FEBRUARY 2016
STAFF REPORT to the NIDA DIRECTOR

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RESEARCH FINDINGS

BASIC AND BEHAVIORAL RESEARCH

Nonmuscle Myosin IIB As a Therapeutic Target For the Prevention Of Relapse To Methamphetamine Use Young EJ, Blouin AM, Briggs SB, Sillivan SE, Lin L, Cameron MD, Rumbaugh G, Miller CA. Mol Psychiatry. 2015.
Memories associated with drug use increase vulnerability to relapse in substance use disorder (SUD), and there are no pharmacotherapies for the prevention of relapse. Previously, the authors reported a promising finding that storage of memories associated with methamphetamine (METH), but not memories for fear or food reward, is vulnerable to disruption by actin depolymerization in the basolateral amygdala complex (BLC). However, actin is not a viable therapeutic target because of its numerous functions throughout the body. Here the authors report the discovery of a viable therapeutic target, nonmuscle myosin IIB (NMIIB), a molecular motor that supports memory by directly driving synaptic actin polymerization. A single intra-BLC treatment with Blebbistatin (Blebb), a small-molecule inhibitor of class II myosin isoforms, including NMIIB, produced a long-lasting disruption of context-induced drug seeking (at least 30 days). Further, postconsolidation genetic knockdown of Myh10, the heavy chain of the most highly expressed NMII in the BLC, was sufficient to produce METH-associated memory loss. Blebb was found to be highly brain penetrant. A single systemic injection of the compound selectively disrupted the storage of METH-associated memory and reversed the accompanying increase in BLC spine density. This effect was specific to METH-associated memory, as it had no effect on an auditory fear memory. The effect was also independent of retrieval, as METH-associated memory was disrupted 24 h after a single systemic injection of Blebb delivered in the home cage. Together, these results argue for the further development of small-molecule inhibitors of NMII as potential therapeutics for the prevention of SUD relapse triggered by drug associations.Molecular Psychiatry advance online publication, 4 August 2015; doi:10.1038/mp.2015.103.

Gq-DREADD Selectively Initiates Glial Glutamate Release and Inhibits Cue-induced Cocaine Seeking Scofield MD, Boger HA, Smith RJ, Li H, Haydon PG, Kalivas PW. Biol Psychiatry. 2015; 78(7): 441-451.
Glial cells of the central nervous system directly influence neuronal activity by releasing neuroactive small molecules, including glutamate. Long-lasting cocaine-induced reductions in extracellular glutamate in the nucleus accumbens core (NAcore) affect synaptic plasticity responsible for relapse vulnerability. The authors transduced NAcore astrocytes with an adeno-associated virus vector expressing hM3D designer receptor exclusively activated by a designer drug (DREADD) under control of the glial fibrillary acidic protein promoter in 62 male Sprague Dawley rats, 4 dominant-negative soluble N-ethylmaleimide-sensitive factor attachment protein receptor mice, and 4 wild-type littermates. Using glutamate biosensors, they measured NAcore glutamate levels following intracranial or systemic administration of clozapine N-oxide (CNO) and tested the ability of systemic CNO to inhibit reinstated cocaine or sucrose seeking following self-administration and extinction training.Administration of CNO in glial fibrillary acidic protein-hM3D-DREADD transfected animals increased NAcore extracellular glutamate levels in vivo. The glial origin of released glutamate was validated by an absence of CNO-mediated release in mice expressing a dominant-negative soluble N-ethylmaleimide-sensitive factor attachment protein receptor variant in glia. Also, CNO-mediated release was relatively insensitive to N-type calcium

channel blockade. Systemic administration of CNO inhibited cue-induced reinstatement of cocaine seeking in rats extinguished from cocaine but not sucrose self-administration. The capacity to inhibit reinstated cocaine seeking was prevented by systemic administration of the group II metabotropic glutamate receptor antagonist LY341495.DREADD-mediated glutamate gliotransmission inhibited cue-induced reinstatement of cocaine seeking by stimulating release-regulating group II metabotropic glutamate receptor autoreceptors to inhibit cue-induced synaptic glutamate spillover.

Evidence Of CNIH3 Involvement In Opioid Dependence Nelson EC, Agrawal A, Heath AC, Bogdan R, Sherva R, Zhang B, Al-Hasani R, Bruchas MR, Chou Y-L, Demers CH, Carey CE, Conley ED, Fakira AK, Farrer LA, Goate A, Gordon S, Henders AK, Hesselbrock V, Kapoor M, Lynskey MT, Madden PAF, Moron JA, Rice JP, Saccone NL, Schwab SG, Shand FL, Todorov AA, Wallace L, Wang T, Wray NR, Zhou X, Degenhardt L, Martin NG, Hariri AR, Kranzler HR, Gelernter J, Bierut LJ, Clark DJ, Montgomery GW. Mol Psychiatry. 2015.
Opioid dependence, a severe addictive disorder and major societal problem, has been demonstrated to be moderately heritable. The authors conducted a genome-wide association study in Comorbidity and Trauma Study data comparing opioid-dependent daily injectors (N=1167) with opioid misusers who never progressed to daily injection (N=161). The strongest associations, observed for CNIH3 single-nucleotide polymorphisms (SNPs), were confirmed in two independent samples, the Yale-Penn genetic studies of opioid, cocaine and alcohol dependence and the Study of Addiction: Genetics and Environment, which both contain non-dependent opioid misusers and opioid-dependent individuals. Meta-analyses found five genome-wide significant CNIH3 SNPs. The A allele of rs10799590, the most highly associated SNP, was robustly protective (P=4.30E-9; odds ratio 0.64 (95% confidence interval 0.55-0.74)). Epigenetic annotation predicts that this SNP is functional in fetal brain. Neuroimaging data from the Duke Neurogenetics Study (N=312) provide evidence of this SNP's in vivo functionality; rs10799590 A allele carriers displayed significantly greater right amygdala habituation to threat-related facial expressions, a phenotype associated with resilience to psychopathology. Computational genetic analyses of physical dependence on morphine across 23 mouse strains yielded significant correlations for haplotypes in CNIH3 and functionally related genes. These convergent findings support CNIH3 involvement in the pathophysiology of opioid dependence, complementing prior studies implicating the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate system.Molecular Psychiatry advance online publication, 4 August 2015; doi:10.1038/mp.2015.102.

Transplantation Of Human Retinal Pigment Epithelial Cells In the Nucleus Accumbens Of Cocaine Self-Administering Rats Provides Protection From Reinstatement Venkiteswaran K, Alexander DN, Puhl MD, Rao A, Piquet AL, Nyland JE, Subramanian MP, Iyer P, Boisvert MM, Handly E, Subramanian T, Grigson PS. Brain Res Bull. 2015 Nov 10. pii: S0361-9230(15)30060-5. doi: 10.1016/j.brainresbull.2015.11.008. [Epub ahead of print].
Chronic exposure to drugs and alcohol leads to damage to dopaminergic neurons and their projections in the 'reward pathway' that originate in the ventral tegmental area (VTA) and terminate in the nucleus accumbens (NAc). This damage is thought to contribute to the signature symptom of addiction: chronic relapse. In this study the authors show that bilateral transplants of human retinal pigment epithelial cells (RPECs), a cell mediated dopaminergic and trophic neuromodulator, into the medial shell of the NAc, rescue rats with a history of high rates of cocaine self-administration from drug-seeking when returned, after 2 weeks of abstinence, to the drug-associated chamber under extinction conditions (i.e., with no drug available). Excellent survival was noted for the

transplant of RPECs in the shell and/or the core of the NAc bilaterally in all rats that showed behavioral recovery from cocaine seeking. Design based unbiased stereology of tyrosine hydroxylase (TH) positive cell bodies in the VTA showed better preservation ($p<0.035$) in transplanted animals compared to control animals. This experiment shows that RPEC grafts provide beneficial effects to prevent chronic relapse in drug addiction via its effects directly on the NAc and its neural network with the VTA.

Endocannabinoid Signaling Mediates Oxytocin-Driven Social Reward Wei D, Lee D, Cox CD, Karsten CA, Peñagarikano O, Geschwind DH, Gall CM, Piomelli D. Proc Natl Acad Sci U S A. 2015 Nov 10;112(45):14084-9. doi: 10.1073/pnas.1509795112. Epub 2015 Oct 26.
Marijuana exerts profound effects on human social behavior, but the neural substrates underlying such effects are unknown. Here the authors report that social contact increases, whereas isolation decreases, the mobilization of the endogenous marijuana-like neurotransmitter, anandamide, in the mouse nucleus accumbens (NAc), a brain structure that regulates motivated behavior. Pharmacological and genetic experiments show that anandamide mobilization and consequent activation of CB1 cannabinoid receptors are necessary and sufficient to express the rewarding properties of social interactions, assessed using a socially conditioned place preference test. The authors further show that oxytocin, a neuropeptide that reinforces parental and social bonding, drives anandamide mobilization in the NAc. Pharmacological blockade of oxytocin receptors stops this response, whereas chemogenetic, site-selective activation of oxytocin neurons in the paraventricular nucleus of the hypothalamus stimulates it. Genetic or pharmacological interruption of anandamide degradation offsets the effects of oxytocin receptor blockade on both social place preference and cFos expression in the NAc. The results indicate that anandamide-mediated signaling at CB1 receptors, driven by oxytocin, controls social reward. Deficits in this signaling mechanism may contribute to social impairment in autism spectrum disorders and might offer an avenue to treat these conditions.

