibility Of Continuous Stress Assessment Via Physiological Sensors In Field Rahman MM, Bari R, Ali AA, Sharmin M, Raij A, Hovsepian K, Hossain SM, Ertin E, Kennedy A, Epstein D, Preston K, Jobes M, Kedia S, Ward W, al'Absi M, Kumar S. ACM BCB 2014 - 5th Proc. ACM Conference on Bioinformatics, Computational Biology and Health Informatics, Newport Beach, CA, pp. 479-488, 2014.
Excessive and repetitive stress can lead to headaches and fatigue, precipitate addictive behaviors (e.g., smoking, drug use), and in the longer term, can elevate risk for cardiovascular diseases and cancer. Continuous assessment of stress from sensors can be used for timely delivery of a variety of interventions to reduce or avoid stress. The authors investigate the feasibility of continuous stress measurement via two field studies using wireless wearable physiological sensors — a four-week study with illicit drug users (n = 40), and a one-week study with daily smokers and social drinkers (n = 30). They find that 11+ hours/day of usable data can be obtained in a 4-week study. Significant learning effect is observed after the first week and data yield is seen to be increasing over time even in the fourth week. The authors propose a framework to analyze sensor data yield and find that losses in wireless channel is now negligible; the main hurdle in further improving data yield is the attachment constraint. The authors show the feasibility of measuring stress minutes preceding events of interest and observe the sensor-derived stress to be rising prior to self-reported stress and smoking events.

Chemistry and Drug Metabolism Section

Cannabinoid Disposition In Oral Fluid After Controlled Vaporizer Administration With and Without Alcohol Hartman RL, Anizan S, Jang M, Yun K, Gorelick DA, Huestis MA. Forensic Toxicol. 2015, e-pub 10 March, 2015.
Oral fluid (OF) is an advantageous matrix for cannabis detection, with on-site tests available for roadside drug-impaired driving screening. Limited data exist for device performance following vaporized cannabis, which reduces exposure to harmful combustion byproducts. The authors assessed cannabinoid OF disposition, with and without alcohol, and evaluated on-site Dräger DrugTest® 5000 performance (Dräger) following controlled vaporized cannabis. Forty-three cannabis smokers (≥1x/3months, ≤3 days/week) reported 10-16 h prior to dosing, and drank placebo or low (target ~0.065% peak breath-alcohol concentration [BrAC]) dose alcohol 10min prior to inhaling 500 mg placebo, low (2.9% THC)-, or high (6.7% THC)-dose vaporized cannabis (within-subjects; 6 possible alcohol-cannabis combinations; 19 completers). BrAC and OF (QuantisalTM, Dräger) were collected before and up to 8.3 h post-dose. Median [range] maximum OF concentrations (Cmax) for low and high doses (no alcohol, N=19) were 848 [32.1-18230] and 764 [25.1-23680] μg/l THC; 6.0 [0-100] and 26.8 [1.0-1106] μg/l cannabidiol; 54.4 [1.8-941] and 29.7 [0-766] μg/l cannabinol; and 24.1 [0-686] and 18.0 [0-414] ng/l 11-nor-9-carboxy-THC (THCCOOH). Lack of significant low-vs.-high-dose THC concentration differences indicated participants may have titrated doses. THC, cannabidiol and cannabinol Cmax occurred immediately post-inhalation, but metabolite THCCOOH tmax showed interindividual variability. Concurrent alcohol did not affect OF cannabinoid concentrations or on-site test sensitivity. At 5 μg/l THC confirmation cutoff, Dräger sensitivity, specificity, and efficiency were 60.8%, 98.2% and 82.5%. Dräger had lower sensitivity after 6.7% THC vaporization (53.8%, THC≥2 μg/l confirmation cutoff) than reported following smoking a 6.8% THC cigarette, but high specificity (99.3%) and comparable efficiency (65.0%). Vaporized THC bioavailability may be lower than smoked.

Confirmation cutoff, time course, intake histories, and additional cannabinoid analytes affect OF interpretation.

Safety and Pharmacokinetics Of Oral Cannabidiol When Administered Concomitantly With Intravenous Fentanyl In Humans Manini AF, Yiannoulos G, Bergamaschi MM, Hernandez S, Olmedo R, Barnes AJ, Winkel G, Sinha R, Jutras-Aswad D, Huestis MA, Hurd YL. J Addict Med. 2015, e-pub Mar 5, 2015.
Cannabidiol (CBD) is hypothesized as a potential treatment for opioid addiction, with safety studies an important first step for medication development. The authors determined CBD safety and pharmacokinetics when administered concomitantly with a high-potency opioid in healthy subjects. This double-blind, placebo-controlled cross-over study of CBD, coadministered with intravenous fentanyl, was conducted at the Clinical Research Center in Mount Sinai Hospital, a tertiary care medical center in New York City. Participants were healthy volunteers aged 21 to 65 years with prior opioid exposure, regardless of the route. Blood samples were obtained before and after 400 or 800 mg of CBD pretreatment, followed by a single 0.5 (session 1) or 1.0 μg/kg (session 2) of intravenous fentanyl dose. The primary outcome was the Systematic Assessment for Treatment Emergent Events (SAFTEE) to assess safety and adverse effects. CBD peak plasma concentrations, time to reach peak plasma concentrations (tmax), and area under the curve (AUC) were measured. SAFTEE data were similar between groups without respiratory depression or cardiovascular complications during any test session. After low-dose CBD, tmax occurred at 3 and 1.5 hours in sessions 1 and 2, respectively. After high-dose CBD, tmax occurred at 3 and 4 hours in sessions 1 and 2, respectively. There were no significant differences in plasma CBD or cortisol (AUC P = NS) between sessions. Cannabidiol does not exacerbate adverse effects associated with intravenous fentanyl administration. Coadministration of CBD and opioids was safe and well tolerated. These data provide the foundation for future studies examining CBD as a potential treatment for opioid abuse.

Smoked Cannabis Psychomotor and Neurocognitive Effects In Occasional and Frequent Smokers Desrosiers NA, Ramaekers JG, Chauchard E, Gorelick DA, Huestis MA. Journal of Analytical Toxicology. 2015, e-pub Mar 4, 2015.
Δ9-Tetrahydrocannabinol (THC), the primary psychoactive constituent in cannabis, impairs psychomotor performance, cognition and driving ability; thus, driving under the influence of cannabis is a public safety concern. The authors documented cannabis' psychomotor, neurocognitive, subjective and physiological effects in occasional and frequent smokers to investigate potential differences between these smokers. Fourteen frequent (≥4x/week) and 11 occasional (<2x/week) cannabis smokers entered a secure research unit ~19 h prior to smoking one 6.8% THC cigarette. Cognitive and psychomotor performance was evaluated with the critical tracking (CTT), divided attention (DAT), n-back (working memory) and Balloon Analog Risk (BART) (risk-taking) tasks at -1.75, 1.5, 3.5, 5.5 and 22.5 h after starting smoking. GLM (General Linear Model) repeated measures ANOVA was utilized to compare scores. Occasional smokers had significantly more difficulty compensating for CTT tracking error compared with frequent smokers 1.5 h after smoking. Divided attention performance declined significantly especially in occasional smokers, with session × group effects for tracking error, hits, false alarms and reaction time. Cannabis smoking did not elicit session × group effects on the n-back or BART. Controlled cannabis smoking impaired psychomotor function, more so in occasional smokers, suggesting some tolerance to psychomotor impairment in frequent users. These data have implications for cannabis-

associated impairment in driving under the influence of cannabis cases.

Pentylindole/Pentylindazole Synthetic Cannabinoids and Their 5-Fluoro Analogs Produce Different Primary Metabolites: Metabolite Profiling For AB-PINACA and 5F-AB-PINACA
Wohlfarth A, Castaneto M, Zhu M, Pang S, Scheidweiler KB, Kronstrand R, Huestis MA. The AAPS Journal. 2015, e-pub Feb 28, 2015.
Whereas non-fluoropentylindole/indazole synthetic cannabinoids appear to be metabolized preferably at the pentyl chain though without clear preference for one specific position, their 5-fluoro analogs' major metabolites usually are 5-hydroxypentyl and pentanoic acid metabolites. The authors determined metabolic stability and metabolites of N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide (AB-PINACA) and 5-fluoro-AB-PINACA (5F-AB-PINACA), two new synthetic cannabinoids, and investigated if results were similar. In silico prediction was performed with MetaSite (Molecular Discovery). For metabolic stability, 1 μmol/L of each compound was incubated with human liver microsomes for up to 1 h, and for metabolite profiling, 10 μmol/L was incubated with pooled human hepatocytes for up to 3 h. Also, authentic urine specimens from AB-PINACA cases were hydrolyzed and extracted. All samples were analyzed by liquid chromatography high-resolution mass spectrometry on a TripleTOF 5600+ (AB SCIEX) with gradient elution (0.1% formic acid in water and acetonitrile). High-resolution full-scan mass spectrometry (MS) and information-dependent acquisition MS/MS data were analyzed with MetabolitePilot (AB SCIEX) using different data processing algorithms. Both drugs had intermediate clearance. The authors identified 23 AB-PINACA metabolites, generated by carboxamide hydrolysis, hydroxylation, ketone formation, carboxylation, epoxide formation with subsequent hydrolysis, or reaction combinations. They identified 18 5F-AB-PINACA metabolites, generated by the same biotransformations and oxidative defluorination producing 5-hydroxypentyl and pentanoic acid metabolites shared with AB-PINACA. Authentic urine specimens documented presence of these metabolites. AB-PINACA and 5F-AB-PINACA produced suggested metabolite patterns. AB-PINACA was predominantly hydrolyzed to AB-PINACA carboxylic acid, carbonyl-AB-PINACA, and hydroxypentyl AB-PINACA, likely in 4-position. The most intense 5F-AB-PINACA metabolites were AB-PINACA pentanoic acid and 5-hydroxypentyl-AB-PINACA.

Validation Of An ELISA Synthetic Cannabinoids Urine Assay Barnes AJ, Spinelli E, Young S, Martin TM, Klette KL, Huestis MA. Ther Drug Monit. 2015, e-pub Feb 19, 2015.
Synthetic cannabinoids are touted as legal alternatives to cannabis, at least when first released, and routine urine cannabinoid screening methods do not detect these novel psychoactive substances. Synthetic cannabinoids are widely available, are a major public health and safety problem, and a difficult challenge for drug testing laboratories. The authors evaluated performance of the NMS JWH-018 direct ELISA kit to sensitively, selectively, and rapidly screen urinary synthetic cannabinoids. The NMS ELISA kit targeting the JWH-018 N-(5-hydroxypentyl) metabolite was utilized to screen 2492 urine samples with 5 and 10µg/L cutoffs. A fully validated LC-MS/MS method for 29 synthetic cannabinoids markers confirmed all presumptive positive and negative results. Performance challenges at ±25 and ±50% of cutoffs determined intra- and inter-plate imprecision around proposed cutoffs. The immunoassay was linear from 1-500µg/L with intra- and inter-plate imprecision of ≤8.2% and <14.0%, respectively. No interferences were present from 93 common drugs of abuse, metabolites, co-administered drugs, over-the-counter medications or structurally similar compounds, and 19 of 73 individual, synthetic cannabinoids (26%) exhibited moderate to high cross-reactivity to JWH-018 N-(5-hydroxypentyl) metabolite. Sensitivity,

specificity, and efficiency results were 83.7%, 99.4% and 97.6% and 71.6%, 99.7% and 96.4%, with the 5 and 10µg/L urine cutoffs, respectively. This high throughput immunoassay exhibited good diagnostic efficiency and documented that the NMS JWH-018 direct ELISA is a viable method for screening synthetic cannabinoids in urine targeting the JWH-018 N-(5-hydroxypentyl) and related analytes. Optimal performance was achieved with a matrix-matched 5µg/L urine cutoff.

Linear Pharmacokinetics Of 3,4-Methylenedioxypyrovalerone (MDPV) and Its Metabolites In the Rat: Relationship To Pharmacodynamic Effects Anizan S, Concheiro M, Lehner KR, Bukhari MO, Suzuki M, Rice KC, Baumann MH, Huestis MA. Addiction Biology. 2014, e-pub Dec 5, 2014.
3,4-Methylenedioxypyrovalerone (MDPV) is a commonly abused synthetic cathinone in the United States and is associated with dangerous side effects. MDPV is a dopamine transporter blocker that is 10-fold more potent than cocaine as a locomotor stimulant in rats. Previous in vitro and in vivo metabolism studies identified 3,4-dihydroxypyrovalerone (3,4-catechol-PV) and 4-hydroxy-3-methoxypyrovalerone (4-OH-3-MeO-PV) as the two primary MDPV metabolites. This study examined MDPV pharmacokinetics and metabolism, along with associated pharmacodynamic effects in rats receiving 0.5, 1.0 and 2.0 mg/kg subcutaneous (s.c.) MDPV. Blood was collected by an indwelling jugular catheter before dosing and at 10, 20, 30, 60, 120, 240 and 480 minutes thereafter. Plasma specimens were analyzed by liquid chromatography coupled to high-resolution tandem mass spectrometry. Maximum concentrations (Cmax) and area-under-the-curve (AUC) for MDPV and two metabolites increased proportionally with administered dose, showing linear pharmacokinetics. MDPV exhibited the highest Cmax at all doses (74.2-271.3 µg/l) and 4-OH-3-MeOH-PV the highest AUC (11 366-47 724 minutes per µg/l), being the predominant metabolite. MDPV time to Cmax (Tmax) was 12.9-18.6 minutes, while 3,4-catechol-PV and 4-OH-3-MeO-PV peaked later with Tmax 188.6-240 minutes after s.c. dosing. Horizontal locomotor activity (HLA) and stereotypy correlated positively with plasma MDPV concentrations, while HLA correlated negatively with MDPV metabolites. These results suggest that the parent compound mediates motor stimulation after systemic MDPV administration, but additionally, metabolites may be inhibitory, may not be active or may not pass the blood brain barrier.

The Corticotropin Releasing Hormone-1 (CRH1) Receptor Antagonist Pexacerfont In Alcohol Dependence: A Randomized Controlled Experimental Medicine Study Kwako LE, Spagnolo PA, Schwandt ML, Thorsell A, David T. George DT, Momenan R, Rio DE, Huestis MA, Anizan SA, Concheiro M, Sinha R, Heilig M. Neuropsychopharmacology. 2015 Mar 13; 40: 1053-1063.
Extensive preclinical data implicate corticotropin-releasing hormone (CRH), acting through its CRH1 receptor, in stress- and dependence-induced alcohol seeking. Here, the authors evaluated pexacerfont, an orally available, brain penetrant CRH1 antagonist for its ability to suppress stress-induced alcohol craving and brain responses in treatment seeking alcohol dependent patients in early abstinence. Fifty-four participants were admitted to an inpatient unit at the NIH Clinical Center, completed withdrawal treatment if needed, and were then randomized to double-blind pexacerfont (300 mg/day for 7 days, followed by 100mg/day for 23 days) or placebo. After reaching steady state, subjects were assessed for alcohol craving in response to stressful or alcohol-related cues, neuroendocrine responses to these stimuli, and fMRI responses to alcohol-related stimuli or stimuli with positive or negative emotional valence. A separate group of 10 patients received single blind pexacerfont following the same dosing regimen, and had cerebrospinal fluid sampled to estimate central nervous system exposure. Pexacerfont treatment had no effect on alcohol craving,

emotional responses, or anxiety. There was no effect of pexacerfont on neural responses to alcohol-related or affective stimuli. These results were obtained despite drug levels in CSF that predict close to 90% central CRH1 receptor occupancy. CRH1 antagonists have been grouped based on their receptor dissociation kinetics, with pexacerfont falling in a category characterized by fast dissociation. These results may indicate that antagonists with slow offset are required for therapeutic efficacy. Alternatively, the extensive preclinical data on CRH1 antagonism as a mechanism to suppress alcohol seeking may not translate to humans.

Prenatal Tobacco Exposure and Infant Stress Reactivity: Role Of Child Sex and Maternal Behavior Eiden RD, Molnar DS, Grander DA, Colder CR, Schuetze P, Huestis MA. Developmental Psychobiology. 2015 Mar; 57(2): 212-225.
This study examined the association between prenatal tobacco exposure (PTE) and infant cortisol reactivity at 9 months of infant age. Child sex and maternal parenting behavior were hypothesized moderators. The sample included 217 (148 tobacco-exposed, 69 non-exposed) mother-child dyads. Data used were obtained from pregnancy assessments, mother-infant feeding interactions at 2 months, and salivary cortisol at 4 time points in response to frustration at 9 months. Results indicated a significant association between PTE and infant cortisol that was moderated by infant sex and maternal intrusiveness. That is, PTE boys had lower cortisol than control boys, but there was no association between PTE and cortisol among girls. There was a significant association between PTE and cortisol among infants of intrusive mothers, but not among infants with non-intrusive mothers. Thus, PTE was associated with cortisol hypo-reactivity such that boys and non-exposed infants experiencing high maternal intrusiveness were at greater risk.

Morphine and Codeine In Oral Fluid After Controlled Poppy Seed Administration Concheiro M, Newmeyer MN, da Costa JL, Flegel R, Gorelick DA, Huestis MA. Drug Testing Analysis. 2014, e-pub Oct 24, 2014.
Opiates are an important drug class in drug testing programs. Ingestion of poppy seeds containing morphine and codeine can yield positive opiate tests and mislead result interpretation in forensic and clinical settings. Multiple publications evaluated urine opiate concentrations following poppy seed ingestion, but only 2 addressed oral fluid (OF) results; neither provided the ingested morphine and codeine dosage. The authors administered two 45g raw poppy seed doses, each containing 15.7mg morphine and 3.1mg codeine, 8h apart to 17 healthy adults. All OF specimens were screened by on-site OF immunoassay Draeger DrugTest 5000, and confirmed with OF collected with Oral-Eze® device and quantified by liquid chromatography tandem mass spectrometry (1µg/L morphine and codeine limits of quantification). Specimens (n=459) were collected before and up to 32h after the first dose. All specimens screened positive 0.5h after dosing and remained positive for 0.5-13h at Draeger 20µg/L morphine cutoff. Maximum OF morphine and codeine concentrations (Cmax) were 177 and 32.6µg/L, with times to Cmax (Tmax) of 0.5-1h and 0.5-2.5h post-dose, respectively. Windows of detection after the second dose extended at least 24h for morphine and to 18h for codeine. After both doses, the last morphine positive OF result was 1h with 40µg/L 2004 proposed US Substance Abuse and Mental Health Services Administration cut-off, and 0.5h with 95µg/L cutoff, recently recommended by the Driving Under the Influence of Drugs and Medicines project. Positive OF morphine results are possible 0.5-1h after ingestion of 15.7mg of morphine in raw poppy seeds, depending upon the cutoff employed.

Molecular Neuropsychiatry Research Branch

Epigenetics Of Stress, Addiction, and Resilience: Therapeutic Implications Cadet JL. Mol Neurobiol. 2014 Dec 11. [Epub ahead of print].
Substance use disorders (SUDs) are highly prevalent. SUDs involve vicious cycles of binges followed by occasional periods of abstinence with recurrent relapses despite treatment and adverse medical and psychosocial consequences. There is convincing evidence that early and adult stressful life events are risks factors for the development of addiction and serve as cues that trigger relapses. Nevertheless, the fact that not all individuals who face traumatic events develop addiction to licit or illicit drugs suggests the existence of individual and/or familial resilient factors that protect these mentally healthy individuals. Here, the author gives a brief overview of the epigenetic bases of responses to stressful events and of epigenetic changes associated with the administration of drugs of abuse. The author also discusses the psychobiology of resilience and alterations in epigenetic markers that have been observed in models of resilience. Finally, the authors suggests the possibility that treatment of addiction should involve cognitive and pharmacological approaches that enhance resilience in at risk individuals. Similar approaches should also be used with patients who have already succumbed to the nefarious effects of addictive substances.

Transcriptional and Epigenetic Substrates Of Methamphetamine Addiction and Withdrawal: Evidence From A Long-Access Self-Administration Model In the Rat Cadet JL, Brannock C, Jayanthi S, Krasnova IN. Mol Neurobiol. 2015 Apr; 51(2): 696-717. doi: 10.1007/s12035-014-8776-8. Epub 2014 Jun 18.
Methamphetamine use disorder is a chronic neuropsychiatric disorder characterized by recurrent binge episodes, intervals of abstinence, and relapses to drug use. Humans addicted to methamphetamine experience various degrees of cognitive deficits and other neurological abnormalities that complicate their activities of daily living and their participation in treatment programs. Importantly, models of methamphetamine addiction in rodents have shown that animals will readily learn to give themselves methamphetamine. Rats also accelerate their intake over time. Microarray studies have also shown that methamphetamine taking is associated with major transcriptional changes in the striatum measured within a short or longer time after cessation of drug taking. After a 2-h withdrawal time, there was increased expression of genes that participate in transcription regulation. These included cyclic AMP response element binding (CREB), ETS domain-containing protein (ELK1), and members of the FOS family of transcription factors. Other genes of interest include brain-derived neurotrophic factor (BDNF), tyrosine kinase receptor, type 2 (TrkB), and synaptophysin. Methamphetamine-induced transcription was found to be regulated via phosphorylated CREB-dependent events. After a 30-day withdrawal from methamphetamine self-administration, however, there was mostly decreased expression of transcription factors including junD. There was also downregulation of genes whose protein products are constituents of chromatin-remodeling complexes. Altogether, these genome-wide results show that methamphetamine abuse might be associated with altered regulation of a diversity of gene networks that impact cellular and synaptic functions. These transcriptional changes might serve as triggers for the neuropsychiatric presentations of humans who abuse this drug. Better understanding of the way that gene products interact to cause methamphetamine addiction will help to develop better pharmacological treatment of methamphetamine addicts.

Chemical Biology Research Branch

Drug Design and Synthesis Section

Effects Of the Kappa Opioid Receptor Antagonist Nor-Binaltorphimine (Nor-BNI) On Cocaine Versus Food Choice and Extended-Access Cocaine Intake In Rhesus Monkeys
Hutsell BA, Cheng K, Rice KC, Negus SS, Banks ML. Addict Biol, 2015, epub Jan 8, 2015.
The dynorphin/kappa opioid receptor (KOR) system has been implicated as one potential neurobiological modulator of the abuse-related effects of cocaine and as a potential target for medications development. This study determined effects of the KOR antagonist nor-binaltorphimine (nor-BNI) on cocaine self-administration under a novel procedure that featured two daily components: (1) a 2-hour 'choice' component (9:00-11:00 am) when monkeys could choose between food pellets and cocaine injections (0-0.1 mg/kg per injection, intravenous) and (2) a 20-hour 'extended-access' component (noon to 8:00 am) when cocaine (0.1 mg/kg per injection) was available under a fixed-ratio schedule to promote high daily cocaine intakes. Rhesus monkeys (n = 4) were given 14 days of exposure to the choice + extended-access procedure then treated with nor-BNI (3.2 or 10.0 mg/kg, intramuscular), and cocaine choice and extended-access cocaine intake were evaluated for an additional 14 days. Consistent with previous studies, cocaine maintained both a dose-dependent increase in cocaine choice during choice components and a high level of cocaine intake during extended-access components. Neither 3.2 nor 10 mg/kg nor-BNI significantly altered cocaine choice or extended-access cocaine intake. In two additional monkeys, nor-BNI also had no effect on cocaine choice or extended-access cocaine intake when it was administered at the beginning of exposure to the extended-access components. Overall, these results do not support a major role for the dynorphin/KOR system in modulating cocaine self-administration under these conditions in non-human primates nor do they support the clinical utility of KOR antagonists as a pharmacotherapeutic strategy for cocaine addiction.