A Cannabinoid CB1 Receptor-Positive Allosteric Modulator Reduces Neuropathic Pain In the Mouse With No Psychoactive Effects Ignatowska-Jankowska BM, Baillie GL, Kinsey S, Crowe M, Ghosh S, Owens RA, Damaj IM, Poklis J, Wiley JL, Zanda M, Zanato C, Greig IR, Lichtman AH, Ross RA. Neuropsychopharmacology. 2015; 40(13): 2948-2959.
The CB1 receptor represents a promising target for the treatment of several disorders including pain-related disease states. However, therapeutic applications of Δ(9)-tetrahydrocannabinol and other CB1 orthosteric receptor agonists remain limited because of psychoactive side effects. Positive allosteric modulators (PAMs) offer an alternative approach to enhance CB1 receptor function for therapeutic gain with the promise of reduced side effects. Here the authors describe the development of the novel synthetic CB1 PAM, 6-methyl-3-(2-nitro-1-(thiophen-2-yl)ethyl)-2-phenyl-1H-indole (ZCZ011), which augments the in vitro and in vivo pharmacological actions of the CB1 orthosteric agonists CP55,940 and N-arachidonoylethanolamine (AEA). ZCZ011 potentiated binding of [(3)H]CP55,940 to the CB1 receptor as well as enhancing AEA-stimulated [(35)S]GTPγS binding in mouse brain membranes and β-arrestin recruitment and ERK phosphorylation in hCB1 cells. In the whole animal, ZCZ011 is brain penetrant, increased the potency of these orthosteric agonists in mouse behavioral assays indicative of cannabimimetic activity, including antinociception, hypothermia, catalepsy, locomotor activity, and in the drug discrimination paradigm. Administration of ZCZ011 alone was devoid of activity in these assays and did not produce a conditioned place preference or aversion, but elicited CB1 receptor-mediated antinociceptive effects in the chronic constriction nerve injury model of neuropathic pain and

carrageenan model of inflammatory pain. These data suggest that ZCZ011 acts as a CB1 PAM and provide the first proof of principle that CB1 PAMs offer a promising strategy to treat neuropathic and inflammatory pain with minimal or no cannabimimetic side effects.

The Effects Of Cocaine On HIV Transcription Tyagi M, Weber J, Bukrinsky M, Simon GL. J Neurovirol. 2015.
Illicit drug users are a high-risk population for infection with the human immunodeficiency virus (HIV). A strong correlation exists between prohibited drug use and an increased rate of HIV transmission. Cocaine stands out as one of the most frequently abused illicit drugs, and its use is correlated with HIV infection and disease progression. The central nervous system (CNS) is a common target for both drugs of abuse and HIV, and cocaine intake further accelerates neuronal injury in HIV patients. Although the high incidence of HIV infection in illicit drug abusers is primarily due to high-risk activities such as needle sharing and unprotected sex, several studies have demonstrated that cocaine enhances the rate of HIV gene expression and replication by activating various signal transduction pathways and downstream transcription factors. In order to generate mature HIV genomic transcript, HIV gene expression has to pass through both the initiation and elongation phases of transcription, which requires discrete transcription factors. In this review, the authors will provide a detailed analysis of the molecular mechanisms that regulate HIV transcription and discuss how cocaine modulates those mechanisms to upregulate HIV transcription and eventually HIV replication.

ADAR2-dependent GluA2 Editing Regulates Cocaine Seeking Schmidt HD, McFarland KN, Darnell SB, Huizenga MN, Sangrey GR, Cha J-HJ, Pierce RC, Sadri-Vakil G. Mol Psychiatry. 2015; 20(11): 1460-1466.
Activation of AMPA receptors (AMPARs) in the nucleus accumbens is necessary for the reinstatement of cocaine-seeking behavior, an animal model of drug craving and relapse. AMPARs are tetrameric protein complexes that consist of GluA1-4 subunits, of which GluA2 imparts calcium permeability. Adenosine deaminase acting on RNA 2 (ADAR2) is a nuclear enzyme that is essential for editing GluA2 pre-mRNA at Q/R site 607. Unedited GluA2(Q) subunits form calcium-permeable AMPARs (CP-AMPARs), whereas edited GluA2(R) subunits form calcium-impermeable channels (CI-AMPARs). Emerging evidence suggests that the reinstatement of cocaine seeking is associated with increased synaptic expression of CP-AMPARs in the nucleus accumbens. However, the role of GluA2 Q/R site editing and ADAR2 in cocaine seeking is unclear. In the present study, the authors investigated the effects of forced cocaine abstinence on GluA2 Q/R site editing and ADAR2 expression in the nucleus accumbens. Their results demonstrate that 7 days of cocaine abstinence is associated with decreased GluA2 Q/R site editing and reduced ADAR2 expression in the accumbens shell, but not core, of cocaine-experienced rats compared with yoked saline controls. To examine the functional significance of ADAR2 and GluA2 Q/R site editing in cocaine seeking, the authors used viral-mediated gene delivery to overexpress ADAR2b in the accumbens shell. Increased ADAR2b expression in the shell attenuated cocaine priming-induced reinstatement of drug seeking and was associated with increased GluA2 Q/R site editing and surface expression of GluA2-containing AMPARs. Taken together, these findings support the novel hypothesis that an increased contribution of accumbens shell CP-AMPARs containing unedited GluA2(Q) promotes cocaine seeking. Therefore, CP-AMPARs containing unedited GluA2(Q) represent a novel target for cocaine addiction pharmacotherapies.

Genome-Wide DNA Methylation Profiling Reveals Epigenetic Changes In the Rat Nucleus Accumbens Associated With Cross-Generational Effects Of Adolescent THC Exposure
Watson CT, Szutorisz H, Garg P, Martin Q, Landry JA, Sharp AJ, Hurd YL.
Neuropsychopharmacology. 2015; 40(13): 2993-3005.
Drug exposure during critical periods of development is known to have lasting effects, increasing one's risk for developing mental health disorders. Emerging evidence has also indicated the possibility for drug exposure to even impact subsequent generations. The authors' previous work demonstrated that adolescent exposure to Δ(9)-tetrahydrocannabinol (THC), the main psychoactive component of marijuana (Cannabis sativa), in a Long-Evans rat model affects reward-related behavior and gene regulation in the subsequent (F1) generation unexposed to the drug. Questions, however, remained regarding potential epigenetic consequences. In the current study, using the same rat model, the authors employed Enhanced Reduced Representation Bisulfite Sequencing to interrogate the epigenome of the nucleus accumbens, a key brain area involved in reward processing. This analysis compared 16 animals with parental THC exposure and 16 without to characterize relevant systems-level changes in DNA methylation. The authors identified 1027 differentially methylated regions (DMRs) associated with parental THC exposure in F1 adults, each represented by multiple CpGs. These DMRs fell predominantly within introns, exons, and intergenic intervals, while showing a significant depletion in gene promoters. From these, they identified a network of DMR-associated genes involved in glutamatergic synaptic regulation, which also exhibited altered mRNA expression in the nucleus accumbens. These data provide novel insight into drug-related cross-generational epigenetic effects, and serve as a useful resource for investigators to explore novel neurobiological systems underlying drug abuse vulnerability.

Naltrexone Maintenance Decreases Cannabis Self-Administration and Subjective Effects In Daily Cannabis Smokers Haney M, Ramesh D, Glass A, Pavlicova M, Bedi G, Cooper ZD.
Neuropsychopharmacology. 2015; 40(11): 2489-2498.
Given that cannabis use is increasing in the United States, pharmacological treatment options to treat cannabis use disorder are needed. Opioid antagonists modulate cannabinoid effects and may offer a potential approach to reducing cannabis use. In this double-blind, placebo-controlled human laboratory study, the authors assessed the effects of naltrexone maintenance on the reinforcing, subjective, psychomotor, and cardiovascular effects of active and inactive cannabis. Nontreatment-seeking, daily cannabis smokers were randomized to receive naltrexone (50 mg: n=18 M and 5 F) or placebo (0 mg; n=26 M and 2 F) capsules for 16 days. Before, during, and after medication maintenance, participants completed 10 laboratory sessions over 4-6 weeks, assessing cannabis' behavioral and cardiovascular effects. Medication compliance was verified by observed capsule administration, plasma naltrexone, and urinary riboflavin. Relative to placebo, maintenance on naltrexone significantly reduced both active cannabis self-administration and its positive subjective effects ('good effect'). Participants in the placebo group had 7.6 times (95% CI: 1.1-51.8) the odds of self-administering active cannabis compared with the naltrexone group. This attenuation of reinforcing and positive subjective effects also influenced cannabis use in the natural ecology. Naltrexone had intrinsic effects: decreasing ratings of friendliness, food intake, and systolic blood pressure, and increasing spontaneous reports of stomach upset and headache, yet dropout rates were comparable between groups. In summary, the authors show for the first time that maintenance on naltrexone decreased cannabis self-administration and ratings of 'good effect' in nontreatment-seeking daily cannabis smokers. Clinical studies in patients motivated to reduce their cannabis use are warranted to evaluate naltrexone's efficacy as a treatment for cannabis use disorder.

Pharmacodynamics Of Folic Acid Receptor Targeted Antiretroviral Nanotherapy In HIV-1-infected Humanized Mice Puligujja P, Araínga M, Dash P, Palandri D, Mosley RL, Gorantla S, Poluektova L, McMillan J, Gendelman H E. Antiviral Res. 2015; 120: 85-88.
Long-acting nanoformulated antiretroviral therapy (nanoART) can sustain plasma drug levels and improve its biodistribution. Cell targeted-nanoART can achieve this and bring drug efficiently to viral reservoirs. However, whether such improvements affect antiretroviral responses remains unknown. To these ends, the authors tested folic acid (FA)-linked poloxamer407-coated ritonavir-boosted atazanavir (FA-nanoATV/r) nanoparticles for their ability to affect chronic HIV-1 infection in humanized mice. Following three, 100mg/kg FA-nanoATV/r intramuscular injections administered every other week to infected animals, viral RNA was at or below the detection limit, cell-associated HIV-1p24 reduced and CD4+ T cell counts protected. The dosing regimen improved treatment outcomes more than two fold from untargeted nanoATV/r. The authors posit that these nanoformulations have potential for translation to human use.