Alcohol-Induced Sedation and Synergistic Interactions Between Alcohol and Morphine: A Key Mechanistic Role For Toll-Like Receptors and Myd88-Dependent Signaling Corrigan F, Wu Y, Tuke J, Coller JK, Rice KC, Diener KR, Hayball JD, Watkins LR, Somogyi AA, Hutchinson MR. Brain Behav Immun. 2015; 45: 245-252.
Increasing evidence demonstrates induction of proinflammatory Toll-like receptor (TLR) 2 and TLR4 signaling by morphine and, TLR4 signaling by alcohol; thus indicating a common site of drug action and a potential novel innate immune-dependent hypothesis for opioid and alcohol drug interactions. Hence, the current study aimed to assess the role of TLR2, TLR4, MyD88 (as a critical TLR-signaling participant), NF-κB, Interleukin-1β (IL-1β; as a downstream proinflammatory effector molecule) and the μ opioid receptor (MOR; as a classical site for morphine action) in acute alcohol-induced sedation (4.5g/kg) and alcohol (2.5g/kg) interaction with morphine (5mg/kg) by assessing the loss of righting reflex (LORR) as a measure of sedation. Wild-type male Balb/c mice and matched genetically-deficient TLR2, TLR4, and MyD88 strains were utilized, together with pharmacological manipulation of MOR, NF-κB, TLR4 and Interleukin-1β. Alcohol induced significant LORR in wild-type mice; this was halved by MyD88 and TLR4 deficiency, and surprisingly nearly completely eliminated by TLR2 deficiency. In contrast, the interaction between morphine and alcohol was found to be MOR-, NF-κB-, TLR2- and MyD88-dependent, but did not involve TLR4 or Interleukin-1β. Morphine-alcohol interactions caused acute elevations in microglial cell counts and NF-κB-p65 positive cells in the motor cortex in concordance with wild-

type and TLR2 deficient mouse behavioral data, implicating neuroimmunopharmacological signaling as a pivotal mechanism in this clinically problematic drug-drug interaction.

Individual Differences In Impulsive Action Reflect Variation In the Cortical Serotonin 5-HT2A Receptor System Fink LH, Anastasio NC, Fox RG, Rice KC, Moeller FG, Cunningham KA. Neuropsychopharmacology, 2015, epub Mar 18, 2015.
Impulsivity is an important feature of multiple neuropsychiatric disorders, and individual variation in the degree of inherent impulsivity could play a role in the generation or exacerbation of problematic behaviors. Serotonin (5-HT) actions at the 5-HT2AR receptor (5-HT2AR) promote and 5-HT2AR antagonists suppress impulsive action (the inability to withhold premature responses; motor impulsivity) upon systemic administration or microinfusion directly into the medial prefrontal cortex (mPFC), a node in the corticostriatal circuit that is thought to play a role in the regulation of impulsive action. The authors hypothesized that the functional capacity of the 5-HT2AR, which is governed by its expression, localization, and protein/protein interactions (eg, postsynaptic density 95 (PSD95)), may drive the predisposition to inherent impulsive action. Stable high-impulsive (HI) and low-impulsive (LI) phenotypes were identified from an outbred rodent population with the 1-choice serial reaction time (1-CSRT) task. HI rats exhibited a greater head-twitch response following administration of the preferential 5-HT2AR agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) and were more sensitive to the effects of the selective 5-HT2AR antagonist M100907 to suppress impulsive action relative to LI rats. A positive correlation was observed between levels of premature responses and 5-HT2AR binding density in frontal cortex ([3H]-ketanserin radioligand binding). Elevated mPFC 5-HT2AR protein expression concomitant with augmented association of the 5-HT2AR with PSD95 differentiated HI from LI rats. The observed differential sensitivity of HI and LI rats to 5-HT2AR ligands and associated distinct 5-HT2AR protein profiles provide evidence that spontaneously occurring individual differences in impulsive action reflect variation in the cortical 5-HT2AR system.

DAT Isn't All That: Cocaine Reward and Reinforcement Require Toll-Like Receptor 4 Signaling Northcutt AL, Hutchinson MR, Wang X, Baratta MV, Hiranita T, Cochran TA, Pomrenze MB, Galer EL, Kopajtic TA, Li CM, Amat J, Larson G, Cooper DC, Huang Y, O'Neill CE, Yin H, Zahniser NR, Katz JL, Rice KC, Maier SF, Bachtell RK, Watkins LR. Mol Psychiatry, 2015, epub Feb 3, 2015.
The initial reinforcing properties of drugs of abuse, such as cocaine, are largely attributed to their ability to activate the mesolimbic dopamine system. Resulting increases in extracellular dopamine in the nucleus accumbens (NAc) are traditionally thought to result from cocaine's ability to block dopamine transporters (DATs). Here the authors demonstrate that cocaine also interacts with the immunosurveillance receptor complex, Toll-like receptor 4 (TLR4), on microglial cells to initiate central innate immune signaling. Disruption of cocaine signaling at TLR4 suppresses cocaine-induced extracellular dopamine in the NAc, as well as cocaine conditioned place preference and cocaine self-administration. These results provide a novel understanding of the neurobiological mechanisms underlying cocaine reward/reinforcement that includes a critical role for central immune signaling, and offer a new target for medication development for cocaine abuse treatment.

(+)-Naltrexone Is Neuroprotective and Promotes Alternative Activation In the Mouse Hippocampus After Cardiac Arrest/Cardiopulmonary Resuscitation Grace PM, Shimizu K, Strand KA, Rice KC, Deng G, Watkins LR, Herson PS. Brain Behav Immun, 2015, epub Mar 13, 2015.
Despite dramatic improvement in cardiopulmonary resuscitation (CPR) and other techniques for cardiac arrest (CA), the majority of survivors continue to show signs of decreased memory or executive cognitive function. Such memory impairment may be due to hippocampal CA1 neuronal death, which is delayed by several days after CA/CPR. Classical microgliosis in the CA1 region may contribute to neuronal death, yet the role of a key activation receptor Toll Like Receptor 4 (TLR4) has not been previously investigated for such neuronal death after CA/CPR. The authors show that (+)-naltrexone was neuroprotective after CA/CPR. TLR4 blockade was associated with decreased expression of markers for microglial/macrophage activation and T cell and B cell infiltration, as well as decreased pro-inflammatory cytokine levels. Notably, IL-10 expression was elevated in response to CA/CPR, but was not attenuated by (+)-naltrexone, suggesting that the local monocyte/microglial phenotype had shifted towards alternative activation. This was confirmed by elevated expression of Arginase-1, and decreased expression of NFκB p65 subunit. Thus, (+)-naltrexone and other TLR4 antagonists may represent a novel therapeutic strategy to alleviate the substantial burden of memory or executive cognitive function impairment after CA/CPR.

Chiral Resolution and Absolute Configuration Of the Enantiomers Of the Psychoactive "Designer Drug" 3,4-Methylenedioxypyrovalerone Suzuki M, Deschamps JR, Jacobson AE, Rice KC. Chirality, 2015; 27(4): 287-293.
Illicit rac-MDPV (3,4-methylenedioxypyrovalerone), manufactured in clandestine labs, has become widely abused for its cocaine-like stimulant properties. It has recently been found as one of the toxic materials in the so-called "bath salts," producing, among other effects, psychosis and tachycardia in humans when introduced by any of the several routes of administration (e.g., intravenous, oral, etc.). The considerable toxicity of this "designer drug" probably resides in one of the enantiomers of the racemate. In order to obtain a sufficient amount of the enantiomers of rac-MDPV to determine their activity, we improved the known synthesis of rac-MDPV and found chemical resolving agents, (+)- and (-)-2'-bromotetranilic acid, that gave the MDPV enantiomers in >96% enantiomeric excess as determined by (1) H nuclear magnetic resonance and chiral high-performance liquid chromatography. The absolute stereochemistry of these enantiomers was determined by single-crystal X-ray diffraction studies.

Probes For Narcotic Receptor Mediated Phenomena 49. N-Substituted Rac-Cis-4a-Arylalkyl-1,2,3,4,4a,9a-Hexahydrobenzofuro[2,3-C]Pyridin-6-Ols Iyer MR, Rothman RB, Dersch CM, Jacobson AE, Rice KC. Eur J Med Chem. 2015; 92: 531-539.
Racemic N-substituted -1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ols containing cis-4a-aralkyl groups were explored as probes for opioid receptors. Specifically cis-4a-phenylpropyl, -phenylbutyl, and-phenylpentyl groups coupled with widely varied substituents on the nitrogen atom were synthesized and their pharmacological profiles at opioid receptors examined. The study yielded compounds with good affinity and moderate to potent antagonist activity at the μ- and δ-opioid receptors, and agonist activity at the κ-opioid receptor. An N-allyl substituent in the C4a phenylpropyl series induced 6-fold higher affinity at δ-than μ-receptors, while an N-CPM substituent in the C4a (CH2)3Ph series led to a compound with high δ-affinity and potent δ-antagonist activity.

Integrative Neuroscience Research Branch

Neuronal Networks Section

Glutamatergic and Dopaminergic Neurons In the Mouse Ventral Tegmental Area Yamaguchi T, Qi J, Wang HL, Zhang S, Morales M. Eur J Neurosci. 2015 Mar; 41(6): 760-772. doi: 10.1111/ejn.12818. Epub 2015 Jan 9.
The ventral tegmental area (VTA) comprises dopamine (DA), γ-aminobutyric acid (GABA) and glutamate (Glu) neurons. Some rat VTA Glu neurons, expressing vesicular glutamate transporter 2 (VGluT2), co-express tyrosine hydroxylase (TH). While transgenic mice are now being used in attempts to determine the role of VGluT2/TH neurons in reward and neuronal signaling, such neurons have not been characterized in mouse tissue. By cellular detection of VGluT2 mRNA and TH immunoreactivity (TH-IR), the authors determined the cellular expression of VGluT2 mRNA within VTA TH-IR neurons in the mouse. They found that some mouse VGluT2 neurons coexpressed TH-IR, but their frequency was lower than in the rat. To determine whether low expression of TH mRNA or TH-IR accounts for this low frequency, the authors evaluated VTA cellular coexpression of TH transcripts and TH protein. Within the medial aspects of the VTA, some neurons expressed TH mRNA but lacked TH-IR; among them a subset coexpressed VGluT2 mRNA. To determine if lack of VTA TH-IR was due to TH trafficking, we tagged VTA TH neurons by Cre-inducible expression of mCherry in TH::Cre mice. By dual immunofluorescence, we detected axons containing mCherry, but lacking TH-IR, in the lateral habenula, indicating that low frequency of VGluT2 mRNA (+)/TH-IR (+) neurons in the mouse is due to lack of synthesis of TH protein, rather than TH protein trafficking. In conclusion, VGluT2 neurons are present in the rat and mouse VTA, but they differ in the populations of VGluT2/TH and TH neurons. Under normal conditions, the translation of TH protein is suppressed in the mouse mesohabenular TH neurons.

A Subpopulation Of Neurochemically-Identified Ventral Tegmental Area Dopamine Neurons Is Excited By Intravenous Cocaine Mejias-Aponte CA, Ye C, Bonci A, Kiyatkin EA, Morales M. J Neurosci. 2015 Feb 4; 35(5): 1965-1978. doi: 10.1523/JNEUROSCI.3422-13.2015.
Systemic administration of cocaine is thought to decrease the firing rates of ventral tegmental area (VTA) dopamine (DA) neurons. However, this view is based on categorizations of recorded neurons as DA neurons using preselected electrophysiological characteristics lacking neurochemical confirmation. Without applying cellular preselection, the authors recorded the impulse activity of VTA neurons in response to cocaine administration in anesthetized adult rats. The phenotype of recorded neurons was determined by their juxtacellular labeling and immunohistochemical detection of tyrosine hydroxylase (TH), a DA marker. They found that intravenous cocaine altered firing rates in the majority of recorded VTA neurons. Within the cocaine-responsive neurons, half of the population was excited and the other half was inhibited. Both populations had similar discharge rates and firing regularities, and most neurons did not exhibit changes in burst firing. Inhibited neurons were more abundant in the posterior VTA, whereas excited neurons were distributed evenly throughout the VTA. Cocaine-excited neurons were more likely to be excited by footshock. Within the subpopulation of TH-positive neurons, 36% were excited by cocaine and 64% were inhibited. Within the subpopulation of TH-negative neurons, 44% were excited and 28% were inhibited. Contrary to the prevailing view that all DA neurons are inhibited by cocaine, The authors found a subset of confirmed VTA DA neurons that is excited by systemic administration of cocaine.

They provide evidence indicating that DA neurons are heterogeneous in their response to cocaine and that VTA non-DA neurons play an active role in processing systemic cocaine.

Norepinephrine Activates Dopamine D4 Receptors In the Rat Lateral Habenula Root DH, Hoffman AF, Good CH, Zhang S, Gigante E, Lupica CR, Morales M. J Neurosci. 2015 Feb 25; 35(8): 3460-3469. doi: 10.1523/JNEUROSCI.4525-13.2015.
The lateral habenula (LHb) is involved in reward and aversion and is reciprocally connected with dopamine (DA)-containing brain regions, including the ventral tegmental area (VTA). The authors used a multidisciplinary approach to examine the properties of DA afferents to the LHb in the rat. They find that >90% of VTA tyrosine hydroxylase (TH) neurons projecting to the LHb lack vesicular monoamine transporter 2 (VMAT2) mRNA, and there is little coexpression of TH and VMAT2 protein in this mesohabenular pathway. Consistent with this, electrical stimulation of LHb did not evoke DA-like signals, assessed with fast-scan cyclic voltammetry. However, electrophysiological currents that were inhibited by L741,742, a DA-D4-receptor antagonist, were observed in LHb neurons when DA uptake or degradation was blocked. To prevent DA activation of D4 receptors, we repeated this experiment in LHb slices from DA-depleted rats. However, this did not disrupt D4 receptor activation initiated by the dopamine transporter inhibitor, GBR12935. As the LHb is also targeted by noradrenergic afferents, the authors examined whether GBR12935 activation of DA-D4 receptors occurred in slices depleted of norepinephrine (NE). Unlike DA, NE depletion prevented the activation of DA-D4 receptors. Moreover, direct application of NE elicited currents in LHb neurons that were blocked by L741,742, and GBR12935 was found to be a more effective blocker of NE uptake than the NE-selective transport inhibitor nisoxetine. These findings demonstrate that NE is released in the rat LHb under basal conditions and that it activates DA-D4 receptors. Therefore, NE may be an important regulator of LHb function.

Dopaminergic and Glutamatergic Microdomains In A Subset Of Rodent Mesoaccumbens Axons Zhang S, Qi J, Li X, Wang HL, Britt JP, Hoffman AF, Bonci A, Lupica CR, Morales M. Dopaminergic and glutamatergic microdomains in a subset of rodent mesoaccumbens axons. Nat Neurosci. 2015 Mar;18(3):386-92. doi: 10.1038/nn.3945. Epub 2015 Feb 9.
Mesoaccumbens fibers are thought to co-release dopamine and glutamate. However, the mechanism is unclear, and co-release by mesoaccumbens fibers has not been documented. Using electron microcopy, the authors found that some mesoaccumbens fibers have vesicular transporters for dopamine (VMAT2) in axon segments that are continuous with axon terminals that lack VMAT2, but contain vesicular glutamate transporters type 2 (VGluT2). In vivo overexpression of VMAT2 did not change the segregation of the two vesicular types, suggesting the existence of highly regulated mechanisms for maintaining this segregation. The mesoaccumbens axon terminals containing VGluT2 vesicles make asymmetric synapses, commonly associated with excitatory signaling. Using optogenetics, the authors found that dopamine and glutamate were released from the same mesoaccumbens fibers. These findings reveal a complex type of signaling by mesoaccumbens fibers in which dopamine and glutamate can be released from the same axons, but are not normally released at the same site or from the same synaptic vesicles.

Cellular Pathobiology Section

A Perspective On Sigma-1 Receptor Research: Past and Future Su TP. Journal of Pharmacological Science 2015; 127: 1.

The description of the sigma-1 receptor came about as a binding site for a subtype of opioid receptors which was soon rectified as a non-opioid receptor of its own. It has been 33 years after the first description of the sigma-1 receptor during which period the receptor has been demonstrated to be a protein with many never-before described features. The reason for this uniqueness of the sigma-1 receptor is partly due to the fact that its sequence does not resemble that of any mammalian proteins, leading to the situation that no pre-existing description could be followed in searching for its potential physiological roles. It is also because of this uniqueness of the sigma-1 receptor that opens up opportunities to search for its functions in many physiological systems particularly as they may relate to human diseases. It is thus a great pleasure to see that the Journal of Pharmacological Sciences is devoting a special issue in the beginning of year 2015 to focus on the sigma-1 receptor research. The sigma-1 receptor has so far been implicated in diseases including Alzheimer's disease, Parkinson's disease, psycho-stimulant addiction, cancer, myocardial hypertension, aging, cognition, depression, fronto-temporal lobar motor neuron degeneration, amyotrophic lateral sclerosis, and HIV-associated neural dementia. As sigma-1 receptors exist in immune systems, functions of sigma-1 receptors in certain immune system have also been reported in the literature. This plethora of involvement of sigma-1 receptors in so many different types of diseases raises a fundamental question: what is the mode of action of the sigma-1 receptor that relates this receptor to so many different diseases? This has been a "burning" question for many researchers both inside and outside of the field of the sigma-1 receptor. The discovery that the sigma-1 receptor is an endoplasmic reticulum (ER) chaperone that resides mainly in the interface between the ER and mitochondrion, referred to as the MAM (mitochondrion-associated ER membrane), has provided a piece of pivotal information to understanding the receptor's function. Further, the demonstration that sigma-1 receptors can translocate to other areas of cells or neurons, when stimulated by its agonists such as neurosteroids or psychostimulants, adds additional dimensions to understanding the receptor's mode of action and associated physiological functions. Thus, we know now that sigma-1 receptors function locally at the MAM but also remotely for example at the plasma membrane. However, whether those two modes of actions of sigma-1 receptors may relate themselves to so many different diseases remain to be totally clarified. For example, are there other modes of action of sigma-1 receptors? Or, modes of action may differ in different organs or tissues? Those are questions to be answered in future investigations. Thus, it seems that the major hurdles to understanding the properties of sigma-1 receptors have been removed because of the advancements of technologies and associated findings as mentioned above. However, several fundamental questions concerning the sigma-1 receptor remain to be totally clarified. For example, what is the driving force that propels the translocation of sigma-1 receptors? What molecular mechanism(s) directs the underpinning targeting of sigma-1 receptors to the other parts of cell or neuron? What molecular mechanism(s) or specificity determines the targeted client protein that sigma-1 receptors will associate with either at the MAM or at remote parts of a cell? How do those molecular mechanisms, if fully established, relate to humans diseases? The major discoveries on the fundamental properties and functions of the sigma-1 receptor mostly occur in the past five years after the receptor's initial discovery in 1982. The next decade should mark a critical and fruitful period when more important and pivotal findings will clarify and shape further our fundamental understanding of this receptor which has eluded our efforts for so long in the past.

Modeling Cocaine-Induced Alterations In Organization and Patterning Of Neocortical Development Using Human Pluripotent Stem Cells Lee CT, Kindberg AA, Freed, WJ, Su TP. Stem Cell & Translational Investigation 2015; 2: e553. doi: 10.14800/scti.553
Disorders of human neocortical development are particularly difficult to study by using animal models because of the marked complexity and unique features of the human cerebral cortex. Developmental effects of cocaine, as well as other drugs and toxins, are particularly challenging to study due to complicating factors such as variations in genetic background, time of exposure, and exposure to multiple substances. Studies aimed at elucidating the effects of cocaine on fetal brain development have used rodent cell lines, primary human cells, and rat models to show that cocaine metabolism by cytochrome P450 results in oxidative ER stress and subsequent impairment of neural progenitor cell proliferation. Recently, in vitro models of neocortical development have been generated by using pluripotent stem cells. One such model, utilizing human pluripotent stem cells, reproduced the formation of neocortical glutamatergic and GABAergic neurons on radial glial scaffolding structure in a temporally sensitive manner mimicking human in vivo neocortical development. Cocaine exposure resulted in the accumulation of reactive oxygen species (ROS), premature neuronal differentiation, accelerated development of deep- and upper-layer glutamatergic neurons, and increased formation of GABAergic interneurons. Each of these changes was inhibited by the cytochrome P450 inhibitor cimetidine. These studies suggest that, in the developing human cerebral cortex, cocaine metabolism through cytochrome P450-dependent ROS generation leads to premature neuronal differentiation of neocortical progenitors and impaired neocortical patterning.

Behavioral Neuroscience Branch

Preclinical Pharmacology Section

Methamphetamine Accelerates Cellular Senescence Through Stimulation Of De Novo Ceramide Biosynthesis Astarita G, Avanesian A, Grimaldi B, Realini N, Justinova Z, Panlilio LV, Basit A, Goldberg SR, Piomelli D. PLoS One 2015. 10(2):e0116961.
Methamphetamine is a highly addictive psychostimulant that causes profound damage to the brain and other body organs. Post mortem studies of human tissues have linked the use of this drug to diseases associated with aging, such as coronary atherosclerosis and pulmonary fibrosis, but the molecular mechanism underlying these findings remains unknown. Here the authors used functional lipidomics and transcriptomics experiments to study abnormalities in lipid metabolism in select regions of the brain and, to a greater extent, peripheral organs and tissues of rats that self-administered methamphetamine. Experiments in various cellular models (primary mouse fibroblasts and myotubes) allowed us to investigate the molecular mechanisms of systemic inflammation and cellular aging related to methamphetamine abuse. The authors report now that methamphetamine accelerates cellular senescence and activates transcription of genes involved in cell-cycle control and inflammation by stimulating production of the sphingolipid messenger ceramide. This pathogenic cascade is triggered by reactive oxygen species, likely generated through methamphetamine metabolism via cytochrome P450, and involves the recruitment of nuclear factor-κB (NF-κB) to induce expression of enzymes in the de novo pathway of ceramide biosynthesis. Inhibitors of NF-κB signaling and ceramide formation prevent methamphetamine-induced senescence and systemic inflammation in rats self-administering the drug, attenuating their health

deterioration. The results suggest new therapeutic strategies to reduce the adverse consequences of methamphetamine abuse and improve effectiveness of abstinence treatments.

Concurrent Access To Nicotine and Sucrose In Rats Panlilio LV, Hogarth L, Shoaib M. Psychopharmacology (Berl). 2014 Nov 1. [Epub ahead of print].
Animal models that allow concurrent access to drug and nondrug reinforcers provide unique insight into the etiology, maintenance, and treatment of drug use. The authors sought to develop and utilize a concurrent access procedure with nicotine and sucrose in rats. Pressing one lever delivered intravenous nicotine, and pressing another lever delivered sucrose pellets, with both reinforcers freely available throughout daily sessions. Rats that had been pretrained with nicotine on some days and sucrose on other days responded on both levers when subsequently given concurrent access, but almost all responded at substantially higher rates on the sucrose lever. In contrast, rats pretrained exclusively with nicotine before being given concurrent access showed individual differences, with about half responding more on the nicotine lever. Treatment with the nicotinic receptor partial agonist varenicline selectively decreased nicotine self-administration. Food restriction and removal of the sucrose lever both increased nicotine self-administration. The finding that rats continue to take nicotine when sucrose is concurrently available-and in many cases take it more frequently than sucrose-demonstrates that nicotine self-administration does not only occur in the absence of alternative reinforcement options. As a model of human nicotine use, concurrent access is more naturalistic and has higher face validity than procedures in which only one reinforcer is available or choosing one reinforce precludes access to other reinforcers. As such, this procedure could be useful for evaluating therapeutic agents and improving our understanding of environmental conditions that promote or discourage nicotine use.