Differences In Bingeing Behavior and Cocaine Reward Following Intermittent Access To Sucrose, Glucose Or Fructose Solutions Rorabaugh JM, Stratford JM, Zahniser NR. Neuroscience. 2015; 301: 213-220.
Daily intermittent access to sugar solutions results in intense bouts of sugar intake (i.e. bingeing) in rats. Bingeing on sucrose, a disaccharide of glucose and fructose, has been associated with a "primed" mesolimbic dopamine (DA) pathway. Recent studies suggest glucose and fructose engage brain reward and energy-sensing mechanisms in opposing ways and may drive sucrose intake through unique neuronal circuits. Here, the authors examined in male Sprague-Dawley rats whether or not (1) intermittent access to isocaloric solutions of sucrose, glucose or fructose results in distinctive sugar-bingeing profiles and (2) previous sugar bingeing alters cocaine locomotor activation and/or reward, as determined by conditioned place preference (CPP). To encourage bingeing, rats were given 24-h access to water and 12-h-intermittent access to chow plus an intermittent bottle that contained water (control) or 8% solutions of sucrose, glucose or fructose for 9days, followed by ad libitum chow diet and a 10-day cocaine (15mg/kg; i.p.) CPP paradigm. By day 4 of the sugar-bingeing diet, sugar bingeing in the fructose group surpassed the glucose group, with the sucrose group being intermediate. All three sugar groups had similar chow and water intake throughout the diet. In contrast, controls exhibited chow bingeing by day 5 without altering water intake. Similar magnitudes of cocaine CPP were observed in rats with a history of sucrose, fructose or chow (control) bingeing. Notably, the glucose-bingeing rats did not demonstrate a significant cocaine CPP despite showing similar cocaine-induced locomotor activity as the other diet groups. Overall, these results show that fructose and glucose, the monosaccharide components of sucrose, produce divergent degrees of bingeing and cocaine reward.

Increased Sensitivity To Cocaine Self-Administration In HIV-1 Transgenic Rats Is Associated With Changes In Striatal Dopamine Transporter Binding McIntosh S, Sexton T, Pattison LP, Childers SR, Hemby SE. J Neuroimmune Pharmacol. 2015; 10(3): 493-505.
Cocaine abuse in HIV patients accelerates the progression and severity of neuropathology, motor impairment and cognitive dysfunction compared to non-drug using HIV patients. Cocaine and HIV interact with the dopamine transporter (DAT); however, the effect of their interaction on DAT binding remains understudied. The present study compared the dose-response functions for intravenous self-administration of cocaine and heroin between male HIV-1 transgenic (HIV-1 Tg) and Fischer 344 rats. The cocaine and heroin dose-response functions exhibit an inverted U-shape for both HIV-1 Tg and F344 rats. For cocaine, the number of infusions for each dose on the

ascending limb was greater for HIV-1 Tg versus F344 rats. No significant changes in the heroin dose-response function were observed in HIV-1 Tg animals. Following the conclusion of self-administration experiments, DAT binding was assessed in striatal membranes. Saturation binding of the cocaine analog [(125)I] 3β-(4-iodophenyl)tropan-2β-carboxylic acid methyl ester ([(125)I]RTI-55) in rat striatal membranes resulted in binding curves that were best fit to a two-site binding model, allowing for calculation of dissociation constant (Kd) and binding density (Bmax) values that correspond to high- and low-affinity DAT binding sites. Control HIV-1 Tg rats exhibited a significantly greater affinity (i.e., decrease in Kd value) in the low-affinity DAT binding site compared to control F344 rats. Furthermore, cocaine self-administration in HIV-1 Tg rats increased low-affinity Kd (i.e., decreased affinity) compared to levels observed in control F344 rats. Cocaine also increased low-affinity Bmax in HIV-1 Tg rats as compared to controls, indicating an increase in the number of low-affinity DAT binding sites. F344 rats did not exhibit any change in high- or low-affinity Kd or Bmax values following cocaine or heroin self-administration. The increase in DAT affinity in cocaine HIV-1 Tg rats is consistent with the leftward shift of the ascending limb of the cocaine dose-response curve observed in HIV-1 Tg vs. F344 rats, and has major implications for the function of cocaine binding to DAT in HIV patients. The absence of HIV-related changes in heroin intake are likely due to less dopaminergic involvement in the mediation of heroin reward, further emphasizing the preferential influence of HIV on dopamine-related behaviors.

The Role Of Ventral Striatal CAMP Signaling In Stress-induced Behaviors Plattner F, Hayashi K, Hernández A, Benavides DR, Tassin TC, Tan C, Day J, Fina MW, Yuen EY, Yan Z, Goldberg MS, Nairn AC, Greengard P, Nestler EJ, Taussig R, Nishi A, Houslay MD, Bibb JA. Nat Neurosci. 2015; 18(8): 1094-1100.
The cAMP and cAMP-dependent protein kinase A (PKA) signaling cascade is a ubiquitous pathway acting downstream of multiple neuromodulators. The authors found that the phosphorylation of phosphodiesterase-4 (PDE4) by cyclin-dependent protein kinase 5 (Cdk5) facilitated cAMP degradation and homeostasis of cAMP/PKA signaling. In mice, loss of Cdk5 throughout the forebrain elevated cAMP levels and increased PKA activity in striatal neurons, and altered behavioral responses to acute or chronic stressors. Ventral striatum- or D1 dopamine receptor-specific conditional knockout of Cdk5, or ventral striatum infusion of a small interfering peptide that selectively targeted the regulation of PDE4 by Cdk5, produced analogous effects on stress-induced behavioral responses. Together, these results demonstrate that altering cAMP signaling in medium spiny neurons of the ventral striatum can effectively modulate stress-induced behavioral states. The authors propose that targeting the Cdk5 regulation of PDE4 could be a new therapeutic approach for clinical conditions associated with stress, such as depression.

Effects Of Consuming A Diet High In Fat and/or Sugar On the Locomotor Effects Of Acute and Repeated Cocaine In Male and Female C57BL/6J Mice Collins GT, Chen Y, Tschumi C, Rush EL, Mensah A, Koek W, France CP. Exp Clin Psychopharmacol. 2015; 23(4): 228-237.
Drug abuse and obesity are serious public health problems. Dopamine plays a central role in mediating the reinforcing effects of drugs and food. Prolonged use of drugs is known to alter the function and/or sensitivity of many neurotransmitter systems, including dopamine; however, the impact of consuming foods high in fat and/or sugar is less clear. These studies characterized the locomotor effects of acute and repeated cocaine in male and female C57BL/6J mice consuming 1 of 4 diets: (a) standard chow + water; (b) standard chow + 10% sucrose solution; (c) high-fat chow + water; or (d) high-fat chow + 10% sucrose solution. The acute locomotor effects of cocaine (3.2-32.0 mg/kg) were evaluated 4 weeks after initiating dietary conditions; the effects of repeated

cocaine administration were evaluated after 5, 6, 7, and 12 weeks. During acute tests, mice consuming a diet high in fat and/or sucrose exhibited greater locomotor responses to cocaine than mice consuming standard chow and water, regardless of sex. Although diet-induced enhancements persisted across repeated cocaine testing, locomotor sensitization developed more rapidly in females drinking sucrose (and consuming either standard or high-fat chow) than in females consuming standard chow and water. In addition to providing evidence that consuming a diet high in fat and/or sugar enhances abuse-related effects of cocaine in ways that might increase vulnerability to abuse cocaine, these studies identified a potentially important sex-related difference in the interaction between nutrition and cocaine effects, with the impacts of sucrose consumption being greater in females than in males.

An Animal Model Of Female Adolescent Cannabinoid Exposure Elicits A Long-lasting Deficit In Presynaptic Long-term Plasticity Lovelace JW, Corches A, Vieira PA, Hiroto AS, Mackie K, Korzus E. Neuropharmacology. 2015; 99: 242-255.
Cannabis continues to be the most accessible and popular illicit recreational drug. Whereas current data link adolescence cannabinoid exposure to increased risk for dependence on other drugs, depression, anxiety disorders and psychosis, the mechanism(s) underlying these adverse effects remains controversial. Here the authors show in a mouse model of female adolescent cannabinoid exposure deficient endocannabinoid (eCB)-mediated signaling and presynaptic forms of long-term depression at adult central glutamatergic synapses in the prefrontal cortex. Increasing endocannabinoid levels by blockade of monoacylglycerol lipase, the primary enzyme responsible for degrading the endocannabinoid 2-arachidonoylglycerol (2-AG), with the specific inhibitor JZL 184 ameliorates eCB-LTD deficits. The observed deficit in cortical presynaptic signaling may represent a neural maladaptation underlying network instability and abnormal cognitive functioning. This study suggests that adolescent cannabinoid exposure may permanently impair brain functions, including the brain's intrinsic ability to appropriately adapt to external influences.

Hyperactivation To Pleasant Interoceptive Stimuli Characterizes the Transition To Stimulant Addiction Stewart JL, May AC, Tapert SF, Paulus MP. Drug Alcohol Depend. 2015; 154: 264-270.
Altered interoception, how the brain processes afferents from the body, may contribute to the urge to take drugs, and subsequently, the development of addiction. Although chronic stimulant dependent individuals exhibit attenuated brain responses to pleasant interoceptive stimuli, it is unclear whether this deficit exists early-on in the process of transition to stimulant addiction. To this end, the authors compared problem stimulant users (PSU; n=18), desisted stimulant users (DSU; n=15), and stimulant naïve comparison subjects (CTL; n=15) during functional magnetic resonance imaging (fMRI) while they anticipated and experienced pleasant soft touch (slow brushstroke to the palm and forearm). Groups did not differ in behavioral performance or visual analog scale ratings of soft touch stimuli. fMRI results indicated that PSU exhibited greater right anterior insula, left inferior frontal gyrus, and right superior frontal gyrus activation than DSU and CTL during the anticipation and experience of soft touch. Moreover, during the experience of soft touch, PSU demonstrated higher bilateral precentral gyrus/middle insula and right posterior temporal gyrus activation than DSU and CTL. In contrast to chronic stimulant dependence, individuals who have recently developed stimulant use disorders show exaggerated neural processing of pleasant interoceptive stimuli. Thus, increased processing of body-relevant information signaling pleasant touch in those individuals who develop problem use may be a predictive interoceptive biomarker. However, future investigations will need to determine whether the combination of probing pleasant

interoception using neuroimaging is sufficiently sensitive and specific to help identify individuals at high risk for future problem use.