Neurocircuitry of Motivation Section

Using C-Fos To Study Neuronal Ensembles In Corticostriatal Circuitry Of Addiction Cruz FC, Rubio JF, Hope BT. doi: 10.1016/j.brainres.2014.11.005; epub ahead of print.
Learned associations between drugs and environment play an important role in addiction and are thought to be encoded within specific patterns of sparsely distributed neurons called neuronal ensembles. This hypothesis is supported by correlational data from in vivo electrophysiology and cellular imaging studies in relapse models in rodents. In particular, cellular imaging with the immediate early gene c-fos and its protein product Fos has been used to identify sparsely distributed neurons that were strongly activated during conditioned drug behaviors such as drug self-administration and context- and cue-induced reinstatement of drug seeking. Here the authors review how Fos and the c-fos promoter have been employed to demonstrate causal roles for Fos-expressing neuronal ensembles in prefrontal cortex and nucleus accumbens in conditioned drug behaviors. This work has allowed identification of unique molecular and electrophysiological alterations within Fos-expressing neuronal ensembles that may contribute to the development and expression of learned associations in addiction. This article is part of a Special Issue entitled SI:Addiction circuits.

Neuroimaging Research Branch

Greater Externalizing Personality Traits Predict Less Error-Related Insula and Anterior Cingulate Cortex Activity In Acutely Abstinent Smokers Carroll AJ, Sutherland MT, Salmeron BJ, Ross TJ, Stein EA. Addiction Biology 2015; 20: 377-389. [Epub 2013 Dec 13. doi: 10.1111/adb.12118].
Attenuated activity in performance-monitoring brain regions following erroneous actions may contribute to the repetition of maladaptive behaviors such as continued drug use. Externalizing is a broad personality construct characterized by deficient impulse control, vulnerability to addiction and reduced neurobiological indices of error processing. The insula and dorsal anterior cingulate cortex (dACC) are regions critically linked with error processing as well as the perpetuation of cigarette smoking. As such, the authors examined the interrelations between externalizing tendencies, erroneous task performance, and error-related insula and dACC activity in overnight-deprived smokers ($n = 24$) and non-smokers ($n = 20$). Participants completed a self-report measure assessing externalizing tendencies (Externalizing Spectrum Inventory) and a speeded Flanker task during functional magnetic resonance imaging scanning. They observed that higher externalizing tendencies correlated with the occurrence of more performance errors among smokers but not non-smokers. Suggesting a neurobiological contribution to such suboptimal performance among smokers, higher externalizing also predicted less recruitment of the right insula and dACC following error commission. Critically, this error-related activity fully mediated the relationship between externalizing traits and error rates. That is, higher externalizing scores predicted less error-related right insula and dACC activity and, in turn, less error-related activity predicted more errors. Relating such regional activity with a clinically relevant construct, less error-related right insula and dACC responses correlated with higher tobacco craving during abstinence. Given that inadequate error-related neuronal responses may contribute to continued drug use despite negative consequences, these results suggest that externalizing tendencies and/or compromised error processing among subsets of smokers may be relevant factors for smoking cessation success.

Withdrawal From Long-Term Methamphetamine Self-Administration 'Normalizes' Neurometabolites In Rhesus Monkeys: A 1H MR Spectroscopy Study Yang S, Belcher A, Chefer S, Vaupel DB, Schindler C, Stein EA, Yang Y. Addiction Biology 2015; 20: 69-79.
(1)H magnetic resonance spectroscopy has demonstrated alterations in several neurometabolites in methamphetamine (METH)-dependent individuals in brain regions implicated in addiction. Yet, it is unclear whether these neurochemicals return to homeostatic levels after an individual abstains from drug use, a difficult question to address due to high recidivism and poor study retention in human subjects. The authors thus utilized a non-human primate model of addiction to explore the effects of long-term drug exposure and withdrawal on brain neurochemistry. Ten rhesus macaque monkeys on an active METH self-administration protocol (average use 4.6 ± 0.8 years, average daily intake between 0.4 and 1.2 mg/kg) and 10 age- and sex-matched drug-naive controls (CONT) served as subjects. Concentrations of several neurochemicals were evaluated at several timepoints following withdrawal from drug availability (10 monkeys at 1 week and 1 and 3 months, and 6 monkeys at 6 and 12 months; CONT examined at one timepoint). At 1 week following METH withdrawal, the authors found increases in myo-inositol in anterior cingulate cortex in the METH group relative to CONT. These alterations showed a linear pattern of decreased levels ('normalization') by 1 year of abstinence. They also found decreases in glutamine and Glx (composed mainly of glutamate and glutamine) in the caudate-putamen of the same animals at early withdrawal that showed a similar

linear pattern of increasing concentration by 1 year. These results demonstrate that despite protracted, long-term use, neurochemical changes seen following long-term drug administration do not persist following prolonged abstinence, suggesting therapeutic effects of long-term withdrawal from drug use.

Neurobiological Impact Of Nicotinic Acetylcholine Receptor Agonists: An Activation Likelihood Estimation Meta-Analysis Of Pharmacologic Neuroimaging Studies Sutherland MT, Riedel M, Ray K, Stein EA, Laird AR. Biological Psychiatry, 2015 Jan 7. pii: S0006-3223(15)00005-0. doi: 10.1016/j.biopsych.2014.12.021. [Epub ahead of print].
Nicotinic acetylcholine receptor (nAChR) agonists augment cognition among cigarette smokers and nonsmokers, yet the systems-level neurobiological mechanisms underlying such improvements are not fully understood. Aggregating neuroimaging results regarding nAChR agonists provides a means to identify common functional brain changes that may be related to procognitive drug effects. The authors conducted a meta-analysis of pharmacologic neuroimaging studies within the activation likelihood estimation framework. They identified published studies contrasting a nAChR drug condition versus a baseline and coded each contrast by activity change direction (decrease or increase), participant characteristics (smokers or nonsmokers), and drug manipulation employed (pharmacologic administration or cigarette smoking). When considering all studies, nAChR agonist administration was associated with activity decreases in multiple regions, including the ventromedial prefrontal cortex (vmPFC), posterior cingulate cortex (PCC), parahippocampus, insula, and the parietal and precentral cortices. Conversely, activity increases were observed in lateral frontoparietal cortices, the anterior cingulate cortex, thalamus, and cuneus. Exploratory analyses indicated that both smokers and nonsmokers showed activity decreases in the vmPFC and PCC, and increases in lateral frontoparietal regions. Among smokers, both pharmacologic administration and cigarette smoking were associated with activity decreases in the vmPFC, PCC, and insula and increases in the lateral PFC, dorsal anterior cingulate cortex, thalamus, and cuneus. These results provide support for the systems-level perspective that nAChR agonists suppress activity in default-mode network regions and enhance activity in executive control network regions in addition to reducing activation of some task-related regions. The authors speculate these are potential mechanisms by which nAChR agonists enhance cognition.

Basal Hippocampal Activity and Its Functional Connectivity Predicts Cocaine Relapse Adinoff B, Gu H Merrick C, McHugh M, Devous MD, Jeon-Slaughter H, Lu H, Yang, Y, and Stein, EA. Biological Psychiatry, 2015 Jan 30. pii: S0006-3223(15)00045-1. doi: 10.1016/j.biopsych.2014.12.027. [Epub ahead of print].
Cocaine-induced neuroplastic changes may result in a heightened propensity for relapse. Using regional cerebral blood flow (rCBF) as a marker of basal neuronal activity, this study assessed alterations in rCBF and related resting state functional connectivity (rsFC) to prospectively predict relapse in patients following treatment for cocaine use disorder (CUD). Pseudocontinuous arterial spin labeling functional magnetic resonance imaging and resting blood oxygen level-dependent functional magnetic resonance imaging data were acquired in the same scan session in abstinent participants with CUD before residential treatment discharge and in 20 healthy matched control subjects. Substance use was assessed twice weekly following discharge. Relapsed participants were defined as those who used stimulants within 30 days following treatment discharge (n = 22); early remission participants (n = 18) did not. Voxel-wise, whole-brain analysis revealed enhanced rCBF only in the left posterior hippocampus (pHp) in the relapsed group compared with the early

remission and control groups. Using this pHp as a seed, increased rsFC strength with the posterior cingulate cortex (PCC)/precuneus was seen in the relapsed versus early remission subgroups. Together, both increased pHp rCBF and strengthened pHp-PCC rsFC predicted relapse with 75% accuracy at 30, 60, and 90 days following treatment. In CUD participants at risk of early relapse, increased pHp basal activity and pHp-PCC circuit strength may reflect the propensity for heightened reactivity to cocaine cues and persistent cocaine-related ruminations. Mechanisms to mute hyperactivated brain regions and delink dysregulated neural circuits may prove useful to prevent relapse in patients with CUD.

Reward Anticipation Is Differentially Modulated By Varenicline and Nicotine In Smokers
Fedota JR, Sutherland MT, Carroll AJ, Ross TJ, Stein EA. Neuropsychopharmacology, 2015 Mar 6. doi: 10.1038/npp.2015.54. [Epub ahead of print].
Recidivism rates for cigarette smokers following treatment often exceed 80%. Varenicline is the most efficacious pharmacotherapy currently available with cessation rates of 25-35% following a year of treatment. While the in vivo binding properties are well known, varenicline's neurobiological mechanisms of action are still poorly understood. Varenicline acts as a nicotinic receptor partial agonist or antagonist depending on the presence or absence of nicotine and has been implicated in the reduction of reward signaling more broadly. The current study probed anticipatory reward processing using a revised monetary incentive delay task during fMRI in cohorts of smokers and non-smokers who completed a two-drug, placebo-controlled, double-blind crossover study. All participants underwent ~17 days of order balanced varenicline and placebo pill administration and were scanned under each condition wearing a transdermal nicotine or placebo patch. Consistent with nicotine's ability to enhance the rewarding properties of nondrug stimuli, acute nicotine administration enhanced activation in response to reward-predicting monetary cues in both smokers and non-smokers. In contrast, varenicline reduced gain magnitude processing, but did so only in smokers. These results suggest that varenicline's down regulation of anticipatory reward processing in smokers, in addition to its previously demonstrated reduction in the negative affect associated with withdrawal, independently and additively alter distinct brain circuits. These effects likely contribute to varenicline's efficacy as a pharmacotherapy for smoking cessation.

Cellular Neurobiology Research Branch

Behavioral Neurophysiology Research Section

Effects Of Prior Cocaine Versus Morphine Or Heroin Self-Administration On Extinction Learning Driven By Over-Expectation Versus Omission Of Reward Lucantonio F, Kambhampati S, Haney RZ, Atalyaer D, Rowland NE, Shaham Y, Schoenbaum G. Biological Psychiatry 2014. pii: S0006-3223(14)00911-1. doi: 10.1016/j.biopsych.2014.11.017. [Epub ahead of print].
Addiction is characterized by an inability to stop using drugs, despite adverse consequences. One contributing factor to this compulsive drug taking could be the impact of drug use on the ability to extinguish drug seeking after changes in expected outcomes. Here, the authors compared effects of cocaine, morphine, and heroin self-administration on two forms of extinction learning: standard extinction driven by reward omission and extinction driven by reward overexpectation. In experiment 1, the authors trained rats to self-administer cocaine, morphine, or sucrose for 3 hours

per day (limited access). In experiment 2, they trained rats to self-administer heroin or sucrose for 12 hours per day (extended access). Three weeks later, they trained the rats to associate several cues with palatable food reward, after which we assessed extinction of the learned Pavlovian response, first by pairing two cues together in the overexpectation procedure and later by omitting the food reward. Rats trained under limited access conditions to self-administer sucrose or morphine demonstrated normal extinction in response to both overexpectation and reward omission, whereas cocaine-experienced rats or rats trained to self-administer heroin under extended access conditions exhibited normal extinction in response to reward omission but failed to show extinction in response to overexpectation. Here the authors show that cocaine and heroin can induce long-lasting deficits in the ability to extinguish reward seeking. These deficits were not observed in a standard extinction procedure but instead only affected extinction learning driven by a more complex phenomenon of overexpectation.

Synaptic Plasticity Section

Central Role For the Insular Cortex In Mediating Conditioned Responses To Anticipatory Cues Kusumoto-Yoshida I, Liu H, Chen, Fontanini A, Bonci A. Proc Natl Acad Sci U S A. 2015 Jan 27; 112(4): 1190-1195.
Reward-related circuits are fundamental for initiating feeding on the basis of food-predicting cues, whereas gustatory circuits are believed to be involved in the evaluation of food during consumption. However, accumulating evidence challenges such a rigid separation. The insular cortex (IC), an area largely studied in rodents for its role in taste processing, is involved in representing anticipatory cues. Although IC responses to anticipatory cues are well established, the role of IC cue-related activity in mediating feeding behaviors is poorly understood. Here, the authors examined the involvement of the IC in the expression of cue-triggered food approach in mice trained with a Pavlovian conditioning paradigm. They observed a significant change in neuronal firing during presentation of the cue. Pharmacological silencing of the IC inhibited food port approach. Such a behavior could be recapitulated by temporally selective inactivation during the cue. These findings represent the first evidence, to the authors' knowledge, that cue-evoked neuronal activity in the mouse IC modulates behavioral output, and demonstrate a causal link between cue responses and feeding behaviors.

Intrinsic Plasticity: An Emerging Player In Addiction Kourrich S, Calu DJ, Bonci A. Nature Reviews Neuroscience 2015; 16: 173-184.
Exposure to drugs of abuse, such as cocaine, leads to plastic changes in the activity of brain circuits, and a prevailing view is that these changes play a part in drug addiction. Notably, there has been intense focus on drug-induced changes in synaptic excitability and much less attention on intrinsic excitability factors (that is, excitability factors that are remote from the synapse). Accumulating evidence now suggests that intrinsic factors such as K+ channels are not only altered by cocaine but may also contribute to the shaping of the addiction phenotype.

Behavioral Neuroscience Branch

Neurobiology of Relapse Section

Effect Of the Novel Positive Allosteric Modulator Of Mglur2 AZD8529 On Incubation Of Methamphetamine Craving After Prolonged Voluntary Abstinence In A Rat Model Caprioli D, Venniro M, Zeric T, Li, X, Adhikary S, Madangopal R, Marchant NJ, Lucantonio F, Schoenbaum G, Bossert JM, Shaham Y Biological Psychiatry 2015 (http://dx.doi.org/10.1016/j.biopsych.2015.02.018).
Cue-induced methamphetamine craving increases after prolonged forced (experimenter-imposed) abstinence from the drug (incubation of methamphetamine craving). Here, the authors determined whether this incubation phenomenon would occur under conditions that promote voluntary (self-imposed) abstinence. They also determined the effect of the novel mGluR2 positive allosteric modulator, AZD8529, on incubation of methamphetamine craving after forced or voluntary abstinence. The authors trained rats to self-administer palatable food (6 sessions) and then to self-administer methamphetamine under two conditions: 12 sessions (9-hr/day) or 50 sessions (3-hr/day). They then assessed cue-induced methamphetamine seeking in extinctions test after 1 or 21 abstinence days. Between tests, the rats underwent either forced abstinence (no access to the food- or drug-paired levers) or voluntary abstinence for 19 days (achieved via a discrete choice procedure between methamphetamine and palatable food; 20 trials per day). The authors also determined the effect of subcutaneous injections of AZD8529 (20 and 40 mg/kg) on cue-induced methamphetamine seeking 1 or 21 days after forced or voluntary abstinence. Under both training and abstinence conditions, cue-induced methamphetamine seeking in the extinction tests was higher after 21 abstinence days than after 1 day (incubation of methamphetamine craving). AZD8529 decreased cue-induced methamphetamine seeking on day 21 but not day 1 of forced or voluntary abstinence. The authors We introduce a novel animal model to study incubation of drug craving and cue-induced drug seeking after prolonged voluntary abstinence, mimicking the human condition of relapse after successful contingency management treatment. Their data suggest that PAMs of mGluR2 should be considered for relapse prevention.

The Central Amygdala Nucleus Is Critical For Incubation Of Methamphetamine Craving Li X, Zeric T, Kambhampati S, Bossert JM, Shaham Y. Neuropsychopharmacology 2015; 40:1297-1306.
Cue-induced methamphetamine seeking progressively increases after withdrawal but mechanisms underlying this “incubation of methamphetamine craving” are unknown. Here the authors studied the role of central amygdala (CeA), ventral medial prefrontal cortex (vmPFC), and orbitofrontal cortex (OFC), brain regions implicated in incubation of cocaine and heroin craving, in incubation of methamphetamine craving. They also assessed the role of basolateral amygdala (BLA) and dorsal medial prefrontal cortex (dmPFC). The authors trained rats to self-administer methamphetamine (10 days; 9-hr/day, 0.1 mg/kg/infusion) and tested them for cue-induced methamphetamine seeking under extinction conditions during early (2 days) or late (4-5 weeks) withdrawal. They first confirmed that ‘incubation of methamphetamine craving’ occurs under their experimental conditions. Next, they assessed the effect of reversible inactivation of CeA or BLA by GABAA+GABAB receptor agonists (muscimol+baclofen, 0.03+0.3 nmol) on cue-induced methamphetamine seeking during early and late withdrawal. The authors also assessed the effect of muscimol+baclofen reversible inactivation of vmPFC, dmPFC, and OFC on ‘incubated’ cue-

induced methamphetamine seeking during late withdrawal. Lever presses in the cue-induced methamphetamine extinction tests were higher during late withdrawal than during early withdrawal (incubation of methamphetamine craving). Muscimol+baclofen injections into CeA but not BLA decreased cue-induced methamphetamine seeking during late but not early withdrawal. Muscimol+baclofen injections into dmPFC, vmPFC or OFC during late withdrawal had no effect on incubated cue-induced methamphetamine seeking. Together with previous studies, results indicate that the CeA plays a critical role in incubation of both drug and non-drug reward craving, and demonstrate an unexpected dissociation in mechanisms of incubation of methamphetamine versus cocaine craving.

Effects Of Social Interaction and Warm Room Temperature On Brain Hyperthermia Induced By the Designer Drugs Methylone and MDPV Kiyatkin EA, Kim A, Wakabayashi KT, Baumann MH, Shaham Y. Neuropsychopharmacology 2015; 40: 436-445.
3,4-Methylenedioxymethcathinone (methylone) and 3,4-methylenedioxypyrovalerone (MDPV) are new drugs of abuse that have gained worldwide popularity. These drugs are structurally similar to 3,4-methylenedioxymethamphetamine (MDMA) and share many of its physiological and behavioral effects in humans, including the development of hyperthermia during acute intoxication. Here, the authors examined the effects of methylone (1-9 mg/kg, s.c.) or MDPV (0.1-1.0 mg/kg, s.c.) on brain temperature homeostasis in rats maintained in a standard laboratory environment (single-housed in a quiet rest at 22°C) and under conditions that model human drug use (social interaction and 29°C ambient temperature). By simultaneously monitoring temperatures in the nucleus accumbens, temporal muscle and facial skin, the authors assessed the effects of methylone and MDPV on intra-brain heat production and cutaneous vascular tone, two critical factors that control brain temperature responses. Both methylone and MDPV dose-dependently increased brain temperature, but even at high doses that induced robust locomotor activation, hyperthermia was modest in magnitude (up to ~2°C). Both drugs also induced dose-dependent peripheral vasoconstriction, which appears to be a primary mechanism determining the brain hyperthermic responses. In contrast to the powerful potentiation of MDMA-induced hyperthermia by social interaction and warm ambient temperature (Kiyatkin et al. 2014), such potentiation was absent for methylone and minimal for MDPV. Taken together, despite structural similarities to MDMA, exposure to methylone or MDPV under conditions commonly associated with human drug use does not lead to profound elevations in brain temperature and sustained vasoconstriction, two critical factors associated with MDMA toxicity.

Molecular Neurobiology Research (becoming section)

Polygenic Score × Intervention Moderation: An Application Of Discrete-Time Survival Analysis To Modeling the Timing Of First Tobacco Use Among Urban Youth Musci RJ, Masyn KE, Uhl G, Maher B, Kellam SG, Ialongo NS. Dev Psychopathol. 2015 Feb; 27(1): 111-122. doi: 10.1017/S0954579414001333. PMID:25640834.
The present study examines the interaction between a polygenic score and an elementary school-based universal preventive intervention trial. The polygenic score reflects the contribution of multiple genes and has been shown in prior research to be predictive of smoking cessation and tobacco use (Uhl et al., 2014). Using data from a longitudinal preventive intervention study, the authors examined age of first tobacco use from sixth grade to age 18. Genetic data were collected

during emerging adulthood and were genotyped using the Affymetrix 6.0 microarray. The polygenic score was computed using these data. Discrete-time survival analysis was employed to test for intervention main and interaction effects with the polygenic score. The authors found a main effect of the intervention, with the intervention participants reporting their first cigarette smoked at an age significantly later than controls. They also found an Intervention × Polygenic Score interaction, with participants at the higher end of the polygenic score benefitting the most from the intervention in terms of delayed age of first use. These results are consistent with Belsky and colleagues' (e.g., Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Belsky & Pleuss, 2009, 2013; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011) differential susceptibility hypothesis and the concept of "for better or worse," wherein the expression of genetic variants are optimally realized in the context of an enriched environment, such as provided by a preventive intervention.

Functional Consequences Of 17q21.31/WNT3-WNT9B Amplification In hPSCs With Respect To Neural Differentiation Lee CT, Bendriem RM, Kindberg AA, Worden LT, Williams MP, Drgon T, Mallon BS, Harvey BK, Richie CT, Hamilton RS, Chen J, Errico SL, Tsai SY, Uhl GR, Freed WJ. Cell Rep. 2015 Jan 27. pii: S2211-1247(14)01103-6. doi: 10.1016/j.celrep.2014.12.050. PMID: 25640183.
Human pluripotent stem cell (hPSC) lines exhibit repeated patterns of genetic variation, which can alter in vitro properties as well as suitability for clinical use. The authors examined associations between copy-number variations (CNVs) on chromosome 17 and hPSC mesodiencephalic dopaminergic (mDA) differentiation. Among 24 hPSC lines, two karyotypically normal lines, BG03 and CT3, and BG01V2, with trisomy 17, exhibited amplification of the WNT3/WNT9B region and rapid mDA differentiation. In hPSC lines with amplified WNT3/WNT9B, basic fibroblast growth factor (bFGF) signaling through mitogen-activated protein kinase (MAPK)/ERK amplifies canonical WNT signaling by phosphorylating LRP6, resulting in enhanced undifferentiated proliferation. When bFGF is absent, noncanonical WNT signaling becomes dominant due to upregulation of SIAH2, enhancing JNK signaling and promoting loss of pluripotency. When bFGF is present during mDA differentiation, stabilization of canonical WNT signaling causes upregulation of LMX1A and mDA induction. Therefore, CNVs in 17q21.31, a "hot spot" for genetic variation, have multiple and complex effects on hPSC cellular phenotype.

Serotonin/Dopamine Interactions In A Hyperactive Mouse: Reduced Serotonin Receptor 1B Activity Reverses Effects Of Dopamine Transporter Knockout Hall FS, Sora I, Hen R, Uhl GR. PLoS One. 2014 Dec 16;9(12): e115009. doi: 10.1371/journal.pone.0115009. eCollection 2014.PMID:25514162.
Knockout (KO) mice that lack the dopamine transporter (SL6A3; DAT) display increased locomotion that can be attenuated, under some circumstances, by administration of drugs that normally produce psychostimulant-like effects, such as amphetamine and methylphenidate. These results have led to suggestions that DAT KO mice may model features of attention deficit hyperactivity disorder (ADHD) and that these drugs may act upon serotonin (5-HT) systems to produce these unusual locomotor decreasing effects. Evidence from patterns of brain expression and initial pharmacologic studies led us to use genetic and pharmacologic approaches to examine the influence of altered 5-HT1B receptor activity on hyperactivity in DAT KO mice. Heterozygous 5-HT1B KO and pharmacologic 5-HT1B antagonism both attenuated locomotor hyperactivity in DAT KO mice. Furthermore, DAT KO mice with reduced, but not eliminated, 5-HT1B receptor

expression regained cocaine-stimulated locomotion, which was absent in DAT KO mice with normal levels of 5-HT1B receptor expression. Further experiments demonstrated that the degree of habituation to the testing apparatus determined whether cocaine had no effect on locomotion in DAT KO or reduced locomotion, helping to resolve differences among prior reports. These findings of complementation of the locomotor effects of DAT KO by reducing 5-HT1B receptor activity underscore roles for interactions between specific 5-HT receptors and dopamine (DA) systems in basal and cocaine-stimulated locomotion and support evaluation of 5-HT1B antagonists as potential, non-stimulant ADHD therapeutics.