A Gene-based Association Method For Mapping Traits Using Reference Transcriptome Data Gamazon ER, Wheeler HE, Shah KP, Mozaffari SV, Aquino-Michaels K, Carroll RJ, Eyler AE, Denny JC, GTEx Consortium, Nicolae DL, Cox NJ, Im HK. Nat Genet. 2015; 47(9): 1091-1098.
Genome-wide association studies (GWAS) have identified thousands of variants robustly associated with complex traits. However, the biological mechanisms underlying these associations are, in general, not well understood. The authors propose a gene-based association method called PrediXcan that directly tests the molecular mechanisms through which genetic variation affects phenotype. The approach estimates the component of gene expression determined by an individual's genetic profile and correlates 'imputed' gene expression with the phenotype under investigation to identify genes involved in the etiology of the phenotype. Genetically regulated gene expression is estimated using whole-genome tissue-dependent prediction models trained with reference transcriptome data sets. PrediXcan enjoys the benefits of gene-based approaches such as reduced multiple-testing burden and a principled approach to the design of follow-up experiments. Our results demonstrate that PrediXcan can detect known and new genes associated with disease traits and provide insights into the mechanism of these associations.

Propagation Of Conformational Changes During M-opioid Receptor Activation Sounier R, Mas C, Steyaert J, Laeremans T, Manglik A, Huang W, Kobilka BK, Déméné H, Granier S. Nature. 2015; 524(7565): 375-378.
μ-Opioid receptors (μORs) are G-protein-coupled receptors that are activated by a structurally diverse spectrum of natural and synthetic agonists including endogenous endorphin peptides, morphine and methadone. The recent structures of the μOR in inactive and agonist-induced active states (Huang et al., ref. 2) provide snapshots of the receptor at the beginning and end of a signalling event, but little is known about the dynamic sequence of events that span these two states. Here the authors use solution-state NMR to examine the process of μOR activation using a purified receptor (mouse sequence) preparation in an amphiphile membrane-like environment. They obtain spectra of the μOR in the absence of ligand, and in the presence of the high-affinity agonist BU72 alone, or with BU72 and a G protein mimetic nanobody. Their results show that conformational changes in transmembrane segments 5 and 6 (TM5 and TM6), which are required for the full engagement of a G protein, are almost completely dependent on the presence of both the agonist and the G protein mimetic nanobody, revealing a weak allosteric coupling between the agonist-binding pocket and the G-protein-coupling interface (TM5 and TM6), similar to that observed for the β2-adrenergic receptor. Unexpectedly, in the presence of agonist alone, the authors find larger spectral changes involving intracellular loop 1 and helix 8 compared to changes in TM5 and TM6. These results suggest that one or both of these domains may play a role in the initial interaction with the G protein, and that TM5 and TM6 are only engaged later in the process of complex formation. The initial interactions between the G protein and intracellular loop 1 and/or helix 8 may be involved in G-protein coupling specificity, as has been suggested for other family A G-protein-coupled receptors.

Brief Cognitive Training Interventions In Young Adulthood Promote Long-term Resilience To Drug-seeking Behavior Boivin JR, Piscopo DM, Wilbrecht L. Neuropharmacology. 2015; 97: 404-413.
Environmental stress and deprivation increase vulnerability to substance use disorders in humans and promote drug-seeking behavior in animal models. In contrast, experiences of mastery and stability may shape neural circuitry in ways that build resilience to future challenges. Cognitive training offers a potential intervention for reducing vulnerability in the face of environmental stress or deprivation. Here, the authors test the hypothesis that brief cognitive training can promote long-term resilience to one measure of drug-seeking behavior, cocaine conditioned place preference (CPP), in mice. In young adulthood, mice underwent cognitive training, received rewards while exploring a training arena (i.e. yoked control), or remained in their home cages. Beginning 4 weeks after cessation of training, the authors conditioned mice in a CPP paradigm and then tested them weekly for CPP maintenance or daily for CPP extinction. They found that a brief 9-day cognitive training protocol reduced maintenance of cocaine CPP when compared to standard housed and yoked conditions. This beneficial effect persisted long after cessation of the training, as mice remained in their home cages for 4 weeks between training and cocaine exposure. When mice were tested for CPP on a daily extinction schedule, the authors found that all trained and yoked groups that left their home cages to receive rewards in a training arena showed significant extinction of CPP, while mice kept in standard housing for the same period did not extinguish CPP. These data suggest that in early adulthood, deprivation may confer vulnerability to drug-seeking behavior and that brief interventions may promote long-term resilience.

Structural Insights Into M-opioid Receptor Activation Huang W, Manglik A, Venkatakrishnan AJ, Laeremans T, Feinberg EN, Sanborn AL, Kato HE, Livingston KE, Thorsen TS, Kling RC, Granier S, Gmeiner P, Husbands SM, Traynor JR, Weis WI, Steyaert J, Dror RO, Kobilka BK. Nature. 2015; 524(7565): 315-321.
Activation of the μ-opioid receptor (μOR) is responsible for the efficacy of the most effective analgesics. To shed light on the structural basis for μOR activation, here the authors report a 2.1 Å X-ray crystal structure of the murine μOR bound to the morphinan agonist BU72 and a G protein mimetic camelid antibody fragment. The BU72-stabilized changes in the μOR binding pocket are subtle and differ from those observed for agonist-bound structures of the β2-adrenergic receptor (β2AR) and the M2 muscarinic receptor. Comparison with active β2AR reveals a common rearrangement in the packing of three conserved amino acids in the core of the μOR, and molecular dynamics simulations illustrate how the ligand-binding pocket is conformationally linked to this conserved triad. Additionally, an extensive polar network between the ligand-binding pocket and the cytoplasmic domains appears to play a similar role in signal propagation for all three G-protein-coupled receptors.

Corticostriatal Afferents Modulate Responsiveness To Psychostimulant Drugs and Drug-Associated Stimuli Kerstetter KA, Wunsch AM, Nakata KG, Donckels E, Neumaier JF, Ferguson SM. Neuropsychopharmacology. 2015.
The medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) are both integral components of the corticobasal ganglia-thalamic circuitry that regulates addiction-related behaviors. However, the role of afferent inputs from mPFC to NAc in these behaviors is unclear. To address this, the authors used a Cre-recombinase-dependent viral vector approach to express Gi/o-coupled DREADDs (designer receptors exclusively activated by designer drugs) selectively in mPFC neurons projecting to the NAc and examined the consequences of attenuating activity of these

neurons on the induction of amphetamine sensitization and on drug taking and drug seeking during cocaine self-administration. Surprisingly, decreasing mPFC afferent activity to the NAc only transiently reduced locomotor sensitization and had no effect on drug taking during cocaine self-administration. However, inhibiting corticostriatal afferent activity during sensitization subsequently enhanced conditioned responding. In addition, this manipulation during drug self-administration resulted in slower rates of extinction and increased responding during drug prime-induced reinstatement-an effect that was normalized by inhibiting these corticostriatal afferents immediately before the drug prime. These results suggest that dampening cortical control over the NAc during drug exposure may lead to long-term changes in the ability of drugs and associated stimuli to drive behavior that has important implications for guiding treatments to prevent relapse.Neuropsychopharmacology advance online publication, 23 September 2015; doi:10.1038/npp.2015.253.

Investigation Of the Role Of Barrestin2 In Kappa Opioid Receptor Modulation In A Mouse Model Of Pruritus Morgenweck J, Frankowski KJ, Prisinzano TE, Aubé J, Bohn LM. Neuropharmacology. 2015; 99: 600-609.
The kappa opioid receptor (KOR) is involved in mediating pruritus; agonists targeting this receptor have been used to treat chronic intractable itch. Conversely, antagonists induce an itch response at the site of injection. As a G protein-coupled receptor (GPCR), the KOR has potential for signaling via G proteins and βarrestins, however, it is not clear which of these pathways are involved in the KOR modulation of itch. In this study the authors asked whether the actions of KOR in pruritus involve βarrestins by using βarrestin2 knockout (βarr2-KO) mice as well as a recently described biased KOR agonist that biases receptor signaling toward G protein pathways over βarrestin2 recruitment. They find that the KOR antagonists nor-binaltorphimine (NorBNI) and 5'-guanidinonaltrindole (5'GNTI) induce acute pruritus in C57BL/6J mice, with reduced effects in KOR-KO mice. βArr2-KO mice display less of a response to KOR antagonist-induced itch compared to wild types, however no genotype differences are observed from chloroquine phosphate (CP)-induced itch, suggesting that the antagonists may utilize a KOR-βarrestin2 dependent mechanism. The KOR agonist U50,488H was equally effective in both WT and βarr2-KO mice in suppressing CP-induced itch. Furthermore, the G protein biased agonist, Isoquinolinone 2.1 was as effective as U50,488H in suppressing the itch response induced by KOR antagonist NorBNI or CP in C57BL/6J mice. Together these data suggest that the antipruritic effects of KOR agonists may not require βarrestins.

Small-molecule Nociceptin Receptor Agonist Ameliorates Mast Cell Activation And Pain In Sickle Mice Vang D, Paul JA, Nguyen J, Tran H,Vincent L, Yasuda D, Zaveri NT, Gupta K. Haematologica. 2015; 100(12): 1517-1525.
Treatment of pain with morphine and its congeners in sickle cell anemia is suboptimal, warranting the need for analgesics devoid of side effects, addiction and tolerance liability. Small-molecule nociceptin opioid receptor ligands show analgesic efficacy in acute and chronic pain models. The authors show that AT-200, a high affinity nociceptin opioid receptor agonist with low efficacy at the mu opioid receptor, ameliorated chronic and hypoxia/reoxygenation-induced mechanical, thermal and deep tissue/musculoskeletal hyperalgesia in HbSS-BERK sickle mice. The antinociceptive effect of AT-200 was antagonized by SB-612111, a nociceptin opioid receptor antagonist, but not naloxone, a non-selective mu opioid receptor antagonist. Daily 7-day treatment with AT-200 did not develop tolerance and showed a sustained anti-nociceptive effect, which improved over time and led to reduced plasma serum amyloid protein, neuropeptides, inflammatory

cytokines and mast cell activation in the periphery. These data suggest that AT-200 ameliorates pain in sickle mice via the nociceptin opioid receptor by reducing inflammation and mast cell activation without causing tolerance. Thus, nociceptin opioid receptor agonists are promising drugs for treating pain in sickle cell anemia.

Neurotensin Induces Presynaptic Depression Of D2 Dopamine Autoreceptor-Mediated Neurotransmission In Midbrain Dopaminergic Neurons Piccart E, Courtney NA, Branch SY, Ford CP, Beckstead MJ. J Neurosci. 2015; 35(31): 11144-11152.
Increased dopaminergic signaling is a hallmark of severe mesencephalic pathologies such as schizophrenia and psychostimulant abuse. Activity of midbrain dopaminergic neurons is under strict control of inhibitory D2 autoreceptors. Application of the modulatory peptide neurotensin (NT) to midbrain dopaminergic neurons transiently increases activity by decreasing D2 dopamine autoreceptor function, yet little is known about the mechanisms that underlie long-lasting effects. Here, the authors performed patch-clamp electrophysiology and fast-scan cyclic voltammetry in mouse brain slices to determine the effects of NT on dopamine autoreceptor-mediated neurotransmission. Application of the active peptide fragment NT8-13 produced synaptic depression that exhibited short- and long-term components. Sustained depression of D2 autoreceptor signaling required activation of the type 2 NT receptor and the protein phosphatase calcineurin. NT application increased paired-pulse ratios and decreased extracellular levels of somatodendritic dopamine, consistent with a decrease in presynaptic dopamine release. Surprisingly, the authors observed that electrically induced long-term depression of dopaminergic neurotransmission that they reported previously was also dependent on type 2 NT receptors and calcineurin. Because electrically induced depression, but not NT-induced depression, was blocked by postsynaptic calcium chelation, these findings suggest that endogenous NT may act through a local circuit to decrease presynaptic dopamine release. The current research provides a mechanism through which augmented NT release can produce a long-lasting increase in membrane excitability of midbrain dopamine neurons. Whereas plasticity of glutamate synapses in the brain has been studied extensively, demonstrations of plasticity at dopaminergic synapses have been more elusive. By quantifying inhibitory neurotransmission between midbrain dopaminergic neurons in brain slices from mice we have discovered that the modulatory peptide neurotensin can induce a persistent synaptic depression by decreasing dopamine release. This depression of inhibitory synaptic input would be expected to increase excitability of dopaminergic neurons. Induction of the plasticity can be pharmacologically blocked by antagonists of either the protein phosphatase calcineurin or neurotensin receptors, and persists surprisingly long after a brief exposure to the peptide. Since neurotensin-dopamine interactions have been implicated in hyperdopaminergic pathologies, these findings describe a synaptic mechanism that could contribute to addiction and/or schizophrenia.

AB-CHMINACA, AB-PINACA, and FUBIMINA: Affinity and Potency Of Novel Synthetic Cannabinoids In Producing Δ9-Tetrahydrocannabinol-Like Effects In Mice Wiley JL, Marusich JA, Lefever TW, Antonazzo KR, Wallgren MT, Cortes RA, Patel PR, Grabenauer M, Moore KN, Thomas BF. J Pharmacol Exp Ther. 2015; 354(3): 328-339.
Diversion of synthetic cannabinoids for abuse began in the early 2000s. Despite legislation banning compounds currently on the drug market, illicit manufacturers continue to release new compounds for recreational use. This study examined new synthetic cannabinoids, AB-CHMINACA (N-[1-amino-3-methyl-oxobutan-2-yl]-1-[cyclohexylmethyl]-1H-indazole-3-carboxamide), AB-PINACA [N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide], and FUBIMINA

[(1-(5-fluoropentyl)-1H-benzo[d]imadazol-2-yl)(naphthalen-1-yl)methanone], with the hypothesis that these compounds, like those before them, would be highly susceptible to abuse. Cannabinoids were examined in vitro for binding and activation of CB1 receptors, and in vivo for pharmacological effects in mice and in Δ(9)-tetrahydrocannabinol (Δ(9)-THC) discrimination. AB-CHMINACA, AB-PINACA, and FUBIMINA bound to and activated CB1 and CB2 receptors, and produced locomotor suppression, antinociception, hypothermia, and catalepsy. Furthermore, these compounds, along with JWH-018 [1-pentyl-3-(1-naphthoyl)indole], CP47,497 [rel-5-(1,1-dimethylheptyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol], and WIN55,212-2 ([(3R)-2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenyl-methanone, monomethanesulfonate), substituted for Δ(9)-THC in Δ(9)-THC discrimination. Rank order of potency correlated with CB1 receptor-binding affinity, and all three compounds were full agonists in [(35)S]GTPγS binding, as compared with the partial agonist Δ(9)-THC. Indeed, AB-CHMINACA and AB-PINACA exhibited higher efficacy than most known full agonists of the CB1 receptor. Preliminary analysis of urinary metabolites of the compounds revealed the expected hydroxylation. AB-PINACA and AB-CHMINACA are of potential interest as research tools due to their unique chemical structures and high CB1 receptor efficacies. Further studies on these chemicals are likely to include research on understanding cannabinoid receptors and other components of the endocannabinoid system that underlie the abuse of synthetic cannabinoids.

Environmental Enrichment Facilitates Cocaine-cue Extinction, Deters Reacquisition Of Cocaine Self-administration and Alters AMPAR GluA1 Expression and Phosphorylation
Gauthier JM, Lin A, Nic Dhonnchadha BÁ, Spealman RD, Man H-Y, Kantak KM. Addict Biol. 2015.
This study investigated the combination of environmental enrichment (EE) with cocaine-cue extinction training on reacquisition of cocaine self-administration. Rats were trained under a second-order schedule for which responses were maintained by cocaine injections and cocaine-paired stimuli. During three weekly extinction sessions, saline was substituted for cocaine but cocaine-paired stimuli were presented. Rats received 4-h periods of EE at strategic time points during extinction training, or received NoEE. Additional control rats received EE or NoEE without extinction training. One week later, reacquisition of cocaine self-administration was evaluated for 15 sessions, and then GluA1 expression, a cellular substrate for learning and memory, was measured in selected brain regions. EE provided both 24 h before and immediately after extinction training facilitated extinction learning and deterred reacquisition of cocaine self-administration for up to 13 sessions. Each intervention by itself (EE alone or extinction alone) was ineffective, as was EE scheduled at individual time points (EE 4 h or 24 h before, or EE immediately or 6 h after, each extinction training session). Under these conditions, rats rapidly reacquired baseline rates of cocaine self-administration. Cocaine self-administration alone decreased total GluA1 and/or pSer845GluA1 expression in basolateral amygdala and nucleus accumbens. Extinction training, with or without EE, opposed these changes and also increased total GluA1 in ventromedial prefrontal cortex and dorsal hippocampus. EE alone increased pSer845GluA1 and EE combined with extinction training decreased pSer845GluA1 in ventromedial prefrontal cortex. EE might be a useful adjunct to extinction therapy by enabling neuroplasticity that deters relapse to cocaine self-administration.

Brain Activation To Negative Stimuli Mediates A Relationship Between Adolescent Marijuana Use and Later Emotional Functioning Heitzeg MM, Cope LM, Martz ME, Hardee JE, Zucker RA. Dev Cogn Neurosci. 2015.
This work investigated the impact of heavy marijuana use during adolescence on emotional functioning, as well as the brain functional mediators of this effect. Participants (n=40) were recruited from the Michigan Longitudinal Study (MLS). Data on marijuana use were collected prospectively beginning in childhood as part of the MLS. Participants were classified as heavy marijuana users (n=20) or controls with minimal marijuana use. Two facets of emotional functioning-negative emotionality and resiliency (a self-regulatory mechanism)-were assessed as part of the MLS at three time points: mean age 13.4, mean age 19.6, and mean age 23.1. Functional neuroimaging data during an emotion-arousal word task were collected at mean age 20.2. Negative emotionality decreased and resiliency increased across the three time points in controls but not heavy marijuana users. Compared with controls, heavy marijuana users had less activation to negative words in temporal, prefrontal, and occipital cortices, insula, and amygdala. Activation of dorsolateral prefrontal cortex to negative words mediated an association between marijuana group and later negative emotionality. Activation of the cuneus/lingual gyrus mediated an association between marijuana group and later resiliency. Results support growing evidence that heavy marijuana use during adolescence affects later emotional outcomes.

HIV-1 Nef Promotes Infection By Excluding SERINC5 From Virion Incorporation Rosa A, Chande A, Ziglio S, De Sanctis V, Bertorelli R, Goh SL, McCauley SM, Nowosielska A, Antonarakis SE, Luban J, Santoni FA, Pizzato M. Nature. 2015; 526(7572): 212-217.
HIV-1 Nef, a protein important for the development of AIDS, has well-characterized effects on host membrane trafficking and receptor downregulation. By an unidentified mechanism, Nef increases the intrinsic infectivity of HIV-1 virions in a host-cell-dependent manner. Here the authors identify the host transmembrane protein SERINC5, and to a lesser extent SERINC3, as a potent inhibitor of HIV-1 particle infectivity that is counteracted by Nef. SERINC5 localizes to the plasma membrane, where it is efficiently incorporated into budding HIV-1 virions and impairs subsequent virion penetration of susceptible target cells. Nef redirects SERINC5 to a Rab7-positive endosomal compartment and thereby excludes it from HIV-1 particles. The ability to counteract SERINC5 was conserved in Nef encoded by diverse primate immunodeficiency viruses, as well as in the structurally unrelated glycosylated Gag from murine leukaemia virus. These examples of functional conservation and convergent evolution emphasize the fundamental importance of SERINC5 as a potent anti-retroviral factor.