Specific Regions Display Altered Gray Matter Volume In M-Opioid Receptor Knockout (MOP-KO) Mice: MRI Voxel - Based Morphometry Sasaki K, Sumiyoshi A, Nonaka H, Kasahara Y, Ikeda K, Hall FS, Uhl GR, Watanabe M, Kawashima R, Sora I. Br J Pharmacol. 2015 Jan; 172(2): 654-667. PMID: 24913308.
μ-opiate receptor knockout mice display several behavioral differences from wild-type (WT) littermates including differential responses to nociceptive stimuli. Brain structural changes have been tied to behavioral alternations noted in transgenic mice with targeting of different genes. The authors thus assessed the brain structure of MOP-KO mice using MRI-voxel based morphometry (VBM) and histological methods. The knockout mice display robust increases in regional gray matter volume in olfactory bulb, several hypothalamic nuclei, periaqueductal gray (PAG), and several cerebellar areas; most confirmed by VBM analysis. The largest increases in gray matter volume were detected in the glomerular layer of the olfactory bulb, arcuate nucleus of hypothalamus, ventrolateral PAG (VLPAG) and cerebellar regions that include paramedian and cerebellar lobules. Histological analyses confirmed several of these results, with increased VLPAG cell numbers and increased thickness of the olfactory bulb granule cell layer and cerebellar molecular and granular cell layers. Deleting expression of the mu receptor gene thus causes previously undescribed structural changes in specific brain regions, but not in all regions with high receptor densities (e.g. thalamus, nucleus accumbens) or that exhibit adult neurogenesis (e.g. hippocampus). Volume differences in hypothalamus and PAG may relate to behavioral alternations that include the hyperalgesia. Although the precise relationship between volume change and receptor deletion could not be determined based on this study alone, these findings suggest that levels of mu receptor expression may influence a broader range of neural structure and function in humans than previously suspected.

Attenuated Methamphetamine-Induced Locomotor Sensitization In Serotonin Transporter Knockout Mice Is Restored By Serotonin 1B Receptor Antagonist Treatment Igari M, Shen HW, Hagino Y, Fukushima S, Kasahara Y, Lesch KP, Murphy DL, Hall FS, Uhl GR, Ikeda K, Yaegashi N, Sora I. Behav Pharmacol. 2015 Feb;26(1-2):167-79. doi: 10.1097/ FBP.0000000000000120. PMID:25485646.
Repeated administration of methamphetamine (METH) enhances acute locomotor responses to METH administered in the same context, a phenomenon termed as 'locomotor sensitization'. Although many of the acute effects of METH are mediated by its influences on the compartmentalization of dopamine, serotonin systems have also been suggested to influence the behavioral effects of METH in ways that are not fully understood. The present experiments examined serotonergic roles in METH-induced locomotor sensitization by assessing: (a) the effect of serotonin transporter (SERT; Slc6A4) knockout (KO) on METH-induced locomotor sensitization; (b) extracellular monoamine levels in METH-treated animals as determined by in-

vivo microdialysis; and (c) effects of serotonin (5-HT) receptor antagonists on METH-induced behavioral sensitization, with focus on effects of the 5-HT1B receptor antagonist SB 216641 and a comparison with the 5-HT2 receptor antagonist ketanserin. Repeated METH administration failed to induce behavioral sensitization in homozygous SERT KO (SERT-/-) mice under conditions that produced substantial sensitization in wild-type or heterozygous SERT KO (SERT+/-) mice. The selective 5-HT1B antagonist receptor SB 216641 restored METH-induced locomotor sensitization in SERT-/- mice, whereas ketanserin was ineffective. METH-induced increases in extracellular 5-HT (5-HTex) levels were substantially reduced in SERT-/- mice, although SERT genotype had no effect on METH-induced increases in extracellular dopamine. These experiments demonstrate that 5-HT actions, including those at 5-HT1B receptors, contribute to METH-induced locomotor sensitization. Modulation of 5-HT1B receptors might aid therapeutic approaches to the sequelae of chronic METH use.

Sex Differences In the Effects Of Adolescent Social Deprivation On Alcohol Consumption In M-Opioid Receptor Knockout Mice Moriya Y, Kasahara Y, Hall FS, Sakakibara Y, Uhl GR, Tomita H, Sora I. Psychopharmacology (Berl). 2014 Nov 4. PMID: 25363463.
Evidence based on clinical and experimental animal studies indicates that adolescent social deprivation influences alcohol consumption in a sex-dependent manner, perhaps by influencing stress responses. However, the mechanisms underlying the interaction between these phenomena remain to be elucidated. Since the μ-opioid receptor (MOP) has been reported to have key roles in social stress responses as well as the reinforcing/addictive effects of ethanol, MOP is a candidate molecule that may link adolescent social deprivation and subsequent alterations in alcohol consumption. To evaluate the involvement of MOP and social isolation-induced changes in alcohol consumption, as well as the effect of sex differences on responses to social isolation, alcohol consumption was assessed using a two-bottle home-cage consumption procedure (8 % ethanol vs. water) in MOP knockout (MOP-KO) and wild type (WT) mice of both sexes exposed to adolescent social deprivation or reared socially. Isolation rearing had no effects upon alcohol consumption of WT mice, whereas it significantly altered alcohol consumption in both male and female MOP-KO mice. Interestingly, social isolation affected ethanol consumption differently in male and female mice. Ethanol consumption was increased in male MOP-KO mice, but decreased in female MOP-KO mice, by isolation rearing. These results indicate that disturbances of MOP function influence the effects of isolation rearing on ethanol consumption in a sex-dependent manner. Consequently, this suggests the possibility that genetic variation that influences MOP function may have differential roles in alcoholism in men and women, and alcoholism treatments that target MOP function may be differentially effective in males and females.

Developmental Alterations In Anxiety and Cognitive Behavior In Serotonin Transporter Mutant Mice Sakakibara Y, Kasahara Y, Hall FS, Lesch KP, Murphy DL, Uhl GR, Sora I. Psychopharmacology (Berl). 2014 Oct; 231(21): 4119-4133 PMID: 24728652
Heterozygous (SERT+/-) and homozygous (SERT-/-) SERT mutant mice are valuable tools for understanding the mechanisms of altered SERT levels. Although these genetic effects are well investigated in adulthood, the developmental trajectory of altered SERT levels for behavior has not been investigated. The authors assessed anxiety-like and cognitive behaviors in SERT mutant mice in early adolescence and adulthood to examine the developmental consequences of reduced SERT levels. Spine density of pyramidal neurons was also measured in corticolimbic brain regions. Adult SERT-/- mice exhibited increased anxiety-like behavior, but these differences were not observed in

early adolescent SERT-/- mice. Conversely, SERT+/- and SERT-/- mice did display higher spontaneous alternation during early adolescence and adulthood. SERT+/- and SERT-/- also exhibited greater neuronal spine densities in the orbitofrontal but not the medial prefrontal cortices. Adult SERT-/- mice also showed an increased spine density in the basolateral amygdala. Developmental alterations of the serotonergic system caused by genetic inactivation of SERT can have different influences on anxiety-like and cognitive behaviors through early adolescence into adulthood, which may be associated with changes of spine density in the prefrontal cortex and amygdala. The altered maturation of serotonergic systems may lead to specific age-related vulnerabilities to psychopathologies that develop during adolescence.

Reducing Aggression and Impulsivity Through School-Based Prevention Programs: A Gene By Intervention Interaction Musci RJ, Bradshaw CP, Maher B, Uhl GR, Kellam SG, Ialongo NS. Prev Sci. 2014; 15(6): 831-840. PMID:24178584.
A variety of school-based, universal preventive interventions have been developed to address behavioral and mental health problems. Unfortunately, few have been evaluated within the context of randomized controlled trials with long-term follow-up. Even fewer still have examined the potential genetic factors that may drive differential impact of the intervention. In the present analysis, the authors examine the extent to which the longitudinal effects of two elementary school-based interventions were moderated by the brain-derived neurotrophic factor (BDNF) gene, which has been linked with aggression and impulsive behaviors. The sample included 678 urban, primarily African American children who were randomly assigned along with their teachers to one of three first grade classroom conditions: classroom-centered (CC) intervention, Family School Partnership (FSP), or a control condition. The teacher ratings of the youth's aggressive and impulsive behavior were obtained at baseline and in grades 6-12. Single-nucleotide polymorphisms (SNPs) from the BDNF gene were extracted from the genome-wide data. Longitudinal latent trait-state-error models indicated a significant interaction between a particular profile of the BDNF SNP cluster (46 % of sample) and CC intervention on impulsivity ($\beta = -.27$, $p < .05$). A similar interaction was observed for the BDNF SNP cluster and the CC intervention on aggression ($\beta = -.14$, $p < .05$). The results suggest that the impacts of preventive interventions in early elementary school on late adolescent outcomes of impulsivity and aggression can be potentially modified by genetic factors, such as BDNF.

Optical Imaging Core, Office of the Scientific Director

Imaging the Insertion Of Superecliptic Phluorin-Labeled Dopamine D2 Receptor Using Total Internal Reflection Fluorescence Microscopy Daly KM, Li Y, Lin DT. Curr Protoc Neurosci. 2015 Jan 5; 70: 5.31.1-5.31.20. doi: 10.1002/0471142301.ns0531s70.
A better understanding of mechanisms governing receptor insertion to the plasma membrane (PM) requires an experimental approach with excellent spatial and temporal resolutions. Here the authors present a strategy that enables dynamic visualization of insertion events for dopamine D2 receptors into the PM. This approach includes tagging a pH-sensitive GFP, superecliptic pHluorin, to the extracellular domain of the receptor. By imaging pHluorin-tagged receptors under total internal reflection fluorescence microscopy (TIRFM), we were able to directly visualize individual receptor insertion events into the PM in cultured neurons. This novel imaging approach can be applied to both secreted proteins and many membrane proteins with an extracellular domain labeled with

superecliptic pHluorin, and will ultimately allow for detailed dissections of the key mechanisms governing secretion of soluble proteins or the insertion of different membrane proteins to the PM.

The Topographical Arrangement Of Cutoff Spatial Frequencies Across Lower and Upper Visual Fields In Mouse V1 Zhang X, An X, Liu H, Peng J, Cai S, Wang W, Lin DT, Yang Y. Sci Rep. 2015 Jan 13; 5: 7734. doi: 10.1038/srep07734.
The visual response to spatial frequency (SF), a characteristic of spatial structure across position in space, is of particular importance for animal survival. A natural challenge for rodents is to detect predators as early as possible while foraging. Whether neurons in mouse primary visual cortex (V1) are functionally organized to meet this challenge remains unclear. Combining intrinsic signal optical imaging and single-unit recording, the authors found that the cutoff SF was much greater for neurons whose receptive fields were located above the mouse. Specifically, they discovered that the cutoff SF increased in a gradient that was positively correlated with the elevation in the visual field. This organization was present at eye opening and persisted through adulthood. Dark rearing delayed the maturation of the cutoff SF globally, but had little impact on the topographical organization of the cutoff SF, suggesting that this regional distribution is innately determined. This form of cortical organization of different SFs may benefit the mouse for detection of airborne threats in the natural environment.

Association Of Novelty-Related Behaviors and Intravenous Cocaine Self-Administration In Diversity Outbred Mice Dickson PE, Ndukum J, Wilcox T, Clark J, Roy B, Zhang L, Li Y, Lin DT, Chesler EJ. Psychopharmacology (Berl). 2015 Mar; 232(6): 1011-1024. doi: 10.1007/s00213-014-3737-5.
The preference for and reaction to novelty are strongly associated with addiction to cocaine and other drugs. However, the genetic variants and molecular mechanisms underlying these phenomena remain largely unknown. Although the relationship between novelty- and addiction-related traits has been observed in rats, studies in mice have failed to demonstrate this association. New, genetically diverse, high-precision mouse populations including Diversity Outbred (DO) mice provide an opportunity to assess an expanded range of behavioral variation enabling detection of associations of novelty- and addiction-related traits in mice. To examine the relationship between novelty- and addiction-related traits, male (n = 51) and female (n = 47) DO mice were tested on open field exploration, hole board exploration, and novelty preference followed by intravenous cocaine self-administration (IVSA; ten 2-h sessions of fixed ratio 1 and one 6-h session of progressive ratio). The authors observed high variation of cocaine IVSA in DO mice with 43 % reaching and 57 % not reaching conventional acquisition criteria. As a group, mice that did not reach these criteria still demonstrated significant lever discrimination. Mice experiencing catheter occlusion or other technical issues (n = 17) were excluded from the analysis. Novelty-related behaviors were positively associated with cocaine IVSA. Multivariate analysis of associations among novelty- and addiction-related traits revealed a large degree of shared variance (45 %). Covariation among cocaine IVSA and novelty-related phenotypes in DO mice indicates that this relationship is amenable to genetic dissection. The high genetic precision and phenotypic diversity in the DO may facilitate discovery of previously undetectable mechanisms underlying predisposition to develop addiction disorders.

Visualization Of NMDA Receptor-Dependent AMPA Receptor Synaptic Plasticity In Vivo
Zhang Y, Cudmore RH, Lin DT, Linden DJ, Huganir RL. Nat Neurosci. 2015 Mar; 18(3): 402-407. doi: 10.1038/nn.3936.
Regulation of AMPA receptor (AMPAR) membrane trafficking is critical for synaptic plasticity, as well as for learning and memory. However, the mechanisms of AMPAR trafficking in vivo remain elusive. Using in vivo two-photon microscopy in the mouse somatosensory barrel cortex, the authors found that acute whisker stimulation led to a significant increase in the intensity of surface AMPAR GluA1 subunit (sGluA1) in both spines and dendritic shafts and a small increase in spine size relative to prestimulation values. Interestingly, the initial spine properties biased spine changes following whisker stimulation. Changes in spine sGluA1 intensity were positively correlated with changes in spine size and dendritic shaft sGluA1 intensity following whisker stimulation. The increase in spine sGluA1 intensity evoked by whisker stimulation was NMDA receptor dependent and long lasting, similar to major forms of synaptic plasticity in the brain. In this study we were able to observe experience-dependent AMPAR trafficking in real time and characterize, in vivo, a major form of synaptic plasticity in the brain.

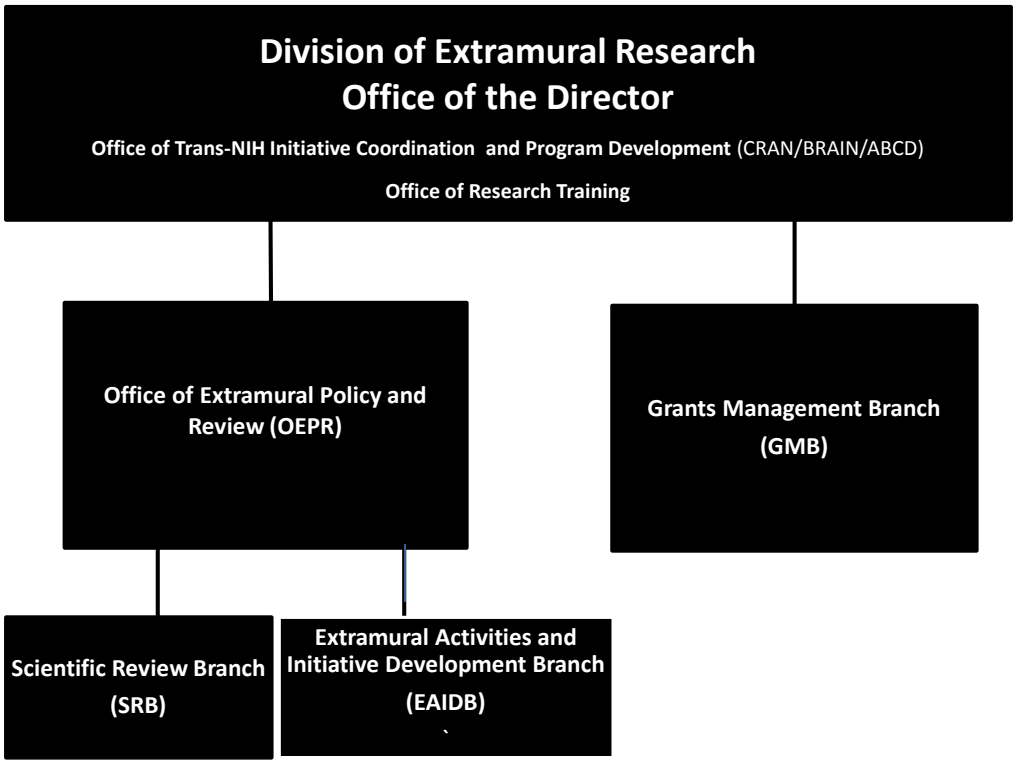
A Miniature, Fiber-Coupled, Wireless, Deep-Brain Optogenetic Stimulator Lee ST, Williams PA, Braine CE, Lin DT, John SWM, Irazoqui PP. Neural Systems and Rehabilitation Engineering, IEEE Transactions vol.PP, no.99, pp.1,1doi: 10.1109/TNSRE.2015.2391282.
Controlled, wireless neuromodulation using miniature implantable devices is a long-sought goal in neuroscience. It will allow many studies and treatments that are otherwise impractical. Recent studies demonstrate advances in neuromodulation through optogenetics, but test animals are typically tethered severely limiting experimental possibilities. Existing non-tethered optical stimulators either deliver light through a cranial window limiting applications to superficial layers of the brain, are not widely accessible due to highly specialized fabrication techniques, or do not demonstrate robust and flexible control of the optical power emitted. To overcome these limitations, the authors have developed a novel, miniature, wireless, deep-brain, modular optical stimulator with controllable stimulation parameters for use in optogenetic experiments. They demonstrate its use in a behavioral experiment targeting a deep brain structure in freely behaving mice. To allow its rapid and widespread adoption, the authors developed this stimulator using commercially available components. The modular and accessible optogenetic stimulator presented advances the wireless toolset available for freely behaving animal experiments.

EXTRAMURAL RESEARCH AND TRAINING PROGRAMS AND REVIEW ACTIVITIES

DIVISION OF EXTRAMURAL RESEARCH (DER)

In February 2015, NIDA established a new Division with responsibility for overseeing its extramural research and training programs and policies. Functions include:

- Develop, implement, and coordinate NIDA's extramural programs, policies, reviews, and operations planning
- Provide leadership and advice on scientific priorities and strategic goals for NIDA's extramural research programs
- Conduct or coordinate with the Center for Scientific Research (CSR) peer review of all NIDA grant applications
- Oversee NIDA's research training and early career development program
- Lead NIDA's involvement in vital trans-NIH initiatives, including Collaborative Research on Addiction at NIH (CRAN), the Adolescent Brain Cognitive Development (ABCD) longitudinal study, and Brain Research through Advancing Innovative Neurotechnologies (BRAIN).
- Coordinate and lead activities of the National Advisory Council on Drug Abuse
- Perform grants management operations, and provide information and guidance for applicants.



DER Office of Research Training

The National Institute on Drug Abuse (NIDA) will sponsor a **Grant-Writing and Career Development Workshop at the College on Problems of Drug Dependence (CPDD) Annual Scientific Meeting** in Phoenix, Arizona on June 17, 2015. The workshop, which is coordinated by the Office of Research Training, Division of Extramural Research, will provide both new and junior investigators with information and tools to advance their research careers. NIDA program staff and research investigators will present on topics heavily centered on NIDA funding opportunities, grantsmanship and the grant application process.

NIDA will be awarding **20 Director's Travel Awards to NIDA-supported Diversity Supplement recipients, NRSA trainees, and NRSA fellows to attend the 2015 CPDD Meeting**, which will be held in Phoenix, Arizona, June 13-18, 2015. The application deadline for these awards was February 5, 2015. Travel awardees are required to attend the Grant-Writing and Career Development Workshop.

NIDA and CPDD will hold a **Predoc/Postdoc Award Lecture** on the evening of June 15, 2015. This meeting will afford junior investigators an opportunity to meet with established investigators to discuss potential collaborations and learn about available training opportunities at NIDA-funded institutions. NIDA program staff will also participate to facilitate the interactions between established and junior investigators, and to discuss scientific interest areas with their future grantees.

DER Office of Policy and Review

Receipt, Referral, and Review

- Total # of grant applications: 1301
- DA primary: 983
- Institute-based reviews: 18 Grant SEPS (243 applications) and 9 Contract SEPS (21 proposals and 2 projects TBD)

Grant Reviews

1. ZDA1 GXM A 01 R; RFA DA15-006 (DP2): Avenir Award Program for Genetics or Epigenetics of Substance Abuse (DP2)
2. ZDA1 SXM M 02 S; Random: PA13-302: Multi-site clinical trials
3. ZDA1 NXR B 03 S; PAR-14-186 (P30): NIDA Core Center of Excellence Grant Program (P30)
4. ZDA1 NXR B 04 S; PAR-13-222 (P50): NIDA Research "Center of Excellence" Grant Program (P50)
5. ZDA1 HXO H 05 S; PA-14-042 (Parent K99/R00): NIH Pathway to Independence Award (K99/R00)
6. ZDA1 MXL F 06 S; PAR-12-066 (R03): NIDA I/START Small Grant Review
7. ZDA1 JXR G 07 S; PAR-14-010 (UH2/UH3): Identification of Gene Variants for Addiction Related Traits by Next-Gen Sequencing in Model Organisms Selectively Bred for Addiction Traits (UH2/UH3)

8. ZDA1 SXM M 08 R; RFA-DA-15-010 (U01): Interventions for Youth who Misuse/Abuse Prescription Stimulant Medications in High School and/or College-Attending Youth (U01)
9. ZDA1 HX0 H 09 R; RFA DA15-007 (DP2): Avenir Award Program for Research on Substance Abuse and HIV/AIDS (DP2)
10. ZDA1 JXR G 10 S; PAR-12-086 (R21): Cutting-Edge Basic Research Awards (CEBRA) (R21)
11. ZDA1 JXR D 11 R; RFA-DA-15-008 (UG1): The National Drug Abuse Treatment Clinical Trials Network (UG1)
12. ZDA1 SXM M 12 S; PAR-12-222 (U01): Cohort Studies of HIV/AIDS and Substance Use (U01)
13. ZDA1 JXR G 13 R; RFA-DA-15-011 & -012: Extracellular Vesicles in HIV/AIDS and Substance Abuse (R01, R21)
14. ZDA1 MXL F 14 S; PA13-347 (R13): R13 Conference Grant Review (PA13-347)
15. ZDA1 JXR G 15 S; PAR 14-230 & 231: Exploratory Studies of Smoking Cessation Interventions for People with Schizophrenia (R21/R33)
16. ZDA1 GXM A 16 R; RFA DA15-006 (DP2): Phase I: Avenir Award Program for Genetics or Epigenetics of Substance Abuse (DP2)
17. ZDA1 HX0 H 17 R; RFA DA15-007 (DP2): Phase I: Avenir Award Program for Research on Substance Abuse and HIV/AIDS (DP2)
18. ZDA1 SXM M 18 S; Random: PA13-302: SEP II: Multi-site clinical trials

Contract Reviews

01. ZDA1 LXF L 31 S; N43DA-15-2242: Mobile Technologies Extending Reach of Primary Care for Substance-Use-Disorders (2242)
02. ZDA1 LXF L 32 S; N44DA-15-5578: Prescription Drug Abuse Policy System (PDAPS) (5578)
03. ZDA1 LXF L 33 S; N44DA-15-5577: High-Impact Substance Abuse Prevention (5577)
04. ZDA1 LXF L 34 S; N44DA-15-5581: Tech Tools to Facilitate Implementation (5581)
05. ZDA1 LXF L 35 S; N01DA-15-2243: Clinical Coordination Center (2243)
06. ZDA1 LXF L 36 S; N01DA-15-1154 (recomp of 9-1140): Educational Outreach to Middle and High School Students (1154)
07. ZDA1 LXF L 76 S; N43-16-1210: Concept Review: Development of Primer and Reference Tool to Assess Neonatal Abstinence Syndrome (1210)
08. ZDA1 LXF L 77 S; N43-16-4434: Concept Review: Pain Mobile Remote Pain Management System (4434)
09. ZDA1 LXF L 78 S; N43DA-15-2244: Concept Review: NIDA Blending Initiative; Moving Science from Research to Practice (2244)

Certificates of Confidentiality

Between December 20th, 2014 and March 31st, 2015, 62 applications for new and amended Certificates of Confidentiality were received. During the last Council round, (August 6th, 2014 and December 19th, 2014), 101 applications for new and amended applications were received and processed. These numbers are frequency counts only and do not provide any insight into the complexity of the applications.