The Impact Of Gonadal Hormones On Cannabinoid Dependence Marusich JA, Craft RM, Lefever TW, Wiley JL. Exp Clin Psychopharmacol. 2015; 23(4): 206-216.
Cannabis is the most widely used illicit substance in the United States. Women report greater positive subjective effects of cannabis, and greater cannabis withdrawal compared to men. Female rodents are more sensitive than males to some acute effects of Δ^9-tetrahydrocannabinol (THC), and females also develop greater tolerance to THC in some assays. The purpose of this study was to determine whether gonadal hormones modulate THC dependence in rats. Adult rats were gonadectomized (GDX) or sham-GDX, and hormone was replaced in half of the GDX rats of each sex (testosterone in males; estradiol and/or progesterone in females). THC (30 mg/kg) or vehicle was administered twice daily for 6.5 days, followed on the seventh day by vehicle or rimonabant challenge and assessment for withdrawal-related behaviors. Sham-GDX females developed greater tolerance than males to THC-induced hypothermia, and GDX females given progesterone showed

greater tolerance to THC-induced locomotor suppression. Rimonabant precipitated withdrawal, as evidenced by increased somatic signs (forepaw tremors, licking) and increased startle amplitude. Testosterone in GDX males decreased withdrawal-induced licking. Estradiol and progesterone in GDX females increased withdrawal-induced chewing, and progesterone increased withdrawal-induced sniffing. These results suggest that estradiol and progesterone may promote the development of dependence, whereas testosterone may protect against dependence. While the present study indicates that testosterone and estradiol produce opposite effects on THC-induced behavior, estradiol appears to play a broader role than testosterone in modulating THC's behavioral effects.

The Effects Of N-Acetylcysteine On Frontostriatal Resting-state Functional Connectivity, Withdrawal Symptoms and Smoking Abstinence: A Double-blind, Placebo-controlled FMRI Pilot Study Froeliger B, McConnell PA, Stankeviciute N, McClure EA, Kalivas PW, Gray KM. Drug Alcohol Depend. 2015; 156: 234-242.
Chronic exposure to drugs of abuse disrupts frontostriatal glutamate transmission, which in turn meditates drug seeking. In animal models, N-Acetylcysteine normalizes dysregulated frontostriatal glutamatergic neurotransmission and prevents reinstated drug seeking; however, the effects of N-Acetylcysteine on human frontostriatal circuitry function and maintaining smoking abstinence is unknown. Thus, the current study tested the hypothesis that N-Acetylcysteine would be associated with stronger frontostriatal resting-state functional connectivity (rsFC), attenuated nicotine withdrawal and would help smokers to maintain abstinence over the study period. The present study examined the effects of N-Acetylcysteine on frontostriatal rsFC, nicotine-withdrawal symptoms and maintaining abstinence. Healthy adult, non-treatment seeking smokers (N=16; mean (SD) age 36.5±11.9; cigs/day 15.8±6.1; years/smoking 15.7±8.9) were randomized to a double-blind course of 2400mg N-Acetylcysteine (1200mg b.i.d.) or placebo over the course of 3½ days of monetary-incentivized smoking abstinence. On each abstinent day, measures of mood and craving were collected and participants attended a lab visit in order to assess smoking (i.e., expired-air carbon monoxide [CO]). On day 4, participants underwent fMRI scanning. As compared to placebo (n=8), smokers in the N-Acetylcysteine group (n=8) maintained abstinence, reported less craving and higher positive affect (all p's<.01), and concomitantly exhibited stronger rsFC between ventral striatal nodes, medial prefrontal cortex and precuneus-key default mode network nodes, and the cerebellum [p<.025; FWE]). Taken together, these findings suggest that N-Acetylcysteine may positively affect dysregulated corticostriatal connectivity, help to restructure reward processing, and help to maintain abstinence immediately following a quit attempt.

Dynamic M(6)A MRNA Methylation Directs Translational Control Of Heat Shock Response Zhou J, Wan J, Gao X, Zhang X, Jaffrey SR, Qian S-B. Nature. 2015; 526(7574): 591-594.
The most abundant mRNA post-transcriptional modification is N(6)-methyladenosine (m(6)A), which has broad roles in RNA biology. In mammalian cells, the asymmetric distribution of m(6)A along mRNAs results in relatively less methylation in the 5' untranslated region (5'UTR) compared to other regions. However, whether and how 5'UTR methylation is regulated is poorly understood. Despite the crucial role of the 5'UTR in translation initiation, very little is known about whether m(6)A modification influences mRNA translation. Here the authors show that in response to heat shock stress, certain adenosines within the 5'UTR of newly transcribed mRNAs are preferentially methylated. They find that the dynamic 5'UTR methylation is a result of stress-induced nuclear localization of YTHDF2, a well-characterized m(6)A 'reader'. Upon heat shock stress, the nuclear YTHDF2 preserves 5'UTR methylation of stress-induced transcripts by limiting the m(6)A 'eraser'

FTO from demethylation. Remarkably, the increased 5'UTR methylation in the form of m(6)A promotes cap-independent translation initiation, providing a mechanism for selective mRNA translation under heat shock stress. Using Hsp70 mRNA as an example, the authors demonstrate that a single m(6)A modification site in the 5'UTR enables translation initiation independent of the 5' end N(7)-methylguanosine cap. The elucidation of the dynamic features of 5'UTR methylation and its critical role in cap-independent translation not only expands the breadth of physiological roles of m(6)A, but also uncovers a previously unappreciated translational control mechanism in heat shock response.

Input- and Output-Specific Regulation Of Serial Order Performance By Corticostriatal Circuits Rothwell PE, Hayton SJ, Sun GL, Fuccillo MV, Lim BK, Malenka RC. Neuron. 2015; 88(2): 345-356.
The serial ordering of individual movements into sequential patterns is thought to require synaptic plasticity within corticostriatal circuits that route information through the basal ganglia. The authors used genetically and anatomically targeted manipulations of specific circuit elements in mice to isolate the source and target of a corticostriatal synapse that regulates the performance of a serial order task. This excitatory synapse originates in secondary motor cortex, terminates on direct pathway medium spiny neurons in the dorsolateral striatum, and is strengthened by serial order learning. This experience-dependent and synapse-specific form of plasticity may sculpt the balance of activity in basal ganglia circuits during sequential movements, driving a disparity in striatal output that favors the direct pathway. This disparity is necessary for execution of responses in serial order, even though both direct and indirect pathways are active during movement initiation, suggesting dynamic modulation of corticostriatal circuitry contributes to the choreography of behavioral routines.

Highly Specific Epigenome Editing By CRISPR-Cas9 Repressors For Silencing Of Distal Regulatory Elements Thakore PI, D'Ippolito AM, Song L, Safi A, Shivakumar NK, Kabadi AM, Reddy TE, Crawford GE, Gersbach CA. Nat Methods. 2015; 12(12): 1143-1149.
Epigenome editing with the CRISPR (clustered, regularly interspaced, short palindromic repeats)-Cas9 platform is a promising technology for modulating gene expression to direct cell phenotype and to dissect the causal epigenetic mechanisms of gene regulation. Fusions of nuclease-inactive dCas9 to the Krüppel-associated box (KRAB) repressor (dCas9-KRAB) can silence target gene expression, but the genome-wide specificity and the extent of heterochromatin formation catalyzed by dCas9-KRAB are not known. The authors targeted dCas9-KRAB to the HS2 enhancer, a distal regulatory element that orchestrates the expression of multiple globin genes, and observed highly specific induction of H3K9 trimethylation (H3K9me3) at the enhancer and decreased chromatin accessibility of both the enhancer and its promoter targets. Targeted epigenetic modification of HS2 silenced the expression of multiple globin genes, with minimal off-target changes in global gene expression. These results demonstrate that repression mediated by dCas9-KRAB is sufficiently specific to disrupt the activity of individual enhancers via local modification of the epigenome.

Insulin Enhances Striatal Dopamine Release By Activating Cholinergic Interneurons and Thereby Signals Reward Stouffer MA, Woods CA, Patel JC, Lee CR, Witkovsky P, Bao L, Machold RP, Jones KT, de Vaca SC, Reith MEA, Carr KD, Rice ME. Nat Commun. 2015; 6: 8543.
Insulin activates insulin receptors (InsRs) in the hypothalamus to signal satiety after a meal. However, the rising incidence of obesity, which results in chronically elevated insulin levels, implies that insulin may also act in brain centres that regulate motivation and reward. The authors

report here that insulin can amplify action potential-dependent dopamine (DA) release in the nucleus accumbens (NAc) and caudate-putamen through an indirect mechanism that involves striatal cholinergic interneurons that express InsRs. Furthermore, two different chronic diet manipulations in rats, food restriction (FR) and an obesogenic (OB) diet, oppositely alter the sensitivity of striatal DA release to insulin, with enhanced responsiveness in FR, but loss of responsiveness in OB. Behavioural studies show that intact insulin levels in the NAc shell are necessary for acquisition of preference for the flavour of a paired glucose solution. Together, these data imply that striatal insulin signalling enhances DA release to influence food choices.