Other Review Activities

The CTN Data and Safety Monitoring Board met February 6, 2015 to discuss CTN 0060, Computer-facilitated intervention for Adolescent Marijuana use Prevention (CAMP).

CONGRESSIONAL AFFAIRS SECTION
(Prepared April 24, 2015)

APPROPRIATIONS

The President's FY 2016 Budget proposes $31.311 billion at the program level for NIH, 3.3% above the enacted FY 2015 program level. For NIDA, the corresponding figures are $1.047 billion and 3.1%.

CONGRESSIONAL HEARINGS/BRIEFINGS

January 21, 2015 – NIDA staff attended a briefing sponsored the RAND Corporation: Insights About Marijuana Legalization in the United States.

January 21, 2015 – NIDA staff attended a briefing sponsored by the Friends of National Institute of Child Health and Human Development: Opioid Use: Protecting the Most Vulnerable -- Addressing Drug Exposure in Mothers and Newborns.

March 3, 2015 – NIH testified in support of its FY 2016 budget request. This was the annual hearing in front of the House Appropriations Committee, Subcommittee on Labor, Health and Human Services, and Education. This year, NIDA Director Dr. Nora Volkow was among the NIH Institute Directors invited by Dr. Collins to attend with him. Several drug abuse and addiction-related questions were asked by subcommittee members (as well as the Chairman of the full committee, Congressman Hal Rogers (R-KY).

March 17, 2015 – NIDA's Dr. Susan Weiss and Dr. Maureen Boyle met via conference call with staff from Senator Brian Schatz' (D-HI) office. They reviewed a range of marijuana research topics.

March 18, 2015 – NIDA Director Dr. Nora Volkow met with and briefed staff from the House Energy and Commerce Committee, Subcommittee on Oversight and Investigations. Topic: Opioid abuse and addiction. This subcommittee is holding a series of hearings on the topic.

March 24, 2015 – NIDA's Dr. Susan Weiss, along with representatives from the FDA, Drug Enforcement Administration and the Department of Justice, met with staff from Senator Kirsten Gillibrand (D-NY). The topic was marijuana use and addiction, and the potential therapeutic uses of marijuana.

March 26, 2015 -- The House Energy and Commerce Committee, Subcommittee on Oversight and Investigations, held its first hearing focused on opioids. Transcript, statements and video available at http://energycommerce.house.gov/press-release/suboversight-continues-its-review-growing-threat-prescription-drug-and-heroin-abuse.

April 3, 2015 – At their request, the Clerks of the Senate Appropriations Committee, Subcommittee on Labor, Health and Human Services, and Education, visited NIH to meet with several IC directors. NIDA's Dr. Nora Volkow was one of the Directors who had the opportunity to brief these staff on important work ongoing at the Institute.

April 6-9, 2015 – Fourth Annual Rx Summit – At the request of Appropriations Committee Chairman Hal Rogers (R-KY), NIDA Director Dr. Nora Volkow and NIH Director Dr. Francis Collins provided plenary remarks at this year's Summit. Over 1400 attendees gathered this year to focus on the opioid abuse, addiction and overdose crisis in the U.S. Also addressing the Summit this year were ONDCP Director Michael Botticelli, HHS Secretary Sylvia Burwell, CDC Director Dr. Tom Frieden, FDA Acting Commissioner Dr. Stephen Ostroff, and former Congressman Patrick Kennedy. Seven members of congressman also attended and spoke as part of a congressional action panel.

April 9, 2015 – Co-located with the Rx Summit, the second annual summit of Smart Approaches to Marijuana featured remarks from NIDA Director Dr. Nora Volkow. Dr. Volkow gave a talk focused on the health effects of marijuana use.

April 23, 2015 -- The House Energy and Commerce Committee, Subcommittee on Oversight and Investigations, held its second hearing focused on opioids. Transcript, statements and video available at http://energycommerce.house.gov/press-release/suboversight-continues-work-combat-prescription-drug-and-opioid-abuse.

April 29, 2015 – Senators Rob Portman (R-OH) and Sheldon Whitehouse (D-RI) took the lead in creating and sponsoring the fourth congressional addiction forum. This forum focused on prevention and treatment issues in youth. NIDA's Dr. Redonna Chandler provided summary remarks on what we know from scientific research on these topics.

LEGISLATION OF INTEREST

H.R. 203 – On January 12, 2015, the House passed the Clay Hunt SAV Act, to direct the Secretary of Veterans Affairs to provide for the conduct of annual evaluations of mental health care and suicide prevention programs of Department of Veterans Affairs, to require a pilot program on loan repayment for psychiatrists who agree to serve in the Veterans Health Administration, and for other purposes. The bill was passed by the Senate on 2/3, and signed into law by the President on 2/12.

H.R. 262 – On January 9, 2015, Representative Barbara Lee (D-CA) introduced the States' Medical Marijuana Property Rights Protection Act, to amend the Controlled Substances Act so as to exempt real property from civil forfeiture due to medical marijuana-related conduct that is authorized by State law. The bill was referred to the Committees on Judiciary and Energy and Commerce.

H.R. 292 -- On January 13, 2015, Representative Michael Burgess (R-TX) introduced the Advancing Research for Neurological Diseases Act of 2015, to amend the Public Health Service Act to provide for systematic data collection and analysis and epidemiological research regarding

Multiple Sclerosis (MS), Parkinson's disease, and other neurological diseases. The bill was referred to the Committee on Energy and Commerce.

H.R. 467 – On January 22, 2015, Representative Eddie Bernice Johnson (D-TX) introduced the STEM Opportunities Act. Among the provisions, the bill would (1) require the Office of Science and Technology Policy (OSTP) to provide federal science agencies with guidance on establishing specified policies to accommodate the needs of researchers who are caregivers; (2) require each federal science agency to annually collect and submit to the National Science Foundation (NSF) institution-level data on a number of items including demographics, primary field, award type, and review rating (as practicable); (3) direct OSTP, in collaboration with NSF, to identify and disseminate to federal science agencies information and best practices useful in educating program officers and members of standing peer review committees at federal science agencies about research on implicit gender, race, or ethnic bias; and methods to minimize the effect of such bias in federal research grant reviews; and (4) require federal science agencies to maintain or develop and implement policies and practices to minimize the effects of implicit bias in federal research grant reviews. The bill was referred to the House Committee on Science, Space, and Technology.

H.R. 525 -- On January 26, 2015, Representative Massie Thomas (R-KY) introduced the Industrial Hemp Farming Act of 2015, to amend the Controlled Substances Act to exclude industrial hemp from the definition of marijuana, and for other purposes. The bill was referred to the Judiciary Committee and Energy and Commerce Committee. See S.134.

H.R. 667 – On February 3, 2015, Representative Earl Blumenaur (D-OR) introduced the Veterans Equal Access act, to authorize the Department of Veterans Affairs health care providers to provide recommendations and opinions to veterans regarding participation in state medical marijuana programs. The bill was referred to the Committee on Energy and Commerce.

H.R. 953 -- On February 12, 2015, Representative James Sensenbrenner (R-WI) introduced the Comprehensive Addiction Recovery Act, to authorize the Attorney General to award grants to address the national epidemics of prescription drug and heroin abuse. The bill was referred to the committees on the Judiciary and Energy and Commerce. See S. 524.

H.R. 1013 – On February 20, 2015, Representative Jared Polis (D-CO) introduced the Regulate Marijuana like Alcohol Act, to decriminalize marijuana at the federal level, to leave to the states the power to regulate marijuana in a similar way to the way they regulate alcohol, and for other purposes. The bill was referred to several committees: Judiciary, Ways and Means, Energy and Commerce, Natural Resources.

H.R. 1014 – On February 20, 2015, Represenative Earl Blumenaur introduced the Marijuana Tax Revenue act of 2015, to amend the IRS code of 1986 to provide for the taxation of marijuana. The bill was referred to the Committee on Ways and Means.

H.R. 1462 – On March 19, 2015, Representative Katherine Clark (D-MA) introduced the Protecting Our Infants Act, to combat the rise of prenatal opioid abuse and neonatal abstinence syndrome. The bill was referred to the Committee on Energy and Commerce. See S.799.

H.R. 1538 – On March 23, 2015, Representative Steve Cohen (D-TN) introduced the CARERS Act, to extend the principle of federalism to State drug policy, provide access to medical marijuana, and enable research into the medicinal properties of marijuana. The bill was referred to the committees on Energy and Commerce, Judiciary, Veterans, and Financial Services. See S.683.

H.R. 1635 – On March 25, 2015, Representative Scott Perry (R-PA) introduced the Charlotte's Web Medical Access Act of 2015, to amend the controlled substances act to exclude cannabidiol-rich plants from the definition of marijuana. The bill was referred to the committees on Energy and Commerce and Judiciary.

H.R. 1774 – On April 14, 2015, Representative Morgan Griffith (R-VA) introduced the Compassionate Access Act, to provide for the rescheduling of marijuana, the medical use of marijuana in accordance with state law, and the exclusion of cannabidiol from the definition of marijuana. The bill was referred to the committees on Energy and Commerce and Judiciary.

H.R. 1855 – On April 16, 2015, Representative Earl Blumenaur (D-OR) introduced the Small Business Tax Equity act, a bill to amend the Internal Revenue Code of 1986 to allow deductions and credits relating to expenditures in connection with marijuana sales conducted in compliance with State law. The bill was referred to the Committee on Ways and Means. See S. 987.

H.R. 1940 – On April 22, 2015, Representative Dana Rohrbacher (R-CA) introduced a bill to amend the Controlled Substances Act to provide for a new rule regarding the application of the Act to marihuana, and for other purposes. The bill was referred to the Committes on Energy and Commerce, Judiciary.

H.R. 1988 -- On April 23, 2015, Representative Marcia Fudge (D-OH) introduced the Breaking Addiction Act of 2015, to provide for the waiver of the Medicaid IMD limitation in order to permit Medicaid coverage for substance use disorder treatment services furnished to certain individuals in a community-based institution for mental diseases. The bill was referred to the committee on Energy and Commerce.

S. 134 – On January 8, 2015, Senator Ron Wyden (D-OR) introduced the Industrial Hemp Farming Act of 2015, to amend the Controlled Substances Act to exclude industrial hemp from the definition of marijuana, and for other purposes. The bill was referred to the Judiciary Committee. See H.R. 525.

S. 318/H.R. 531– On January 29, 2015, and January 26, 2015, Senator Barbara Mikulski (D-MD) and Representative Rosa DeLauro (D-CT) introduced S. 318 and H.R. 531, respectively, the Accelerating Biomedical Research Act. These bills would prioritize funding for the National Institutes of Health to discover treatments and cures, to maintain global leadership in medical innovation, and to restore the purchasing power the NIH had after the historic doubling campaign that ended in fiscal year 2003. The bills were referred to Senate and House Committees on the Budget.

S. 281 – On January 28, 2015, Senator Roy Blunt (R-MO) introduced a bill to require a Federal agency to include language in certain educational advertising materials indicating that such

materials are produced and disseminated at taxpayer expense. The bill was referred to the Senate Committee on Homeland Security and Governmental Affairs.

S. 289 – On January 28, 2015, Senator Richard Durbin (D-IL) introduced the American Cures Act. The bill would authorize additional investment for NIH, CDC, Department of Defense Health Programs, and Veterans Medical & Prosthetics Research Program and also create a budget cap adjustment through the remaining years of the Budget Control Act. The bill was referred to the Senate Committee on the Budget.

S. 320 – On January 29, 2015, Senator Elizabeth Warren (D-MA) introduced S. 320, the Medical Innovation Act. The bill would authorize the collection of supplemental payments increase investments in medical research. The bill was referred to the Senate Committee on Health, Education, Labor and Pensions. See H.R. 744.

S. 524 – On February 12, 2015, Senator Sheldon Whitehouse (D-RI) introduced the Comprehensive Addiction Recovery Act, to authorize the Attorney General to award grants to address the twin epidemics of prescription drug and heroin abuse. The bill was referred to the Judiciary Committee. See H.R. 953

S.683 – On March 10, 2015, Senator Cory Booker (D-NJ) introduced the CARERS Act, to extend the principle of federalism to State drug policy, provide access to medical marijuana, and enable research into the medicinal properties of marijuana. The bill was referred to the Judiciary Committee. See H.R. 1538.

S. 728 - On March 12, 2015, Senator Charles Schumer (D-NY) introduced the Sober Truth on Preventing Underage Drinking Reauthorization Act, or the STOP Act. This bill would direct the Secretary to continue to conduct research and collect data on the short and long-range impact of alcohol use and abuse upon adolescent brain development and other organ systems as well as work in collaboration with the Directors of NIAAA and NIDA, among other federal officials, on the Interagency Coordinating Committee Annual Report on underage drinking and prevention. This legislation would prohibit making, selling, distributing, or possessing powdered alcohol. The bill was referred to the Senate Committee on Health, Education, Labor, and Pensions.

S. 799 – On March 19, 2015, Senator Mitch McConnell (R-KY) introduced the Protecting Our Infants Act, to combat the rise of prenatal opioid abuse and neonatal abstinence syndrome. The bill was referred to the Committee on Health, Education, Labor and Pensions. See H.R. 1462.

S. 987 – On April 16, 2015, Senator Ron Wyden (D-OR) introduced the Small Business Tax Equity Act, to amend the Internal Revenue Code of 1986 to allow deductions and credits relating to expenditures in connection with marijuana sales conducted in compliance with State law. The bill was referred to the Committee on Finance. See H.R. 1855.

INTERNATIONAL ACTIVITIES

Funding Opportunity Announcement

NIDA Reissues International Collaborative Research Program Announcements

NIDA has reissued its Program Announcements (PAs) soliciting collaborative research proposals between investigators from domestic U.S. institutions and researchers in other countries. The PAs—International Research Collaboration on Drug Abuse and Addiction Research—will be in effect until May 8, 2018. Researchers may choose one of three grant programs in response to these broad calls for innovative research proposals:

- R01: PA-15-142
- R21: PA-15-143
- R03: PA-15-141.

Applications are encouraged in all areas of NIDA-supported science, including basic laboratory studies, clinical studies, epidemiological studies, community-based studies, and services research. Research priority areas include:

- Acute and chronic effects of marijuana, especially on the neurobiology and function of the brain, and the impacts of policies and laws regarding marijuana possession and use
- Linkages between HIV and drug use, especially seek, test, treat, and retain strategies to reach and test high-risk individuals and initiate and monitor HAART therapy for those who test positive
- The nature and extent of amphetamine-type stimulant abuse and synthetic and other designer drug abuse, their short- and long-term consequences, and prevention and treatment approaches
- Inhalant abuse, including epidemiological data, development and implementation of effective prevention programs, neurobiological impacts, and public awareness initiatives
- Prenatal impact of smoking and the effects on young people and adolescents of early exposure to tobacco, especially on cognitive development, progression to addiction, and development of other diseases
- Testing technologies to assess the prevalence of driving under the influence of drugs, the role of drugs in accidents, and the costs and benefits of laws and other programs to reduce the incidence and impact of drugged driving.

Meetings

IP Director and Former NIDA Humphrey Fellows Join UNODC Informal International Scientific Network

Following a 2014 informal scientific consultation facilitated by NIDA Director Nora D. Volkow, M.D., and requests by United Nations member states, the United Nations Office on Drugs and Crime (UNODC) has created an Informal International Scientific Network to enhance collaboration between member states and scientists on the issues of drug use and addiction. NIDA IP Director Steven W. Gust, Ph.D., and two former NIDA Hubert H. Humphrey Drug Abuse Research Fellows will serve on the panel and participated in the inaugural meeting of the network March 10-11, 2015, in Vienna, Austria. The former NIDA Humphrey fellows are Suzan Ben Ezra, who leads the Treatment and Rehabilitation Division of the Israeli Anti Drug Authority, and Jallal Toufiq, who directs the Moroccan National Centre on Drug Prevention, Treatment, and Research. The network will serve as a resource for UNODC, the Commission on Narcotic Drugs, and member states as they prepare for the 2016 United Nations General Assembly Special Session on the world drug

problem. The Network members represent a wide range of drug abuse research disciplines and global regions.

Research Results

Former Fellow Publishes Research on Cannabis Toxicity in Europe

A review of European Drug Emergencies Network (Euro-DEN) data published ahead of print February 5, 2015, in the *Journal of Medical Toxicology* concluded that most patients diagnosed with cannabis toxicity received no treatment for symptoms including agitation, psychosis, anxiety, and vomiting. However, the authors of Presentation to the Emergency Department Following Cannabis Use: A Multi-Centre Case Series from Ten European Countries, identified a fatal case of cannabis-related cardiovascular toxicity, and warned that emergency department physicians may not immediately recognize the role of cannabis in cardiac arrest. One of the authors is former NIDA Hubert H. Humphrey Fellow Roumen Sedefov, M.D., who now heads the supply reduction and new trends unit at the European Monitoring Centre for Drugs and Drug Addiction.

Fellowships

NIDA, SAMHSA Host Humphrey Fellows

The 2014-2015 NIDA Hubert H. Humphrey Drug Abuse Research Fellows met with federal officials April 1 and 2 to learn about research priorities, initiatives, and resources offered by NIDA and the Substance Abuse and Mental Health Services Administration (SAMHSA). IP Director Steven W. Gust, Ph.D., and Associate Director Dale Weiss hosted the fellows at NIDA. The following NIDA staff spoke with the fellows: Carmen Rosa, M.S., CCTN; Cora Lee Wetherington, Ph.D., DCNBR; Richard A. Jenkins, Ph.D., DESPR; and Geoffrey Laredo, M.P.A., and Maureen Boyle, Ph.D., OSPC. SAMHSA International Officer Winnie Mitchell hosted the fellows' visit to that agency, where the fellows met with representatives from the centers for Behavioral Health and Statistics and Quality, Mental Health Services, Substance Abuse Prevention, and Substance Abuse Treatment.

Former NIDA Humphrey Fellow Edits Journal Supplement on Harm Reduction

Monica Beg, M.B.B.S., M.P.H., Chief of the United Nations Office on Drugs and Crime (UNODC) HIV/AIDS Section and a 2001-2002 NIDA Hubert H. Humphrey Drug Abuse Research Fellow, was one of three guest editors of *Science Addressing Drugs and HIV: State of the Art of Harm Reduction*, a February 2015 peer-reviewed supplement to the *International Journal of Drug Policy* (26[Supplement 1]). The other editors were NIDA grantee Steffanie A. Strathdee, Ph.D., University of California San Diego, and Michel Kazatchkine, M.D., UN Special Envoy on HIV/AIDS in Eastern Europe and Central Asia. The supplement includes six thematic papers and the text of a scientific statement adopted at a March 2014 UNODC Scientific Consultation on ways to prevent and treat drug-related HIV/AIDS. The meeting and the journal focused on six thematic areas:

- The cost effectiveness of harm reduction
- HIV, drugs and the legal environment
- Women and drugs
- Harm reduction in prisons
- Compulsory detention as drug treatment and the impact on HIV outcomes
- Prevention, treatment and care of hepatitis C among people who inject drugs.

INVEST/CTN Fellow Discusses Drug Abuse in Nepal
In a February 25, 2015, presentation for the University of Washington Nepal Speaker Series, Chandra K. Jha, Ph.D., reviewed relapse risks among Nepalese drug users and described evidence-based recommendations to provide drug detoxification and rehabilitation services in the country. A native of Nepal, Dr. Jha is an INVEST/CTN Drug Abuse Research Fellow working with University of Washington professor Dennis M. Donovan, Ph.D., at the CTN Pacific Northwest Node.

Other International Activities

Dr. Ruben Baler, OSPC, presented 3 lectures on 1) Delay Discounting and modern environments, 2) Marijuana trends in the US, and 3) Addiction and Complexity, at the IV International Congress of Dual Pathology in Barcelona, Spain, on April 16-21, 2015.

Dr. Ivan Montoya, DPMCDA, was invited to give a plenary lecture at the 41st annual meeting of the Spanish Society of Drug and Alcohol Dependence in Logrono on March 14th, 2015.

Dr. Ivan Montoya was invited to give Grand Rounds at the University of Seville's School of Medicine on March 11th, 2015.

On March 5, 2015, Dr. Harold Perl, DESPR, Prevention Research Branch represented NIDA as a Federal Liaison to the International Scientific Advisory Committee for the Substance Abuse Research Center, Jazan University, Saudi Arabia, in Jazan, Saudi Arabia.

On March 3-4, 2015, Dr. Harold Perl organized and taught a 2-day workshop on developing research projects in drug addiction for scientists associated with the Substance Abuse Research Center, Jazan University, Saudi Arabia, in Jazan, Saudi Arabia.

Dr. Yu (Woody) Lin, DCNBR and NIDA AAPI Workgroup, contributed to the development of 2015 International Conference on Global Health: Prevention and Treatment of Substance Use Disorders and HIV. The workgroup co-sponsored this international conference together with Dr. Yih-Ing Hser, NIDA grantee and the director of UCLA Center for Advancing Longitudinal Drug Abuse Research. The conference aimed to foster development of a collaborative capacity among scientists, clinicians and communities of Asian, American and Pacific Islander domestically and globally, an important mission and ongoing efforts of the Workgroup. It was held April 22–24, 2015 in Hangzhou, China.

Dr. Marilyn Huestis, IRP, was invited to conduct training and render expert advice to the Health Sciences Authority (HSA) of Singapore from March 23-26, 2015.

Dr. Marisela Morales, IRP, gave an invited lecture at The Third Symposium on Latin American Research Networks in Drug Addiction, San Juan, Puerto Rico.

Dr. Yavin Shaham, IRP, gave an invited lecture at the Weizmann Institute, Hebrew University, Tel Aviv University.

Dr. Yavin Shaham, IRP, gave an invited lecture at Beijing University.

PROGRAM ACTIVITES

New NIDA RFAs

On February 10, 2015, NIDA issued an RFA entitled **Advancing Exceptional Research on HIV/AIDS and Substance Abuse (R01) RFA-DA-16-001.** This FOA will support highly innovative R01 applications on HIV/AIDS and drug abuse and will complement the Avant-Garde Award Program for HIV/AIDS research. The Avant-Garde award supports individuals who conduct high-risk, high-reward research and does not require a detailed research plan. Applications submitted under this FOA are required to have a detailed research plan and preliminary data. This FOA focuses on innovative research projects that have the potential to open new areas of HIV/AIDS research and/or lead to new avenues for prevention and treatment of HIV/AIDS among substance abusers. The nexus with substance abuse should be clearly described. This FOA is open to both individual researchers and research teams and is not limited to any one area of research on HIV and substance use. Open date: June 30, 2015. Application due date(s): July 31, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): July 31, 2015, by 5:00 PM local time of applicant organization.

New NIDA Program Announcements

On April 7, 2015, NIDA issued a PA entitled **Pilot and Feasibility Studies in Preparation for Drug and Alcohol Abuse Prevention Trials (R34) PA-15-177**. This Funding Opportunity Announcement (FOA) for R34 applications seeks to support: (a) pilot and/or feasibility testing of innovative new, revised, or adapted prevention intervention approaches to prevent or delay the initiation and onset of drug and alcohol use, the progression to problem use or alcohol and other substance use disorder, reduce drinking and driving and deaths related to impaired driving and the drug- or alcohol-related acquisition or transmission of HIV infection and viral hepatitis among diverse populations and settings; and (b) pre-trial feasibility testing for prevention services and systems research. It is expected that research conducted via this R34 mechanism will consist of early stage efficacy, effectiveness or services research that will provide intervention pilot and/or feasibility data that is a pre-requisite for preparing and submitting subsequent applications for larger scale drug or alcohol abuse prevention and/or drug- or alcohol-related HIV prevention intervention studies. This R34 FOA does not support applications for which the sole focus is development of intervention protocols, manuals, or the standardization of protocols; rather, any development work must be imbedded within a pilot/feasibility study. Of particular interest are prevention interventions targeting the healthcare system. Open date: May 16, 2015. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On March 17, 2015, NIDA issued PAs entitled **International Research Collaboration on Drug Abuse and Addiction Research (R03) PA-15-141, (R01) PA-15-142, (R21) PA-15-143**. This Funding Opportunity Announcement (FOA) encourages collaborative research applications on drug abuse and addiction that take advantage of special opportunities that exist outside the United States. Special opportunities include access to unusual talent, resources, populations, or environmental

conditions in other countries that will speed scientific discovery. Projects should have relevance to the mission of NIDA and where feasible should address NIDA's international scientific priority areas (http://www.drugabuse.gov/international/research-priorities). While the priorities will change from year to year, in FY15 priority areas include: linkages between HIV/AIDS and drug abuse; prevention, initiation, and treatment of nicotine and tobacco use (especially among vulnerable populations such as children, adolescents, pregnant women, and those with co-morbid disorders); the neuroscience of marijuana and cannabinoids; and the effect of changes in laws and policies on marijuana and its impact. Open date: May 5, 2015 (R01), May 16, 2015 (R03, R21). Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On February 13, 2015, NIDA issued a PAR entitled **Identification of Genetic and Genomic Variants by Next-Gen Sequencing in Non-human Animal Models (U01) PAR-15-120**. The goals of this initiative are to identify gene variants of traits associated with addiction and substance abuse in selectively bred, and outbred non-human animal models using methodologies of Next Gen-Sequencing, mapping, and genotyping. Open date: May 30, 2015. Application due date(s): June 30, 2015; October 20, 2015; March 1, 2016; June 30, 2016; October 20, 2016; March 1, 2017; June 30, 2017; October 20, 2017; March 1, 2018, by 5:00 PM local time of applicant organization. AIDS application due date(s): June 30, 2015; October 20, 2015; March 1, 2016; June 30, 2016; October 20, 2016; March 1, 2017; June 30, 2017; October 20, 2017; March 1, 2018, by 5:00 PM local time of applicant organization.

On February 11, 2015, NIDA issued a PAR entitled **NIDA Mentored Clinical Scientists Development Program Award in Drug Abuse and Addiction (K12) PAR-15-119**. This funding opportunity announcement (FOA) encourages applications for institutional research career development (K12) programs that propose to support intensive supervised research training and career development experiences for clinician scientists (scholars) leading to research independence in the area of drug abuse and addiction. For this FOA, clinician scientists may include (but are not limited to) physicians, clinical psychologists, epidemiologists, doctoral-level social workers, pharmacists, and behavioral scientists. Scholars are expected to be supported for 3-5 years on consecutive 12-month appointments. Candidates selected for support as scholars must hold a doctorate and commit a minimum of 9 person-months (equivalent to 75% of full-time professional effort) to conducting clinical research and career development activities associated with the proposed program. Open date: May 12, 2015. Application due date(s): June 12, 2015; June 12, 2016; June 12, 2017, by 5:00 PM local time of applicant organization. AIDS application due date(s): September 7, 2015; September 7, 2016; September 7, 2017, by 5:00 PM local time of applicant organization.

On February 5, 2015, NIDA issued PAs entitled **Gene-Environment Interplay in Substance Use Disorders (R01) PA-15-110, (R03) PA-15-111, (R21) PA-15-112**. This Funding Opportunity Announcement (FOA) seeks to stimulate and expand research on the interplay of genetic and environmental factors in the genesis, course, and outcomes of substance and alcohol use disorders (SUDs). Previous work in genetic epidemiology and molecular genetics has established that SUDs are highly heritable, developmental disorders with important genetic substrates. Building on these findings, new studies using genetically informative approaches are needed to elucidate the complex

interplay of genetic and environmental factors in developmental trajectories of SUDs and comorbid conditions, deepen and refine phenotypic definitions of SUDs, and meet the methodologic challenges of the field. Such studies hold great potential to promote understanding of the true contributions of both genetic and environmental factors to initiation, progression, comorbidity, adverse outcomes, and cessation of SUDs; to elucidate mechanisms of risk; and to enhance opportunities for translation to treatment, prevention, gene-finding and molecular studies. Open date: May 5, 2015 (R01), May 16 (R03, R21). Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

New FOAs Issued by the NIH Roadmap

On April 16, 2015, the NIH Common Fund issued a Roadmap RFA entitled **Undiagnosed Diseases Gene Function Research (R21) RFA-RM-15-004.** This Funding Opportunity intends to support gene function studies in collaboration with the Undiagnosed Diseases Network (UDN) building upon the NIH Intramural Research Program's Undiagnosed Diseases Program (NIH-UDP). Responsive applications will propose to investigate the underlying genetics, biochemistry and/or pathophysiology of newly diagnosed diseases in association with the respective gene variant(s) identified through the UDN. In recent years, gene function studies combined with genetic and genomic analyses and metabolic studies have greatly improved diagnoses of these very rare diseases and advanced scientific knowledge of the underlying pathogenesis. This initiative is funded through the NIH Common Fund, which supports cross-cutting programs that are expected to have exceptionally high impact. Open date: May 24, 2015. Application due date(s): June 24, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

New FOAs Issued by the NIH Blueprint for Neuroscience Research

Lifespan Human Connectome Project: Baby Connectome (U01) RFA-MH-16-160

Lifespan Human Connectome Project: Development (U01) RFA-MH-16-150

Lifespan Human Connectome Project: Aging (U01) RFA-AG-16-004

New FOAs Issued by the BRAIN INITIATIVE

BRAIN Initiative: Optimization of Novel Tools and Technologies for Neuroscience Research (R44) PAR-15-121

New RFAs Issued by Other NIH/HHS Components in which NIDA is a participant

NIH-PEPFAR Collaboration on Implementation Science for HIV: Towards an AIDS-free Generation (R01) RFA-AI-15-020

NIH-PEPFAR Collaboration on Implementation Science for HIV: Towards an AIDS-free Generation (R21) RFA-AI-15-021

Limited Competition: International epidemiology Databases to Evaluate AIDS (IeDEA) (U01) RFA-AI-15-017

Big Data to Knowledge (BD2K) Advancing Biomedical Science Using Crowdsourcing and Interactive Digital Media (UH2) RFA-CA-15-006

New PAs Issued by Other NIH/HHS Components in which NIDA is a participant

Summer Research Education Experience Programs (R25) PAR-15-184

Jointly Sponsored Ruth L. Kirschstein National Research Service Award Institutional Predoctoral Training Program in the Neurosciences (T32) PAR-15-178

Administrative Supplements for Research on HIV/AIDS and Aging (Admin Supp) PA-15-137

Advancing Mechanistic Probiotic/Prebiotic and Human Microbiome Research (R01) PA-15-135

Advancing Translational and Clinical Probiotic/Prebiotic and Human Microbiome Research (R01) PA-15-127

Administrative Supplements for Common Basic Sociobehavioral Mechanisms and Processes that Facilitate or Impede Self-Management of Chronic Conditions (Admin Supp) PA-15-122

New NIH FOAs Issued in Collaboration with the FDA Center for Tobacco Products

On April 23, 2015, NIDA, in collaboration with numerous other NIH components and with the FDA Center for Tobacco Products, issued an RFA entitled **Tobacco Regulatory Science Small Grant Program for New Investigators (R03) RFA-OD-15-004.** The purpose of this Funding Opportunity Announcement (FOA) is to support New Investigators in the biomedical, behavioral, and social sciences who are in the early stages of establishing independent careers in tobacco regulatory research. The R03 grant mechanism supports different types of projects including pilot and feasibility studies; secondary analysis of existing data; small, self-contained research projects; development of research methodology; and development of new research technology. Applicants are encouraged to conduct projects that ultimately have potential to inform regulations on tobacco product manufacturing, distribution, and marketing. Research projects must address the research priorities related to the regulatory authority of the Food and Drug Administration (FDA) Center for Tobacco Products (CTP) as mandated by the Family Smoking Prevention and Tobacco Control Act (FSPTCA), Public Law 111-31. Open date: July 20, 2015. Application due date(s): August 20, 2015, February 23, 2016, July 20, 2016, February 23, 2017, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On April 9, 2015, NIDA, in collaboration with numerous other NIH components and with the FDA Center for Tobacco Products, issued an Administrative Supplement entitled **Administrative Supplements for Tobacco Regulatory Research on Tobacco Flavors and Flavorings (Admin Supp) PA-15-183.** The purpose of this funding opportunity is to generate data regarding the following two topics related to flavors and flavorings in cigarettes, cigars (including little cigars and cigarillos), and e-cigarettes. Only applications proposing research projects relevant to one or more of the two topics will be considered for funding: 1) When tobacco product flavorings and additives are heated or burned, what chemicals are formed from the thermal degradation processes (pyrolysis and/or oxidation), including chemicals that are on the FDA's established Harmful and Potentially Harmful Constituent list, as well as any other toxic chemicals not on the list? What are the levels of the chemicals that are formed? 2) What in vitro assays are capable of comparative toxicological assessments that can examine the harm potential between different flavorings commonly used in cigarettes, cigars and e-cigarettes; comparing the flavorings after burning or heating (at temperatures achieved by conventional pyrolysis and non-conventional heating methods, such as ones used in aerosol formation)? Open date: April 29, 2015. Application due date(s): May 29, 2015 by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

Other Program Activities

CTN Update

Seventeen applications in response to the RFA DA-15-008, entitled "The National Drug Abuse Treatment Clinical Trials Network (UG1)," were reviewed on March 31, 2015.

A total of 60 protocols have been initiated since 2001, including multi-site clinical trials (43), multi-site surveys (3), studies in special populations (8), and secondary analyses of data across various trials (6). In addition, 28 ancillary studies have been supported by CTN and non-CTN funds. Over 19,000 participants have been enrolled in CTN studies.
Information on protocols can be found at:
http://www.drugabuse.gov/about-nida/organization/cctn/ctn/research-studies

NIDA's Blending Initiative

Accelerating the dissemination of research-based drug abuse treatment into clinical practice is a priority for the National Institute on Drug Abuse (NIDA) and represents the core mission of the Blending Initiative (http://www.drugabuse.gov/blending-initiative).

The latest educational effort − *Talking to Patients about Health Risk Behaviors,* continues to reach multiple healthcare providers including physicians, nurses, physician assistants, pharmacists and others. As of February 1, 2015, 41,316 persons have accessed the program and 20,861 certificates have been issued since its October launch. The two programs comprising this novel educational opportunity provide a unique forum where the CME course and the Patient Simulation jointly provide practical guidance for physicians and other clinicians in effective Motivational Interviewing techniques that will facilitate conversations with patients to address Health Risk Behaviors. The CME Course guides physicians and other clinicians through practical skills building and technique

development using videos to model effective communication, while the Patient Simulation allows for real time testing and reinforcement of these skills in the clinical setting. Links to the education are found at http://www.drugabuse.gov/blending-initiative/cme-ce-simulation.

Through the Blending Initiative, NIDA partners with professional organizations and other institutions dedicated to the training and education of junior fellows/residents to support the development of expertise in substance use disorders (SUDs) within medical and clinical settings. These training awards aim: 1) to promote knowledge of evidence-based SUD treatment within medical specialties, 2) to advance medical care for patients with substance use disorders, and 3) to facilitate the academic growth, advanced education, and development of future researchers and clinicians in SUDs and medicine and thereby invest in the future of the field. As of the end of 2014, the Blending Initiative has partnered with four organizations to fulfill these goals. These organizations are:

- Society of Teachers of Family Medicine
- American Academy of Child and Adolescent Psychiatry
- Society for Adolescent Health and Medicine
- American College of Emergency Physicians/Emergency Medicine Foundation

During this period the Blending Initiative supported seminars and exhibits at the following national meetings:

Society for Adolescent Health and Medicine, March 18-21, 2015

American Association for the Treatment of Opioid Dependence, March 28-April 1, 2015

COLLABORATIVE RESEARCH ON ADDICTION (CRAN) ACTIVITIES

Collaborative Research on Addiction at NIH (CRAN) is a consortium of Institutes supporting research on drug use, abuse and addiction. Included are the: National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute on Drug Abuse (NIDA), and National Cancer Institute (NCI). For more information about CRAN, see: www.addictionresearch.nih.gov

• A CRAN grantee workshop is planned for Tuesday, and Wednesday, May 12 – 13, 2015, for recipients of administrative or competitive supplements. The workshop will take place at the National Cancer Institute (NCI) Shady Grove Campus in Rockville, Maryland. This meeting is an opportunity for Federal staff and grantees to receive updates on the status of CRAN research as well as some of the difficulties involved in conducting multi-substance research. In addition to poster sessions and oral presentations, we anticipate having several panel discussions involving grantees, CRAN project officers and members of the CRAN coordinating committee.

• A webinar is planned for June 10th, 1PM to 3PM for grantees who were funded under the CRAN RFAs: Using Social Media to Understand and Address Substance Use and Addiction. It will give grantees a chance to learn about each other's projects and progress so far, and to discuss potential areas of shared interest.

Adolescent Brain Cognitive Development (ABCD) Study: FOAs released on February 4th 2015; Application Due Date: April 14, 2015.
• This is a multi-Institute project led by CRAN, in partnership with the Eunice Kennedy Shriver Institute of Child Health and Human Development (NICHD), National Institute of Mental Health (NIMH), National Institute on Minority Health and Health Disparities (NIMHD), Office of Behavioral and Social Sciences Research (OBSSR), National Institute on Neurological Disorders and Stroke (NINDS), and the Office of Research on Women's Health (ORWH).

• The goal of the project is to establish a national, multisite, longitudinal cohort study to prospectively examine the neurodevelopmental and behavioral effects of substance use from early adolescence (approximately age 9-10) through the period of risk for substance use and substance use disorders.

• A collaborative research mechanism is being used for this project (U01, and U54s) and its structure shall consist of three highly integrated components: (1) a set of Research Project Sites; (2) a central Data Analysis and Informatics Center, and (3) a Coordinating Center.

• Technical assistance was provided through a webinar, held on Feb 24, 2015, and available as an audio recording following the webinar, and by the issuance of FAQs.

Drs. Will Aklin, Geetha Subramaniam (NIDA), Brett Hagman (NIAAA) and Annette Kaufman (NCI), as part of a CRAN working group, published a notice to change the age range to include young adults up to 25 years of age in PA-15-036 "Research Aimed at Novel Behavioral Targets to Improve Adolescent Substance Abuse Treatment and Prevention Interventions (R01) (R34)."

Specifically, the original FOA specified inclusion of adolescents. The current revision extends the inclusionary age range to 25 years old based on emerging data on brain development that suggests the brain may not reach full maturity until early or mid-20s (years of age), and because substance use disorders may not emerge until young adulthood. This revision will allow for individual variation in brain development up through a time period when predictable brain development has stabilized.
http://grants.nih.gov/grants/guide/notice-files/NOT-DA-15-062.html
http://grants.nih.gov/grants/guide/notice-files/NOT-DA-15-061.html

COMMUNICATIONS

PUBLICATIONS & ONLINE RESOURCES

Commonly Abused Drugs Chart: http://www.drugabuse.gov/drugs-abuse/commonly-abused-drugs **–** Revised February 2015

Hallucinogens and Dissociative Drugs Research Report – Revised February 2015

Drugs: Shatter the Myths – Revised March 2015

Step-by-Step Guide for seeking drug abuse treatment (Spanish-language version)**:** http://www.drugabuse.gov/related-topics/treatment **–** March 2015

Easy-to-Read Drug Facts Spanish-language revisions: Marijuana, Cocaine, Heroin, Painkillers, Meth, Alcohol, Cigarettes and tobacco, Other drugs of abuse; http://easyread.drugabuse.gov/en-espanol.php **–** Revised March 2015

Marijuana Research Report – Revised April 2015

Is Marijuana Medicine? (Drug Facts) – Revised April 2015

NIDA NOTES (now online only)

Video: Thomas Kosten talks about the antidrug vaccines, focusing on their potential uses in treatment and prevention, and who may be appropriate candidates for receiving them

NIDA Notes CEU Module: *NIDA Notes* has collaborated with the Institute for Research, Education, and Training in Addictions, to offer social workers and substance abuse clinicians CEU for reading *NIDA Notes* articles. The first educational module focuses on prescription opioids.

Additional selected articles on the NIDA Notes home page report that marijuana may affect future offspring's susceptibility to heroin; some patients who are addicted to opioid painkillers achieve stable abstinence with detoxification followed by naltrexone therapy; methadone and buprenorphine are equally effective for patients addicted to opioid painkillers; parenting education by paraprofessionals yields sustained benefits for children of American Indian teen mothers, may be a model for improving health in resource-poor areas

NIDAMED

This March's issue of *Academic Medicine* features the evaluation of our NIDAMED Centers of Excellence (CoE) for Physician Information interactive module, The Clinical Assessment of Substance Use Disorders which was created and evaluated by the University of Pennsylvania and Drexel School of Medicine's CoE. Paul N. Lanken, MD, Dennis H. Novack, MD, Christof Daetwyler, MD, Robert Gallop, PhD, J. Richard Landis, PhD, Jennifer Lapin, PhD, Geetha A. Subramaniam, MD, and Barbara A. Schindler, MD. (March, 2015). Efficacy of an Internet-Based Learning Module and Small-Group Debriefing on Trainees' Attitudes and Communication Skills Toward Patients With Substance Use Disorders: Results of a Cluster Randomized Controlled Trial, *Academic Medicine, Volume 90*, pp: 261-394.

In June, the newly formed NIMDAED Coalition of Healthcare Organizations, including The American Academy of Pediatrics, the California Academy of Family Physicians, the America Society of Addiction Medicine, the American Osteopathic Association, the American Academy of Physician Assistants, and the American Association of Nurse Practitioners, will be meeting with NIDA to develop an adolescent substance use prevention/early intervention continuing medical education/continuing education (CME/CE) module, expected launch Spring 2016.

VIDEOS

- Pain Awareness Month: Dr.Martha Somerman on Research and Pain Management http://youtu.be/TCwLE1_K0qU
- 2015 Reto Nacional sobre el Coeficiente Intelectual (IQ) sobre las Drogas: Respuestas científicas: http://youtu.be/pzRu6YLBkbI
- 2015 IQ Challenge: Scientist Answers: http://youtu.be/jznIvcwkGU4
- The Herren Project and NIDA team up for National Drug Facts Week: http://youtu.be/7LQzLLhB6dU
- Animated Infographic: Monitoring the Future 2014 SurveyResults: https://youtu.be/iQDhYlYp81c
- NIDA's 2015 Avant-Garde Awards Announced: https://youtu.be/qVHBOKdLChQ
- Wilson Compton Discusses Marijuana/SAMSHA Joint Project
- What's New at NIDA: Office of Science Policy and Communication Director's notes for March: https://youtu.be/aESAqTzTMF0

CTN-Related Publications

Four editions of the **CTN Bulletin Board** were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and Node activity in the CTN. The Bulletin has wide readership within and outside the CTN and NIDA.

Data from 34 CTN studies and 5 DPMC studies are now available on the **NIDA Data Share website** http://datashare.nida.nih.gov/. Over 3,500 data sets have been downloaded by researchers from 72 countries. These data sets are in compliance with HIPAA and CDISC (Clinical Data

Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap. The NIDA Data Share is also part of the Neuroscience Information Framework (NIF), which is a dynamic inventory of Web-based neuroscience resources: data, materials, and tools accessible via any computer connected to the Internet.

The **NIDA Common Data Elements (CDE) web portal** (http://cde.drugabuse.gov/) provides a single source for CTN recommended CDEs for Substance Use Disorders. All the CDEs displayed on this website are created and housed in the National Cancer Institute (NCI) cancer Data Standards Repository (caDSR) (https://cdebrowser.nci.nih.gov/CDEBrowser/). Currently, 17 instruments have been added to this web site with plans to add more.

Other Publications

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MEDIA SUPPORT OF EVENTS AND MEETINGS

2015 Chat Day and National Drug Facts Week (NDFW)

NIDA conducted its annual Chat Day (January 30) and NDFW (January 26-February 1), which included approximately 1500 events in all 50 states and several countries. Over 130 high schools registered for Chat Day and hundreds of questions were answered by NIDA scientists. NIDA developed and distributed press and promotional materials, cultivated radio and organizational

partnerships, pitched to select media, coordinated two Radio Media Tours for English and Spanish speaking audiences, and promoted the week via traditional and social media outreach. Visit http://teens.drugabuse.gov/national-drug-facts-week for more information.

Population Assessment of Tobacco and Health (PATH) Study
On Thursday, February 26, interim preliminary data on tobacco use from the Population Assessment of Tobacco and Health (PATH) study was presented by NIDA, FDA and Westat staff, as well as the principal investigator. The data was presented during a symposium at the Society for Research on Nicotine & Tobacco 21st Annual Meeting in Philadelphia. NIDA worked in advance of the meeting with FDA staff to prepare talking points and a fact sheet for potential media inquiries. National coverage included stories in *Associated Press* and *Reuters*.

PRESS RELEASES

March 2, 2015 - Dr. Susan Weiss appointed division director at NIDA
NIDA scientist to lead new Division of Extramural Research
Susan R.B. Weiss, Ph.D., has been selected to lead the Division of Extramural Research (DER), a newly formed Division at the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health. In addition to overseeing NIDA's extramural research grant program, the new division will carry out NIDA's research training and early career development program, and lead NIDA's involvement in vital trans-NIH initiatives that include Collaborative Research on Addiction at NIH, the Adolescent Brain Cognitive Development study, and Brain Research through Advancing Innovative Neurotechnologies. As DER Director, Dr. Weiss will establish scientific priorities and strategic goals for the Institute's extramural research programs; manage the concept and peer review of all NIDA grant applications in coordination with NIH's Center for Scientific Review; and coordinate and lead activities of the National Advisory Council on Drug Abuse. "Dr. Weiss has shown exceptional talent in every position she has held here at NIDA and is the perfect choice for this immensely complex leadership position," said NIDA Director Nora D. Volkow, M.D. "She has a strong knowledge of addiction science and understands the challenges related to the grants process. She is also enormously skilled in the intricacies of science policy related to drug abuse issues."