Decreased Nicotinic Receptor Availability In Smokers With Slow Rates Of Nicotine Metabolism Dubroff JG, Doot RK, Falcone M, Schnoll RA, Ray R, Tyndale RF, Brody AL, Hou C, Schmitz A, Lerman C. J Nucl Med. 2015; 56(11): 1724-1729.
The nicotine metabolite ratio (NMR), a stable measure of hepatic nicotine metabolism via the CYP2A6 pathway and total nicotine clearance, is a predictive biomarker of response to nicotine replacement therapy, with increased quit rates in slower metabolizers. Nicotine binds directly to nicotinic acetylcholine receptors (nAChRs) to exert its psychoactive effects. This study examined the relationship between NMR and nAChR (α4β2* subtype) availability using PET imaging of the radiotracer 2-(18)F-fluoro-3-(2(S)-azetidinylmethoxy)pyridine (2-(18)F-FA-85380, or 2-(18)F-FA).Twenty-four smokers-12 slow metabolizers (NMR < 0.26) and 12 normal metabolizers (NMR ≥ 0.26)-underwent 2-(18)F-FA-PET brain imaging after overnight nicotine abstinence (18 h before scanning), using a validated bolus-plus-infusion protocol. Availability of nAChRs was compared between NMR groups in a priori volumes of interest, with total distribution volume (VT/fP) being the measure of nAChR availability. Cravings to smoke were assessed before and after the scans.Thalamic nAChR α4β2* availability was significantly reduced in slow nicotine metabolizers (P = 0.04). Slow metabolizers exhibited greater reductions in cravings after scanning than normal metabolizers; however, craving was unrelated to nAChR availability.The rate of nicotine metabolism is associated with thalamic nAChR availability. Additional studies could examine whether altered nAChR availability underlies the differences in treatment response between slow and normal metabolizers of nicotine.

Adolescent Intermittent Alcohol Exposure: Dysregulation Of Thrombospondins and Synapse Formation Are Associated With Decreased Neuronal Density In the Adult Hippocampus Risher M-L, Sexton HG, Risher WC, Wilson WA, Fleming RL, Madison RD, Moore SD, Eroglu C, Swartzwelder HS. Alcohol Clin Exp Res. 2015.
Adolescent intermittent alcohol exposure (AIE) has profound effects on neuronal function. The authors have previously shown that AIE causes aberrant hippocampal structure and function that persists into adulthood. However, the possible contributions of astrocytes and their signaling factors remain largely unexplored. The authors investigated the acute and enduring effects of AIE on astrocytic reactivity and signaling on synaptic expression in the hippocampus, including the impact of the thrombospondin (TSP) family of astrocyte-secreted synaptogenic factors and their neuronal receptor, alpha2delta-1 (α2δ-1). Their hypothesis is that some of the influences of AIE on neuronal function may be secondary to direct effects on astrocytes. The authors conducted Western blot analysis on TSPs 1 to 4 and α2δ-1 from whole hippocampal lysates 24 hours after the 4th and 10th doses of AIE, then 24 days after the last dose (in adulthood). They used immunohistochemistry to assess astrocyte reactivity (i.e., morphology) and synaptogenesis (i.e., colocalization of pre- and postsynaptic puncta).Adolescent AIE reduced α2δ-1 expression, and colocalized pre- and postsynaptic puncta after the fourth ethanol (EtOH) dose. By the 10th dose, increased TSP2 levels

were accompanied by an increase in colocalized pre- and postsynaptic puncta, while α2δ-1 returned to control levels. Twenty-four days after the last EtOH dose (i.e., adulthood), TSP2, TSP4, and α2δ-1 expression were all elevated. Astrocyte reactivity, indicated by increased astrocytic volume and area, was also observed at that time.Repeated EtOH exposure during adolescence results in long-term changes in specific astrocyte signaling proteins and their neuronal synaptogenic receptor. Continued signaling by these traditionally developmental factors in adulthood may represent a compensatory mechanism whereby astrocytes reopen the synaptogenic window and repair lost connectivity, and consequently contribute to the enduring maladaptive structural and functional abnormalities previously observed in the hippocampus after AIE.

Impact Of Chronic Morphine On Delta Opioid Receptor-expressing Neurons In the Mouse Hippocampus Erbs E, Faget L, Ceredig RA, Matifas A, Vonesch J-L, Kieffer BL, Massotte D. Neuroscience. 2015; 313: 46-56.
Delta opioid (DOP) receptors participate to the control of chronic pain and emotional responses. Recent data also identified their implication in spatial memory and drug-context associations pointing to a critical role of hippocampal delta receptors. To better appreciate the impact of repeated drug exposure on their modulatory activity, the authors used fluorescent knock-in mice that express a functional delta receptor fused at its carboxy-terminus with the green fluorescent protein in place of the native receptor. They then tested the impact of chronic morphine treatment on the density and distribution of delta receptor-expressing cells in the hippocampus. A decrease in delta receptor-positive cell density was observed in the CA1, CA3 and dentate gyrus without alteration of the distribution across the different GABAergic populations that mainly express delta receptors. This effect partly persisted after four weeks of morphine abstinence. In addition, the authors observed increased DOP receptor expression at the cell surface compared to saline-treated animals. In the hippocampus, chronic morphine administration thus induces DOP receptor cellular redistribution and durably decreases delta receptor-expressing cell density. Such modifications are likely to alter hippocampal physiology, and to contribute to long-term cognitive deficits.

EphA4 Has Distinct Functionality From EphA7 In The Corticothalamic System During Mouse Brain Development Son AI, Hashimoto-Torii K, Rakic P, Levitt P, Torii M. J Comp Neurol. 2015.
Deciphering the molecular basis for guiding specific aspects of neocortical development remains a challenge due to the complexity of histogenic events and the vast array of protein interactions that mediate these events. The Eph family of receptor tyrosine kinases is implicated in a number of these neurodevelopmental activities. Eph receptors have been known to be capable of responding to several ephrin ligands within their respective subgroups, often eliciting similar downstream effects. However, several recent studies have reported specificity between receptor-ligand pairs within each subfamily, the functional relevance of which is not defined. Here, the authors show that a receptor of the EphA subfamily, EphA4, has distinct effects from its close relative EphA7 in the developing brain. Both EphA4 and EphA7 interact similarly with corresponding ligands expressed in the developing neocortex. However, only EphA7 shows strong interaction with ligands in the somatosensory thalamic nuclei; EphA4 affects only cortical neuronal migration with no visible effects on the guidance of CT axons, while EphA7 affects both cortical neuronal migration and CT axon guidance. These data provide new evidence that Eph receptors in the same subfamily are not simply interchangeable, but functionally specified through selective interactions with distinct ligands in vivo.

Brain Region-Specific Trafficking Of the Dopamine Transporter Block ER, Nuttle J, Balcita-Pedicino JJ, Caltagarone J, Watkins SC, Sesack SR, Sorkin A. J Neurosci. 2015; 35(37): 12845-12858.
The dopamine (DA) transporter (DAT) controls dopaminergic neurotransmission by removing extracellular DA. Although DA reuptake is proposed to be regulated by DAT traffic to and from the cell surface, the membrane trafficking system involved in the endocytic cycling of DAT in the intact mammalian brain has not been characterized. Hence, the authors performed immunolabeling and quantitative analysis of the subcellular and regional distribution of DAT using the transgenic knock-in mouse expressing hemagglutinin (HA) epitope-tagged DAT (HA-DAT) and by using a combination of electron microscopy and a novel method for immunofluorescence labeling of HA-DAT in acute sagittal brain slices. Both approaches demonstrated that, in midbrain somatodendritic regions, HA-DAT was present in the plasma membrane, endoplasmic reticulum, and Golgi complex, with a small fraction in early and recycling endosomes and an even smaller fraction in late endosomes and lysosomes. In the striatum and in axonal tracts between the midbrain and striatum, HA-DAT was detected predominantly in the plasma membrane, and quantitative analysis revealed increased DAT density in striatal compared with midbrain plasma membranes. Endosomes were strikingly rare and lysosomes were absent in striatal axons, in which there was little intracellular HA-DAT. Acute administration of amphetamine in vivo (60 min) or to slices ex vivo (10-60 min) did not result in detectable changes in DAT distribution. Altogether, these data provide evidence for regional differences in DAT plasma membrane targeting and retention and suggest a surprisingly low level of endocytic trafficking of DAT in the striatum along with limited DAT endocytic activity in somatodendritic areas. The dopamine transporter (DAT) is the key regulator of the dopamine neurotransmission in the CNS. In the present study, the authors developed a new approach for studying DAT localization and dynamics in intact neurons in acute sagittal brain slices from the knock-in mouse expressing epitope-tagged DAT. For the first time, the fluorescence imaging analysis of DAT was combined with the immunogold labeling of DAT and quantitative electron microscopy. In contrast to numerous studies of DAT trafficking in heterologous expression systems and dissociated cultured neurons, studies in intact neurons revealed a surprisingly low amount of endocytic trafficking of DAT at steady state and after acute amphetamine treatment and suggested that non-vesicular transport could be the main mechanism establishing DAT distribution within the dopaminergic neuron.

Distinct Profiles Of Functional Discrimination Among G Proteins Determine the Actions Of G Protein-Coupled Receptors Masuho I, Ostrovskaya O, Kramer GM, Jones CD, Xie K, Martemyanov KA. Sci Signal. 2015 Dec 1; 8(405):ra123. doi: 10.1126/scisignal.aab4068.
Members of the heterotrimeric guanine nucleotide-binding protein (G protein)-coupled receptor (GPCR) family play key roles in many physiological functions and are extensively exploited pharmacologically to treat diseases. Many of the diverse effects of individual GPCRs on cellular physiology are transduced by heterotrimeric G proteins, which are composed of α, β, and γ subunits. GPCRs interact with and stimulate the binding of guanosine triphosphate (GTP) to the α subunit to initiate signaling. Mammalian genomes encode 16 different G protein α subunits, each one of which has distinct properties. The authors developed a single-platform, optical strategy to monitor G protein activation in live cells. With this system, they profiled the coupling ability of individual GPCRs for different α subunits, simultaneously quantifying the magnitude of the signal and the rates at which the receptors activated the G proteins. They found that individual receptors engaged multiple G proteins with varying efficacy and kinetics, generating fingerprint-like profiles. Different classes of GPCR ligands, including full and partial agonists, allosteric modulators, and antagonists,

distinctly affected these fingerprints to functionally bias GPCR signaling. Finally, the authors showed that intracellular signaling modulators further altered the G protein-coupling profiles of GPCRs, which suggests that their differential abundance may alter signaling outcomes in a cell-specific manner. These observations suggest that the diversity of the effects of GPCRs on cellular physiology may be determined by their differential engagement of multiple G proteins, coupling to which produces signals with varying signal magnitudes and activation kinetics, properties that may be exploited pharmacologically.