Dr. Weiss first came to NIDA in 2002 as a health scientist administrator working in the Science Policy Branch, where she became branch chief the following year. In 2011, she was asked to serve as acting director of the Office of Science Policy and Communications, overseeing all of NIDA's interactions with its many stakeholders — students, researchers, community groups, the media, Congress, other NIH Institutes and U.S. Department of Health and Human Services agencies, and the White House Office of National Drug Control Policy. In 2012, she was asked to join NIDA's executive leadership team as Associate Director for Scientific Affairs providing guidance and oversight on scientific matters relating to program development, management, research training, and science planning.

Dr. Weiss received her Ph.D. in psychology from the University of Maryland, College Park, and earlier in her career was chief of the Unit on Behavioral Biology at the National Institute of Mental Health, later serving as Senior Director for Research for the National Mental Health Association.

She is one of NIDA's foremost experts on the complex science of addiction; marijuana science and policy; and the many factors contributing to the nation's prescription drug abuse problem.

"Throughout my professional career, I have worked across the spectrum of basic, clinical, and translational research where science, communications, and science policy meet," said Dr. Weiss. "I am excited about my new role that will focus on the science we support through extramural grants and on strengthening the already robust collaborations between NIDA's scientific interests and those of other NIH Institutes and Centers."

NIDA administers more that $775 million in grant funding for about 2,000 grants through funding opportunity announcements and research training programs.
http://www.drugabuse.gov/news-events/news-releases/2015/03/dr-susan-weiss-appointed-division-director-nida

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February 9, 2015 - 2015 Avant-Garde Awards offer extraordinary ideas in HIV/AIDS research

NIH's awards showcase potentially transformative research on prevention, immune system, drug development, and "minibrain" models made of human tissue

With proposals ranging from innovative therapies to the development of unique organoid models of the brain, five scientists have been selected to receive the 2015 Avant-Garde Award for HIV/AIDS Research from the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health. The five scientists will each receive $500,000 per year for five years to support their research. NIDA's annual Avant-Garde Award competition, now in its eighth year, is intended to stimulate high-impact research that may lead to groundbreaking opportunities for the prevention and treatment of HIV/AIDS in drug users.

"Despite the success of combined antiretroviral therapies in the treatment of HIV/AIDS, HIV remains a chronic disease with a host of debilitating side effects that are exacerbated in those suffering from substance use disorders," said NIDA Director Nora D. Volkow, M.D. "These scientists have proposed creative approaches that could transform the way we think about HIV/AIDS research, and could lead to the development of exciting new tools and strategies to prevent infections and improve the lives of substance abusers infected with HIV."

Awardees are listed below:

Don C. Des Jarlais, Ph.D., Mount Sinai Beth Israel, New York City

Project: Combined Prevention to Reduce Initiation into Injecting Drug Use

Dr. Des Jarlais will lead a multi-component HIV prevention intervention study in two sites with growing concerns about heroin use — New York City and Tallinn, Estonia in Eastern Europe. Researchers will focus on combining a number of interventions with demonstrated effectiveness in reducing the number of drug users who transition to injection drugs. "There are a number of evidence-based programs for reducing initiation into injecting drug use, including the Heroin Sniffer project, the Break the Cycle project, Couples-based HIV counseling and low threshold drug treatment," said Des Jarlais. "This project will apply a combined prevention approach to reduce initiation into injecting drug use."

Eli Gilboa, Ph.D., University of Miami School of Medicine
Project: Reversing HIV T cell Dysfunction by Aptamer Targeting of Therapeutic siRNAs
Dr. Gilboa proposes the development of novel drugs that successfully restore the function of T cells — important in immune response — and would have the potential to be therapeutically transformative for AIDS patients, including substance users in whom drugs further undermine their immune function. "A major challenge for HIV-infected patients is that the immune system, particularly for drug abuse patients, is becoming progressively dysfunctional," said Gilboa. "The Avant-Garde Award provides us with the unique opportunity to develop a novel nucleic acids based drug and drug delivery platform to block key intracellular pathways that mediate immune dysfunction."

Nichole Klatt, Ph.D., University of Washington, Seattle
Project: Impact of Cannabis on Inflammation and Viral Persistence in Treated HIV/SIV
Dr. Klatt proposes development of HIV cure strategies by using non-psychoactive cannabinoids as potential therapeutic agents. Since cannabinoids, derivatives of cannabis, have been used to treat nausea and pain and have been shown to be anti-inflammatory in animal models, Dr. Klatt theorized that cannabinoids could be effective in reducing inflammation common in HIV patients.
"The goal of our Avant-Garde research is to understand how cannabis may alter gastrointestinal immunity, inflammation and viral reservoirs in HIV-infected people," said Klatt. "We want to determine the mechanisms by which cannabis exerts its effects and develop non-psychoactive cannabinoids as a potential adjunct treatment for HIV infection."

Alan D. Levine, Ph.D., Case Western Reserve University, Cleveland
Project: Repairing the Intestinal Epithelium from the Dual Action of HIV and Drug Use
Dr. Levine will investigate the loss of intestinal barrier protection initiated by HIV infection and the resultant, systemic inflammation due to chronic exposure to gut-derived microbial products. This situation is exacerbated in the drug-abusing HIV infected population in whom drugs exert toxic effects on the gastrointestinal tract which synergize with HIV. "It is an honor and quite humbling to be recognized via the NIDA Avant-Garde Award and to follow in the path of previous recipients who are outstanding, internationally acclaimed HIV and drug abuse investigators," said Levine. "This award will enable us to define the molecular and cellular mechanisms that increase intestinal permeability via a loss in epithelial integrity and homeostasis, and to test the hypothesis that repairing barrier function is a novel approach to HIV- and illicit drug-promoted mucosal damage."

Tariq M. Rana, Ph.D., University of California San Diego
Project: Modeling HIV/AIDS Associated Neurological Disorders with Human Pluripotent Cells
Dr. Rana will use an innovative approach to better understand the molecular mechanisms of brain disorders caused by HIV and its interaction with the damage from the use of methamphetamine. This project will build miniature models of the brain — developed with stem cells — to investigate brain injuries caused by HIV that are associated with neurocognitive disorders and the interactions with methamphetamine exposures. "The human cerebral cortex has evolved strikingly as compared to those of other species, and no animal model accurately captures human-specific brain functions," said Dr. Rana. "The creation of minibrains — or organoids — will permit, for the first time, study of the toxic effects of addiction and HIV on the human brain in a dish. This offers us the exciting

opportunity to design patient-specific model systems, which could potentially revolutionize drug discovery and precision medicine for central nervous system disorders."

These awardees were among the many applicants whose proposals reflect diverse scientific disciplines and approaches to HIV/AIDS research. The Avant-Garde Awards are modeled after the NIH Pioneer Awards and are granted to scientists of exceptional creativity who propose high-impact research that could open new avenues for prevention and treatment of HIV/AIDS among drug abusers.

For information about NIDA's AIDS Research Program, including the Avant-Garde Award Program for HIV/AIDS Research, go to www.drugabuse.gov/AIDS. Read about selected highlights of past Avant-Garde awardees. Gilboa, Des Jarlais, Rana, Klatt and Levine are funded under grant numbers DA039560, DA039542, DA039562, DA037979 and DA037997, respectively.
http://www.drugabuse.gov/news-events/news-releases/2015/02/2015-avant-garde-awards-offer-extraordinary-ideas-in-hivaids-research

SCIENCE SPOTLIGHTS AND ANNOUNCEMENTS

February 9, 2015: *NIDA researchers discover further complexity in brain reward circuitry.*
NIDA scientists have identified new complexities within the brain's reward circuitry that involves two major chemicals involved in drug addiction -- dopamine and glutamate. They found that dopamine and glutamate were typically stored separately from one another and released from different synapses of the nerve cell. This finding reveals a greater layer of complexity in signaling within brain reward circuits than had previously been recognized.
http://www.drugabuse.gov/news-events/news-releases/2015/02/nida-researchers-discover-further-complexity-in-brain-reward-circuitry

February 11, 2015: *NIDA Director Dr. Nora Volkow to Participate in Facebook Chat about TEDMED Presentation.*
NIDA Director Dr. Nora Volkow will participate in a LIVE Facebook chat, hosted by TEDMED, on Thursday, February 12, at 1 p.m. EST to discuss what we can learn about compulsive overeating from studying the brain chemistry of people with drug addictions.
http://www.drugabuse.gov/news-events/news-releases/2015/02/nida-director-dr-nora-volkow-to-participate-in-facebook-chat-about-tedmed-presentation

March 18, 2015: *Medication finds new use in sustaining opioid quit success.*
New research suggests that clonidine, a medication for high blood pressure and attention deficit hyperactivity disorder (ADHD), can enhance buprenorphine's ability to treat opioid dependence. This combination of medications reduces stress-induced craving and prolongs opioid abstinence during outpatient treatment for heroin or prescription pain reliever dependence, compared to buprenorphine alone.
http://www.drugabuse.gov/news-events/news-releases/2015/03/medication-finds-new-use-in-sustaining-opioid-quit-success

March 30, 2015: *Study looks at effects of socioeconomic factors on child brain development and achievement.*
New research suggests that family income, and to a lesser degree parental education, are associated with brain structure differences in children and young adults. Focusing on brain regions critical for language, memory, and executive function in participants aged three to 20 years, scientists found that small differences in income were associated with relatively large differences in brain surface area in young people from the lowest-income families. This effect was smaller in higher-income families. Higher income was also associated with better performance in tests of cognitive ability. Increased levels of parental education were also related to increased brain surface area, although this effect was smaller when compared to the influence of income.
http://www.drugabuse.gov/news-events/news-releases/2015/03/study-looks-effects-socioeconomic-factors-child-brain-development-achievement

March 31, 2015: *Research shows that teens and adults are uncertain about legalities of marijuana law in Washington State.*
A NIDA-funded study showed that while parents in the state of Washington are discussing with their children the legalization of recreational marijuana use among adults, they are unsure what is legal and illegal under the new laws. The study showed that many parents and teens do not know the laws surrounding the age limit for marijuana use, how much marijuana can be possessed, or that homegrown marijuana is illegal. The findings support the need for improved educational outreach about the law as well as prevention efforts.
http://www.drugabuse.gov/news-events/news-releases/2015/03/research-shows-teens-adults-are-uncertain-about-legalities-marijuana-law-in-washington-state

April 15, 2015: *Gene variant related to greater difficulty in quitting smoking and earlier lung cancer diagnosis.*
People with a specific form of the CHRNA5 gene take an average of four years longer to quit smoking and are at greater risk for developing lung cancer four years earlier, compared to smokers without this gene variant. This is according to a meta-analysis, funded by various NIH Institutes, including NIDA, of 24 studies examining variants in the CHRNA5 gene within participants of European ancestry. By some measures, approximately 18% of people with this ancestry carry the high-risk variant.
http://www.drugabuse.gov/news-events/news-releases/2015/04/gene-variant-related-to-greater-difficulty-in-quitting-smoking-earlier-lung-cancer-diagnosis

April 30, 2015: *Medication plus ongoing care provided in emergency departments is promising approach for opioid dependence.*
NIDA-funded research comparing treatment approaches for opioid dependent patients in emergency departments (ED) suggests that combining the medication buprenorphine with ongoing care is more effective than simply providing referrals to addiction treatment, with or without a brief intervention. This adds to the growing body of literature suggesting that opioid-dependent patients may benefit from immediate initiation of medication while awaiting more comprehensive substance use disorder treatment.
http://www.drugabuse.gov/news-events/news-releases/2015/04/medication-plus-ongoing-care-provided-in-emergency-departments-promising-approach-opioid-dependence

INTERVIEW HIGHLIGHTS: January 2015 – March 2015

Associated Press – Dr. Wilson Compton was interviewed about e-cigarettes.
CNN – Dr. Nora Volkow was interviewed about marijuana.
Forbes – Dr. Nora Volkow was interviewed about marijuana.
FOX News – Dr. Marilyn Heustis was interviewed about K2/Spice.
Men's Health - Dr. Wilson Compton was interviewed about drug overdoses.
Nature (4) – Drs. Nora Volkow and Joni Rutter were interviewed about the ABCD (marijuana) study, marijuana research, neuroscience of addiction and addiction genetics.
NPR – Dr. Nora Volkow was interviewed about marijuana.
NPR – Dr. Marilyn Heustis was interviewed about K2/Spice.
Science News – Drs. Mike Baumann and Marilyn Huestis were interviewed about designer drugs and K2/Spice.
Seattle Times - Dr. Susan Weiss was interviewed about the ABCD (marijuana) study.
The New York Times – Dr. Nora Volkow was interviewed about heroin.
The New Yorker Magazine - Dr. Mike Baumann was interviewed about bath salts.
Time(2) – Drs. Wilson Compton and Susan Weiss were interviewed about vaccines and the ABCD (marijuana) study.
The Wall Street Journal - Dr. Wilson Compton was interviewed about painkiller addiction.
U.S. News & World Report - Dr. Joni Rutter was interviewed about addiction genetics.

MEETINGS AND CONFERENCES

On April 23, 2015, NIDA again participated in **Take Your Child to Work Day** by having numerous activities both in the Neuroscience Center and on the main NIH campus. Activities included: ***Brains Up Close, Animal Brain Matching, Looking through the Microscope, Hands on Science, Brain Science Coloring Contest, Sharpen Your Brain, Dr. Sciencehead and Brain Derby***. In addition, NIDA once again partnered with NIMH staff who sponsored the activity, ***Put on Your Thinking Cap.*** We also partnered with Archie Fobbs from the National Museum of Health and Medicine who gave an interactive presentation titled ***Your Brain – How It Works and What Happens When It's Injured*** and with Dr. Mark Burke from Howard University who sponsored ***Make a Brain***. Enthusiastic children were able to rotate through the stations and learn about the brain as well as how drugs can impact the brain and body. NIDA and NIMH staff who developed and led the activities included Cathrine Sasek, Stephanie Older, Mary Kautz, Dave Thomas, Roger Sorensen, Heather Kimmel, Maureen Boyle, Kris Bough, Quandra Scudder, Hirsch Davis, Kim DiFonzo, Jen Sizemore, Juli Rose, Josie Anderson, Brian Marquis, Shirley Simson, and Phyllis Quartey-Ampofo.

On March 19, 2015, NIDA participated in the **16th annual Brain Awareness Week** activities at the National Museum of Health and Medicine. Brain Awareness Week is a worldwide celebration of the brain designed to bring neuroscience to children and adults of all ages. NIDA played "***NIDA Brain Derby,***" an interactive fast-moving game designed to teach children about drugs of abuse and neuroscience. The grade levels of the children who participated ranged from 5-8th grade. NIDA's game was enthusiastically received and the children not only learned new things, but they also had a

great time. The NIDA staff who participated included Drs. Cathrine Sasek, Roger Sorensen, Dave Thomas, Dave White, Rik Kline, Heather Kimmel, and Tessa Hall.

NIDA's Office of Diversity and Health Disparities (ODHD) convened a two-day **NIDA Diversity Supplements Workshop** on Thursday and Friday, April 16-17, 2015, at NIDA Headquarters. The workshop brought together 21 current NIDA diversity supplement recipients at the pre-doctoral, postdoctoral, and early career investigator levels, and 20 undergraduate and post baccalaureate-level students from NIDA's *Diversity-promoting Institutions Drug Abuse Research Program (DIDARP)*, to meet and network with NIDA program staff and senior officials, and with NIDA-funded investigators (among them, former NIDA diversity supplement recipients and program directors of three of NIDA's T32 Programs). Workshop participants received valuable information and guidance on NIDA research priorities and funding opportunities, on graduate school and postdoctoral training opportunities at NIDA's research training sites, and on transitioning to independent research careers. This venue also provided recruitment opportunities for the students who are looking to pursue graduate training in substance abuse research. Poster presentations by current diversity supplement recipients highlighted Day Two of the workshop. Pamela Goodlow of ODHD hosted and coordinated the two-day workshop. Dr. Albert Avila, Director, ODHD, presented overviews of NIDA and ODHD activities, and NIDA and NIH funding opportunities.

The NIDA Office of Diversity and Health Disparities led the **19th Annual 2015 NIDA Summer Research Internship Program.** Coordinated by Julie Huffman, the program was a major success, providing 64 high school and undergraduate students with an eight week summer research experience in NIDA funded research labs across the United States. This year, NIDA received over 360 applications from highly qualified high school and undergraduate students in the area of biomedical, behavioral, clinical and the social sciences as it relates to substance-abuse research. A total of 74 applicants received offers, and 64 students accepted an internship. Selected interns were from all backgrounds including: African-American, American Indian/Alaska Native, Asian-American, Hispanic/Latino, Native Hawaiian/Pacific Islander, and White/Caucasian. The NIDA Summer Internship program is designed to build the research pipeline among our budding scientists. Since its inception, over 815 students have been provided invaluable research opportunities. NIDA funded investigators who volunteered to serve as mentors, as well as NIDA staff who assisted with reviewing applications, were instrumental to the program's success.

On February 26-27, 2015, the Office of Diversity and Health Disparities (ODHD) hosted a two-day **Grant Writing and Research Development Workshop** at NIDA in Rockville, Maryland. The overarching goal of the workshop is to provide information on the NIH application and review process aimed at improving the funding of outstanding underrepresented early stage investigators in substance abuse research. Chaired by Dr. Albert Avila, this workshop convened 16 early stage substance abuse investigators, NIDA Program Officials, and NIDA-supported faculty mentors in an intensive workshop setting. During the workshop, new investigators learned of NIDA's research and funding priorities and opportunities, the NIH grants submission and review process, and heard from established investigators on pathways to independence. In addition, participants met individually with NIDA program staff and NIDA funded researchers to receive feedback on their research aims and proposals.

NIDA's Child and Adolescent Workgroup and the Nicotine/Tobacco Interest Group hosted a viewing of the public webinar discussion of the report release of **"Public Health Implications of Raising the Minimum Age of Legal Access to Tobacco Products"** on March 12, 2015 by members of the Institute of Medicine committee at NIDA HQ in Rockville, MD.

The **NIDA CTN Steering Committee Meeting** was held April 14-16, 2015 in Gaithersburg, MD.

From December 2014 to March 2015, the IRP Office of Education and Career Development, Office of the Scientific Director (OECD), together with the NIH Office of Intramural Training and Education, have offered the following workshops or seminars: Giving an Effective Scientific Talk, Preparing for the MCAT and GRE, Correlation of Disease Genes to Phenotypes, Networking for Scientists, Introduction to Grant Writing, Data Visualization, Professional School Planning and Applying, Approaches to Mentoring (3-week seminar), EndNote Web (webinar), FARE Abstract Workshop, K99 Grant Workshop, Creating and Presenting an Award-Winning Poster, Writing and Publishing a Scientific Paper (4-week course), Scientists Teaching Science, Advanced Heatmaps in RStudio, Future of the PhD: Career Options, and Writing Personal Statement for Professional School.

Drs. Nancy Pilotte and Roger Sorensen organized a symposium entitled, **"Refining the Circuitry of Addiction with Cutting-Edge Tools"** at the Neuroscience Center in Rockville, MD on April 10, 2015. Presentations include: Investigating the contributions of distinct prefrontal cortex projection subpopulations to drug seeking using optogenetics and rabies tracing (Rachel Smith/Texas A&M University); Circuit and Genetic Tools to Examine Striatal Cell Subtype Mechanisms in Drug Abuse (Mary Kay Lobo/University of Maryland School of Medicine); Balancing Act: Using DREADDs to delineate the neural circuits that regulate addiction and decision-making (Susan Ferguson/Seattle Children's Research Institute); and Cracking addiction circuitry through optogenetic manipulation and cellular-resolution imaging (Ilana Witten/Princeton University)

On March 25 and 26, 2015, NIDA DPMCDA leadership (David McCann, Phil Skolnick, and Ivan Montoya) presented and chaired sessions during a meeting entitled **"Measures of Outcome for Stimulant Trials (MOST)"** The meeting was jointly planed by NIDA DPMCDA, the FDA, and the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities Networks (ACTTION) public-private partnership with the FDA. It represented the second meeting of the ACTTION Consortium for Addiction Research on Efficacy and Safety (CARES). The primary focus was to: 1) review past efforts in validating outcome measures for clinical trials in cocaine and methamphetamine dependence and 2) identify a research agenda for further efforts toward this goal.

At the **Society for Research in Child Development Biennial Meeting** in Philadelphia, PA, several sessions were sponsored by NIDA on March 19-20, 2015. Dr. Cheryl Anne Boyce co-chaired the symposium "Perspectives for Advancing Child Maltreatment Research and Public Health Implementation" with Dr. Melissa Brodowski, Administration for Children and Families (ACF) and Dr. Melissa Teresa Merrick, Centers for Disease Control and Prevention (CDC) on March 19, 2015. In follow up to a recent SRCD Policy Report, Dr. Boyce chaired a paper symposium "Neuroscience Discovery Informing Child Maltreatment." NIDA's Child and Adolescent Workgroup also coordinated "Research, Priorities and Review Opportunities at NIH and NIDA as part of the Federal

Agency Poster Session where meeting participants were able to meet with federal staff. A research training session on March 20, 2015 entitled "Mock NIH Application and NIH Processes Revealed" included presentations by Dr. Boyce with NIDA colleagues Dr. Aria Crump, Dr. Belinda Sims and Dr. Tisha Wiley (DESPR); and NIH colleagues Dr. Lisa Freund (NICHD), Dr. LeShawndra Price (NIMH), Dr. Mariela Shirley (representing ORWH) and Dr. Anna Riley (CSR). NICHD staff including Dr. Marita Hopmann, Dr. James Griffin, Dr. Layla Esposito, Dr. Lisa Freund, Dr. Kathy Mann Koepke and Dr. Wendy Grolnick (NIH/AAAS Fellow) presented the mock review during that session.

Dr. Ruben Baler, OSPC, presented a workshop on "Addiction: The Neuroscience of Risk and resilience" at CADCA's 25th National Leadership Forum, Gaylord National Harbor, MD, on February 3, 2015.

Dr. Jose Ruiz, DER, presented "Overview of the NIH Peer Review Process and Electronic Submission of Grant Applications," during the NIDA Grant Writing and Research Development workshop held February 26-27, 2015.

Dr. Ruiz was invited to speak at the "Diversity Supplements Workshop," held at NIDA Headquarters in Bethesda, MD on Thursday and Friday, April 16-17, 2015.
Both event were sponsored and run by the NIDA Office of Diversity and Health Disparities.

Dr. Rao Rapaka, DBNBR, attended the 2nd Symposium on Personalized NanoMedicine in Miami, and delivered the Keynote Speech entitled "Novel nanatechnological approaches and their potential applications to drug abuse research" and also served as chair for the Design and Development of Nanoparticles for Personalized Nanomedicine session.

Dr. Minda Lynch, DBNBR, participated in a Society for Neuroscience D.C. chapter Career Panel in April, 2015, in Washington, D.C.

Dr. John Satterlee, DBNBR, presented "Update on Phase 2 Common Fund Planning: Enabling Exploration of the Eukaryotic Epitranscriptome (E4)" to the NIH Council of Councils, Bethesda, MD, Jan 31, 2015.

Dr. John Satterlee presented "Neuroepigenomics: Resources, Obstacles, and Opportunities" at NIAAA Intramural, Rockville, MD, Feb 25, 2015.

Dr. Jonathan Pollock, DBNBR, attended and chaired a breakout session at the Population-Based Rodent Resources for Environmental Health Sciences at the National Institute on Environmental Health Sciences, March 18-19, 2015, Research Triangle,North Carolina.

Dr. Yu (Woody) Lin, DCNBR, was invited by the American Academy of Pain Medicine to organize, moderate and present at training workshop entitled, The Career and Life in Clinical Pain Research. This program outreaching effort aims to foster an increased workforce of clinician scientists among members of the Society. The training was held at the Society's 31th annual conference on March 21, 2015 at National Harbor, MD.

Dr. Yu (Woody) Lin and Dr. Lara Dhingra, Director of the Pain Special Interest Group of the Society of Behavioral Medicine co-organized a symposium entitled, NIH Funding Opportunities on Chronic Pain and Strategies for Optimizing Grant Proposals, held on April 22 – 25, 2015 in San Antonio, TX.

Dr. Harold Gordon, DCNBR, presented at a NIDA grant writing workshop for young investigators held on February 26-27 at the Neuroscience Center, Rockville, MD.

Dr. Steven Grant, DCNBR, spoke at the NIH Funding Workshop at the Cognitive Neuroscience Society Annual Meeting held on March 28– 31, 2015 in San Francisco, CA.

Dr. Cheryl Anne Boyce, DCNBR, attended the National Multicultural Conference and Summit on January 15-16, 2015 in Atlanta, GA.

On March 10, 2015, Dr. Cheryl Anne Boyce presented "Babies, Boys and Men of Color: Perspectives on NIH Funding and Opportunities and Partnerships Related to Developmental Research and Addiction" during the SAMSHA sponsored meeting entitled, Pathways to Behavioral Health Equity: Addressing Disparities Experienced by Boys and Men of Color held March 8-10, 2015 in Washington, DC.

On March 17, 2015, Dr. Cheryl Anne Boyce attended the Spring 2015 Leadership Retreat of the Pediatric HIV/AIDS Cohort Study (PHACS) at the Bolger Hotel and Conference Center in Potomac, MD.

Dr. Cheryl Anne Boyce attended The Prescription Drug Abuse Interagency Meeting on March 17, 2015, hosted by the Office of National Drug Control Policy which was held in Washington, DC. The purpose of the meeting was to bring together Federal government representatives to provide an update on implementation of the prescription drug abuse prevention plan and agency activities concerning consequences including Neonatal Abstinence Syndrome (NAS).

Dr. Samia Noursi, Women and Sex/Gender Differences Research Program and DCNBR, co-chaired a preconference session at the National Conference on Health and Domestic Violence (March 19-21, 2015) entitled "DHHS Intimate Partner Violence Screening and Counseling Research Symposium: Report Findings and Intimate Partner Violence Research Priorities." The session was co-chaired with Drs. Nancy Lee, Deputy Assistant Secretary for Health – Women's Health, and Director, Office on Women's Health, DHHS and Marylouise Kelley, Director, Family Violence Prevention & Services, Family and Youth Services Bureau, Administration for Children and Families, DHHS. This session was attended by over 100 participants and shared the results from the intimate partner violence screening and counseling research symposium held in December 2013 by the Coordinating Committee for Women's Health at the Department of Health and Human Services (DHHS). The symposium was held at the National Institutes of Health (NIH) and was coordinated by many DHHS agencies and was co-chaired by Dr. Noursi.

Dr. Cora Lee Wetherington, Women and Sex/Gender Differences Research Program and DCNBR, co-chaired with Drs. Sherry McKee, Yale University School of Medicine, and Andrea Weinberger, Yeshiva University, the pre-conference workshop, "Moving Beyond 'Mice to Men':

Innovations in Translational Gender-Sensitive Tobacco Research", at the annual meeting of the Society for Research on Nicotine and Tobacco, February 25-28, 2015 in Philadelphia, PA.

Dr. Cora Lee Wetherington gave a talk, "Sex/Gender Research at NIH: What's on the Horizon?" at the workshop, "Moving Beyond 'Mice to Men': Innovations in Translational Gender-Sensitive Tobacco Research", at the annual meeting of the Society for Research on Nicotine and Tobacco, February 25-28, 2015 in Philadelphia, PA.

Dr. Cora Lee Wetherington gave a talk, "Sex/Gender Matters in Your Drug Abuse Research," at the NIDA Meeting with the HHS Humphrey Fellows, Neuroscience Center, April 1, 2015.

Dr. David Thomas, DCNBR, gave a presentation on March 18th, 2015 at the Neuroscience & Society Symposium hosted by The American Association for the Advancement of Science & The Dana Foundation in Washington DC. This presentation was on pain treatment and the National Pain Strategy.

Dr. David Thomas gave a presentation on April 1, 2015 at the Annual Meeting of the American Pharmacology and Experimental Therapeutics meeting held in Boston, MA. The title of his talk was "NIH Efforts to Reduce Prescription Opioid Abuse and Improve Pain Treatment."

Dr. David Thomas gave two presentations on April 17, 2015 to the Interagency Pain Research Coordinating Committee meeting in Bethesda, Md. The titles of his talks were "The Centers of Excellence for Pain Education" and "The Role of Opioids in the Treatment of Chronic Pain."

Dr. Joseph Frascella, Director, DCNBR, gave a presentation entitled, "The Adolescent Brain: Ripe for Addiction? at the Spring Symposium of the Child and Adolescent Psychiatric Society of Greater Washington. This year's theme of the symposium was *Addictions and the Adolescent Brain* and was held on March 7, 2015 at Suburban Hospital in Bethesda, Maryland.

Dr. Joseph Frascella gave a presentation entitled, "Food, Addiction and the Brain" as part of a session of the Annual Meeting of the DC Metro Academy of Nutrition and Dietetics, *Evolution or Revolution: Facilitating Change in Nutrition Practice* held on April 10, 2015 in Washington, DC.

Dr. Cheryl Anne Boyce, DCNBR, served as a reviewer for the Center for Disease Control and Prevention Funding Opportunity Announcement entitled, "Comparison and Validation of Screening Tools For Substance Use Among Pregnant Women" on March 18, 2015.

On February 2, 2015, Dr. Harold Perl, DESPR, organized and led a panel titled, "Linking Community Prevention Activities and Healthcare Systems Under Healthcare Reform" at SAMHSA's 11th Annual Prevention Day, held in conjunction with the CADCA National Leadership Forum, at National Harbor, Maryland.

On February 5, 2015, Dr. Jacqueline Lloyd, DESPR, organized and chaired a panel session titled, "The Changing Marijuana Policy Environment: A Critical Time for Prevention" at the 25th Annual CADCA National Leadership Forum at the National Harbor, Maryland. The panel presenters included Dr. Judy Chang, Dr. William Crano, and Dr. Richard Spoth.

Dr. Jacqueline Lloyd presented at the Society for Social Work Research 19th Annual Conference on an NIH panel session titled, "Research Opportunities at NIH" in New Orleans, Louisiana on January 15, 2015.

Dr. Belinda Sims, DESPR, presented at the Biennial Meeting of the Society for Research in Child Development on a NIH panel session entitled, "Mock NIH Application Review and NIH Processes Revealed," in Philadelphia, Pennsylvania on March 20, 2015.

Dr. Belinda Sims presented at the Biennial Meeting of the Society for Research in Child Development on a federal interagency panel session entitled, "Investigating Early Childhood: Determining Your Match with Agency Initiatives and Priorities, and Available Datasets," in Philadelphia, Pennsylvania on March 19, 2015.

Dr. Aria Crump, DESPR, acted as a panel discussant for the presentation "Why not to get high: Developmental, clinical, and neuroscience research findings on reasons for not using drugs during adolescence" on March 21, 2015 at the Biennial Meeting of the Society for Research on Child Development in Philadelphia, PA.

Dr. Aria Crump participated on a federal panel entitled "Grant Myths, Legends and Rumors: NIH Processes Revealed" on March 20, 2015 at the Biennial Meeting of the Society for Research on Child Development in Philadelphia, PA.

Dr. David McCann, DPMCDA, gave a presentation entitled "Challenges in Developing Medications to Treat Substance Use Disorders (and other CNS Indications)" at the Annual Meeting of the Psychiatric Research Society in Park City, UT on February 4, 2015.

Dr. David McCann presented a poster entitled "What is the Impact of Professional Subjects on Medication Efficacy Trials?" at the Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics in New Orleans, LA on March 5, 2015.

Dr. Jag Khalsa, DPMCDA, gave two talks, one on "HCV in IDUs and Management" and another on "Coronary Atherosclerosis in HIV infected Cocaine Abusers", at the Annual Meeting of Personalized Medicine/Nanomedicine at FIU, Miami, on January 29-30, 2015.

On March 16-17, 2015, Dr. Betty Tai, Director, CCTN, was invited to attend NIAAA's Common Data Elements for Alcoholic Hepatitis (CDE-AH) Workshop, 5625 Fishers Lane (5th Floor Conference room), Rockville, MD. Her presentation topic was "Common data elements for substance use disorders in electronic health records: the NIDA Clinical Trials Network experience".

Dr. Betty Tai is the NIDA Representative and serves on the NIH Task Force on Clinical Trial Stewardship Reforms, which meets monthly.

In February-March 2015, Dr. Paul Wakim, CCTN, gave three 3-hour lectures over 3 days to NIAID staff on "Practical Statistical Reasoning in Clinical Trials". The course covered: trial design; analysis plan; trial monitoring; interim analyses; primary analysis; sensitivity, secondary and subgroup analyses; and reporting results. The lectures were given at NIAID headquarters and

transmitted live by video-conferencing to another location. Continuing education credits were offered to attendees.

Dr. Udi Ghitza, CCTN, organized, chaired, and spoke at a session "Preventing Opioid Overdose Deaths: Practical Skills for Clinicians" at the 2015 National Rx Drug Abuse Summit held April 6-9, 2015 in Atlanta, Georgia.

Dr. Amy Newman, IRP, chaired a symposium entitled "Are you SERTain it is DAT?" at the 48th Annual Winter Conference on Brain Research meeting in Big Sky, MO, in January 2015.

Dr. Amy Newman gave an invited lecture at the Center of Addiction Research, University of Texas Medical Branch, Galveston, TX.

Dr. Amy Newman gave an invited lecture at the Department of Chemistry, Howard University, Washington D.C., in February 2015.
Dr. Amy Newman was invited to give the Special Lecture at the Behavior, Biology, and Chemistry Translational Research in Addiction meeting, in San Antonio, TX in March and served as a panel member for the Pathways to Careers in Science Workshop at this meeting.

Dr. Stephen Heishman, Director, Office of Education and Career Development (OECD), IRP, attended the annual meeting of the Society for Research on Nicotine and Tobacco (SRNT) in Philadelphia in February 2015. He continued his role of advisory co-chair of the Trainee Network of SRNT and represented NIDA IRP at a trainee mixer attended by over 150 graduate students and postdocs.

Dr. Mary Pfeiffer, Assistant Director, Office of Education and Career Development (OECD), IRP, attended the annual meeting of the National Postdoctoral Association in Baltimore in March 2015. She participated in workshops on English as a Second Language education, mentorship, developing postdoc education programs, and establishing training metrics.

Dr. Michael Baumann, IRP, was invited to give an oral presentation entitled "Next generation cathinones differentially affect monoamine transporters" for the neuroscience seminar series at Florida Atlantic University, Boca Raton, FL, on February 24, 2015.

Dr. Michael Baumann presented research data at an invited seminar entitled "Chasing the designer drug phenomenon: 'Breaking bad' for public health" for the Neuropharmacology Interest Group of the National Institute of Mental Health on March 20, 2015.

Dr. Eliot L. Gardner, IRP, gave the keynote opening plenary CME lecture on "Disordered behavior: The neurobiology and underlying basis of craving, relapse, and addiction" at the Addiction Medicine Academy meetings, Clearwater, FL, in March 2015.

Dr. Marilyn Huestis, IRP, was invited to present "Marijuana: From the street to the clinic" on February 11, 2015 at the FDA CDER Seminar.

Dr. Karl Scheidweiler and Dr. Marilyn Huestis, IRP, were invited to teach a short course on toxicological mass spectrometry applications at the Mass Spectrometry Applications to the Clinical Lab (MSACL) on March 29, 2015.

On April 2, 2015, Dr. Kenzie Preston, Chief of the Clinical Pharmacology and Therapeutics Research Branch of NIDA's Intramural Research Program, presented "Continuous in-the-field measurement of physiological correlates of drug use, craving, stress, and mood in opioid/cocaine users." Dr. Preston discussed her group's work with biosensors, specifically heart rate monitoring in the laboratory setting (cocaine administration) and in the field.

Dr. Marilyn Huestis briefed Office of National Drug Control Policy Director Michael Botticelli on recent research findings on drugs and driving and novel psychoactive substances on February 26, 2015.

Dr. Marilyn Huestis was an invited speaker for the technical program symposia on new developments in doping detection on March 8-11 at the Pittcon Conference in New Orleans, LA. Her talk was on "Novel psychoactive substances: The new face of drug abuse."

Dr. Geoffrey Schoenbaum's lab at IRP helped co-organize a meeting on computational neuroscience with Princeton titled RLDM: The Multidisciplinary Conference on Reinforcement Learning and Decision-Making, to be held in Alberta: http://rldm.org . His lab also confirmed support for and began organizing the Third Quadrennial Meeting on Orbitofrontal Function, The Orbitofrontal Cortex and Cognition in the City of Lights, to be held in Paris, France: http://ofc2015.isir.upmc.fr

Dr. George Uhl, IRP, presented an invited talk at Johns Hopkins University

Dr. George Uhl presented an invited talk at the University of New Mexico,

Dr. George Uhl presented an invited talk at the Uniformed Services School of Health Sciences.

Dr. George Uhl presented an invited talk at NIDA's IRP.

Dr. Marisela Morales, IRP, gave an invited lecture at Monitoring Molecules in Neuroscience, Los Angeles CA.

Dr. Elliot Stein, IRP, delivered a talk at the Society for Research in Nicotine and Tobacco, Philadelphia, PA, Feb, 2015 entitled "CYP2A6 genotype differentially shapes striatal-cortical brain circuits and reward processing in smokers but not nonsmokers".

Dr. Zuzana Justinova, IRP, was co-chair and organizer of the Steven R. Goldberg Memorial Symposium that was held at the NIDA-IRP in Baltimore on March 11, 2015. Dr. Justinova and Dr. Charles Schindler gave invited presentations at this symposium.

Dr. Yavin Shaham, IRP, gave an invited lecture at the University of California at San Francisco,

Dr. Yavin Shaham, IRP, gave an invited lecture at the NIH Research Day.

PLANNED MEETINGS

Dr. Yu (Woody) Lin, DCNBR, organized a symposium at 2015 NIDA International Forum entitled, NIDA AIDS and Addiction Research in Vietnam. A panel of NIDA grantees will introduce their work and collaborations in battle against HIV and AIDS epidemics in that country. They will share their recent experience and accomplishment, as well as challenges and approaches to overcome barriers. The meeting is co-sponsored by NIDA DCNBR, AAPI Workgroup, International Program and AIDS Research Program. It will be held on June 12–15, 2015 in Phoenix, AZ.

STAFF HIGHLIGHTS

Staff Honors and Awards

Dr. David Epstein, IRP, is co-chair of the Science Committee for the 2015 CEASE Baltimore tobacco-control research meeting.

Dr. Marilyn Huestis, IRP, received the Distinguished Fellow Award at the American Academy of Forensic Sciences (AAFS) annual meeting on February 18, 2015.

Dr. Marilyn Huestis received the Women Scientists Advisors 2015 NIDA Investigator Excellence in Research Award.

Dr. Richard Jenkins, DESPR, was appointed an Editorial Board member of American Journal of Community Psychology effective March 1, 2015.

Dr. Zuzana Justinova, IRP, received the NIDA Women Scientists Advisors Staff Scientist Award for her productive research career and mentoring of young scientists.

Dr. Yu (Woody) Lin, DCNBR, received the 2015 American Academy of Pain Medicine (AAPM) Presidential Commendations for bringing together the National Institutes of Health and the AAPM membership through a better understanding of NIH grant programs.

Dr. Samia Noursi, Women and Sex/Gender Differences Research Deputy Coordinator, DCNBR, joined, by invitation, the Editorial Board of Violence Research Digest: Translating Research into Policy and Practice. The Violence Research Digest is a new resource created by the National Partnership to End Interpersonal Violence (NPEIV; www.NPEIV.org), in particular its action team "Translation and Dissemination." The overarching mission of this team is to facilitate communication among researchers, policy makers, service providers and practitioners, in such a way that treatment and policy making is informed by research, and researchers are responsive to input from the field.

Dr. Karran Phillips, IRP, was selected to be the Special Symposia Chair for the Society of General Internal Medicine, 2015.

Dr. Rao Rapaka, DBNBR, was selected to receive the “2015 OXFORD International Society for Science of Botanicals (ICSB), Distinguished Achievement Award.” He was cited for creativity, leadership and his contributions to promoting research on natural products’ chemistry, herbals and designer drugs. The award will be presented at the 15th International conference on April13, 2015.

Dr. John Satterlee, DBNBR, is the program lead for RFA-RM-14-008 Study of Nuclear Bodies and Compartments (U01), a new initiative of the Common Fund 4D Nucleome Program.

Dr. Yavin Shaham, IRP, accepted an offer to serve as an Associate (Handling) Editor at Neuropsychopharmacology (the official journal of the ACNP organization.)

Dr. Elliot Stein, IRP, was appointed to the Advisory Boards of the Charleston Alcohol Research Center, Medical University of South Carolina, and the Translational Neuroimaging Analysis Center, Wake Forest School of Medicine.

Dr. Brandon Warren, IRP, received a $2000 IBRO Travel award.

Dr. Cora Lee Wetherington was profiled by the Office of NIH History and Stetten Museum's social media for Women's History Month, March 2015. Social media included Twitter, Pinterest, Facebook, and Tumblr.

Drs. Comfort Boateng and **Rachel Slack**, IRP, were recipients of travel awards for the Behavior, Biology, and Chemistry: Translational Research in Addiction Meeting, in San Antonio, TX and presented talks at that meeting.

Staff Changes

New Employees

Kristen Huntley, Ph.D. joined NIDA's Center for Clinical Trials Network (CCTN) group as a Health Scientist Administrator on March 8, 2015. She came to CCTN from the National Center for Complementary and Integrative Health (NCCIH) where she administered a portfolio of grants focused on the mechanisms of action, efficacy, and effectiveness of complementary health practices used for pain and symptom management in medical and mental health conditions. She led NCCIH efforts to build collaborations with other federal agencies, including the military and veteran populations. She has been most instrumental in facilitating the convening of an NCCIH Council Working Group to make recommendations to NCCIH regarding strengthening research collaborations, and conducting embedded research in clinical care in VA and DoD health care systems leveraging resources and use of medical record data. Previously, Dr. Huntley served as a scientific review officer at NIDA. Before that, she was on the faculty of Case Western Reserve University School of Medicine, Department of Pediatrics and worked as a project manager at Hauser and Associates, Inc., a market research firm in Paramus, New Jersey. Dr. Huntley received a BS in psychology from The University of Texas at Austin, and an M.S. and Ph.D. in clinical psychology from Texas A&M University.

Vani Pariyadath, Ph.D. joined DCNBR as a Program Officer in the Clinical Neuroscience Branch on March 23, 2015. Vani received her Bachelor's degree in Computer Science in 2003, from the University of Pune, and a Master's degree in Cognitive Science in 2005, from the University of Allahabad, both in India. She then joined Dr. David Eagleman's lab in Houston, Texas to begin doctoral research on time perception. Her graduate work investigated the neural underpinnings of time perception, specifically through understanding how duration perception and its underlying neurocircuitry are shaped by novelty and predictability. In the spring of 2010, after receiving a Ph.D. in Neuroscience from Baylor College of Medicine (Houston, Texas), Vani joined the Neuroimaging Research Branch at the NIDA-IRP to carry out postdoctoral research under Dr. Elliot Stein's mentorship. Her work here focused on understanding vulnerability to drug addiction using

behavioral measures combined with multiple MRI techniques. Vani's primary research investigated individual differences in reward and punishment learning, and how these differences are shaped by childhood adversity and how they might influence the risk for nicotine addiction. In addition, she was involved in a project examining the acute effects of MDMA (ecstasy) administration, and in another that applied machine learning approaches to identify neural features predictive of smoking status. Vani's areas of scientific interest and expertise include the cognitive neuroscience of decision-making, risk factors for drug addiction, reward and reinforcement circuits, time perception, and the application of big analytical methods to brain imaging. Her interests are in using behavioral measures and neuroimaging to address questions in these areas.

Destiny Aighe joined NIDA's OM/OA NIDA R&D Branch as a Contract Specialist on April 19, 2015. Destiny comes to NIDA from the private sector.

Gary Berkson joined NIDA's OM/OA NIDA R&D Branch as a Contract Specialist on April 19, 2015. Gary comes to NIDA from the private sector.

Daniel Collector joined the IRP's Molecular Neuropsychiatry Research Branch as a post-baccalaureate IRTA in January 2015.

Arthur Godino, a graduate student from the Ecole Normale Supérieure de Lyon, France is being trained to conduct epigenetic studies under the supervision of Drs. Oscar Torres and Subramaniam Jayanthi in the Molecular Neuropsychiatry Research Branch. He is pursuing a master's degree in Biology in Lyon and will apply these techniques when he returns to France.

Jacqueline Keighron, Ph.D., has joined the IRP's Medication Development Program as a post-doctoral fellow. Dr. Keighron will be involved in research projects about the functional characterization of different afferent inputs to the ventral tegmental area using optogenetic and voltammetry procedures.

Keshia McDonald joined NIDA's OM/OA Station Support Branch as a Contract Specialist on April 19, 2015. Keshia comes to NIDA from the private sector.

Christopher Weaver joined NIDA's OM/OA NIDA R&D Branch as a Contract Specialist on April 19, 2015. Christopher comes to NIDA from the private sector.

Departures

Dr. Eve Reider of DESPR's Prevention Research Branch accepted a position at the National Center for Complementary and Integrative Health (NCCIH) (formerly NCCAM) in March 2015. During her 15 year tenure at NIDA, Eve focused her efforts on the goals of advancing prevention science and improving public health. At NCCIH, she will be leading their military/veteran initiative and expanding their prevention/health promotion portfolio.

Dr. George Uhl, IRP, accepted a position as Associate Chief of Staff for Research at the New Mexico VA Health care system, and President of the Biomedical Research Foundation of New

Mexico. He became a Guest Researcher at, and will continue to lead under the direction of J-L Cadet, the NIDA Molecular Neurobiology Research laboratory, which is becoming a section in Dr. Cadet's Molecular Neuropsychiatry Research Branch at the NIDA IRP.

Debasis Goswami, an Information Technology Specialist in the Office of Management's Information and Resource Management Branch left NIDA on March 3, 2015 for a position at NHLBI.

Patrick Kenney, a Contract Specialist in the OM/OA NIDA R&D Branch, left NIDA on March 21, 2015, for a position with the Veteran's Administration.

Shaun Miles, a Contract Specialist in the OM/OA Station Support Branch left NIDA on February 21, 2015, for a position with the Department of the Navy.

Retirements

David (Davey) Jones, a loyal and dedicated Mail and File Clerk in the Office of Management's Administrative Management and Analysis Branch retired from Federal Service on April 3, 2015 after 45 years of outstanding service to NIDA.

Harriette Jordan, a Secretary in the Office of Management's Administrative Management and Analysis Branch who has made substantial contributions to NIDA's mission and served in variety of key roles during her 20 year tenure, retired on April 3, 2015 after 35 years of Federal Service.

GRANTEE HONORS

Dr. Karl Deisseroth, D. H. Chen Professor of Bioengineering and of Psychiatry and Behavioral Sciences at Stanford University was awarded the Lurie Prize by the FNIH foundation.

Dr. Adam M. Leventhal, Associate Professor at the University of Southern California Keck School of Medicine, was awarded the Jarvik-Russell Early Career Award at the 2015 Society for Research on Nicotine and Tobacco meeting. This award, named after Murray Jarvik and Michael Russell, recognizes scientists early in their careers who have made extraordinary contributions to the field of nicotine and tobacco research.