Specific Inter-residue Interactions as Determinants of Human Monoacylglycerol Lipase Catalytic Competency: A Role for Global Conformational Changes Tyukhtenko S, Karageorgos I, Rajarshi G, Zvonok N, Pavlopoulos S, Janero DR, Makriyannis A. J Biol Chem. 2015 Nov 10. pii: jbc.M115.670257. [Epub ahead of print].
The serine hydrolase monoacylglycerol lipase (MGL) functions as the main metabolizing enzyme of 2-arachidonoyl glycerol, an endocannabinoid signaling lipid whose elevation through genetic or pharmacological MGL ablation exerts therapeutic effects in various preclinical disease models. To inform structure-based MGL inhibitor design, the authors report the direct NMR detection of a reversible equilibrium between active and inactive states of human MGL (hMGL) that is slow on the NMR time scale and can be modulated in a controlled manner by pH, temperature, and select point mutations. Kinetic measurements revealed that hMGL substrate turnover is rate-limited across this equilibrium. The authors identify a network of aromatic interactions and hydrogen bonds that regulates hMGL active-inactive state interconversion. The data highlight specific inter-residue interactions within hMGL modulating the enzymes function and implicate transitions between active (open) and inactive (closed) states of the hMGL lid domain in controlling substrate access to the enzymes active site.

Strategies to Reduce Tin and Other Metals in Electronic Cigarette Aerosol Williams M, To A, Bozhilov K, Talbot P. PLoS One. 2015 Sep 25;10(9):e0138933. doi:10.1371/journal.pone.0138933.
Metals are present in electronic cigarette (EC) fluid and aerosol and, may present health risks to users. The objective of this study was to measure the amounts of tin, copper, zinc, silver, nickel and chromium in the aerosol from four brands of EC and to identify the sources of these metals by examining the elemental composition of the atomizer components. Four brands of popular EC were dissected and the cartomizers were examined microscopically. Elemental composition of cartomizer components was determined using integrated energy dispersive X-ray microanalysis, and the concentrations of the tin, copper, zinc silver, nickel, and chromium in the aerosol were determined for each brand using inductively coupled plasma optical emission spectroscopy. All filaments were made of nickel and chromium. Thick wires were copper coated with either tin or silver. Wires were joined to each other by tin solder, brazing, or by brass clamps. High concentrations of tin were detected in the aerosol when tin solder joints were friable. Tin coating on copper wires also contributed to tin in the aerosol. Tin concentrations in EC aerosols varied both within and between brands. Tin in aerosol was reduced by coating the thick wire with silver rather than tin, placing stable tin solder joints outside the atomizing chamber, joining wires with brass clamps or by brazing rather than soldering wires. These data demonstrate the feasibility of removing tin and other unwanted metals from EC aerosol by altering designs and using materials of suitable quality.

Neural Correlates Of Error Monitoring In Adolescents Prospectively Predict Initiation Of Tobacco Use Anokhin AP, Golosheykin S. Dev Cogn Neurosci. 2015 Aug 10. pii: S1878-9293(15)00080-8. doi: 10.1016/j.dcn.2015.08.001. [Epub ahead of print].
Deficits in self-regulation of behavior can play an important role in the initiation of substance use and progression to regular use and dependence. One of the distinct component processes of self-regulation is error monitoring, i.e. detection of a conflict between the intended and actually executed action. Here the authors examined whether a neural marker of error monitoring, Error-Related Negativity (ERN), predicts future initiation of tobacco use. ERN was assessed in a prospective longitudinal sample at ages 12, 14, and 16 using a flanker task. ERN amplitude showed a significant increase with age during adolescence. Reduced ERN amplitude at ages 14 and 16, as well as slower rate of its developmental changes significantly predicted initiation of tobacco use by age 18 but not transition to regular tobacco use or initiation of marijuana and alcohol use. The present results suggest that attenuated development of the neural mechanisms of error monitoring during adolescence can increase the risk for initiation of tobacco use. The present results also suggest that the role of distinct neurocognitive component processes involved in behavioral regulation may be limited to specific stages of addiction.

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. 2015; 20(11): 1467-1478.
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 10(6) 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.

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; 20(11): 1406-1419.

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.

Evidence Against Dopamine D1/D2 Receptor Heteromers Frederick AL, Yano H, Trifilieff P, Vishwasrao HD, Biezonski D, Mészáros J, Urizar E, Sibley DR, Kellendonk C, Sonntag KC, Graham DL, Colbran RJ, Stanwood GD, Javitch JA. Mol Psychiatry. 2015; 20(11): 1373-1385.
Hetero-oligomers of G-protein-coupled receptors have become the subject of intense investigation, because their purported potential to manifest signaling and pharmacological properties that differ from the component receptors makes them highly attractive for the development of more selective pharmacological treatments. In particular, dopamine D1 and D2 receptors have been proposed to form hetero-oligomers that couple to Gαq proteins, and SKF83959 has been proposed to act as a biased agonist that selectively engages these receptor complexes to activate Gαq and thus phospholipase C. D1/D2 heteromers have been proposed as relevant to the pathophysiology and treatment of depression and schizophrenia. The authors used in vitro bioluminescence resonance energy transfer, ex vivo analyses of receptor localization and proximity in brain slices, and behavioral assays in mice to characterize signaling from these putative dimers/oligomers. The authors were unable to detect Gαq or Gα11 protein coupling to homomers or heteromers of D1 or D2 receptors using a variety of biosensors. SKF83959-induced locomotor and grooming behaviors were eliminated in D1 receptor knockout (KO) mice, verifying a key role for D1-like receptor activation. In contrast, SKF83959-induced motor responses were intact in D2 receptor and Gαq KO mice, as well as in knock-in mice expressing a mutant Ala(286)-CaMKIIα that cannot autophosphorylate to become active. Moreover, the authors found that, in the shell of the nucleus accumbens, even in neurons in which D1 and D2 receptor promoters are both active, the receptor proteins are segregated and do not form complexes. These data are not compatible with SKF83959 signaling through Gαq or through a D1/D2 heteromer and challenge the existence of such a signaling complex in the adult animals that we used for our studies.

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; 20(12): 1525-1537.
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.

Trace Amine-Associated Receptor 1 Regulation Of Methamphetamine Intake And Related Traits Harkness JH, Shi X, Janowsky A, Phillips TJ. Neuropsychopharmacology. 2015; 40(9): 2175-2184.
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 with Taar1 wild-type 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 function increases sensitivity to aversive effects of MA, and may thereby protect against MA use.

Dopamine D2 Modulation Of Sign and Goal Tracking In Rats Lopez JC, Karlsson R-M, O'Donnell P. Neuropsychopharmacology. 2015; 40(9): 2096-2102.
In Pavlovian conditioning, sign- and goal-tracking behaviors represent different approaches towards the conditioned stimulus. These behavioral patterns have been associated with predictive or incentive properties of the conditioned stimulus, with a crucial involvement of the mesolimbic dopamine system. As it is possible that sign tracking behavior is more sensitive to dopamine modulation, the authoors evaluated the dopamine-dependence of sign- and goal-tracking behavior. They assessed responses to both a D2 agonist and an antagonist, and tested performance in a behavioral paradigm known to activate dopamine projections and in an animal model that affects mesolimbic and mesocortical function. Sign trackers displayed a greater sensitivity to a D2 agonist and smaller prepulse inhibition of the acoustic startle response than goal trackers, suggesting a reduced inhibitory ability. In addition, a neonatal ventral hippocampal lesion resulted in the loss of incentive salience of cues in sign trackers. Overall, these data indicate that sign-tracking behavior is more heavily controlled by dopamine than goal tracking.

Individual Differences In Cue-Induced Motivation and Striatal Systems In Rats Susceptible To Diet-Induced Obesity Robinson MJF, Burghardt PR, Patterson CM, Nobile CW, Akil H, Watson SJ, Berridge KC, Ferrario CR. Neuropsychopharmacology. 2015; 40(9): 2113-2123. Pavlovian cues associated with junk-foods (caloric, highly sweet, and/or fatty foods), like the smell of brownies, can elicit craving to eat and increase the amount of food consumed. People who are more susceptible to these motivational effects of food cues may have a higher risk for becoming obese. Further, overconsumption of junk-foods leading to the development of obesity may itself heighten attraction to food cues. Here, the authors used a model of individual susceptibility to junk-foods diet-induced obesity to determine whether there are pre-existing and/or diet-induced increases in attraction to and motivation for sucrose-paired cues (ie, incentive salience or 'wanting'). The authors also assessed diet- vs obesity-associated alterations in mesolimbic function and receptor expression. They found that rats susceptible to diet-induced obesity displayed heightened conditioned approach prior to the development of obesity. In addition, after junk-food diet exposure, those rats that developed obesity also showed increased willingness to gain access to a sucrose cue. Heightened 'wanting' was not due to individual differences in the hedonic impact ('liking') of sucrose. Neurobiologically, Mu opioid receptor mRNA expression was lower in striatal 'hot-spots' that generate eating or hedonic impact only in those rats that became obese. In contrast, prolonged exposure to junk-food resulted in cross-sensitization to amphetamine-induced locomotion and downregulation of striatal D2R mRNA regardless of the development of obesity. Together these data shed light on individual differences in behavioral and neurobiological consequences of exposure to junk-food diets and the potential contribution of incentive sensitization in susceptible individuals to greater food cue-triggered motivation.

Nicotinic Mechanisms Modulate Ethanol Withdrawal and Modify Time Course and Symptoms Severity Of Simultaneous Withdrawal From Alcohol and Nicotine Perez E, Quijano-Cardé N, De Biasi M. Neuropsychopharmacology. 2015; 40(10): 2327-2336. Alcohol and nicotine are among the top causes of preventable death in the United States. Unfortunately, people who are dependent on alcohol are more likely to smoke than individuals in the general population. Similarly, smokers are more likely to abuse alcohol. Alcohol and nicotine codependence affects health in many ways and leads to poorer treatment outcomes in subjects who want to quit. This study examined the interaction of alcohol and nicotine during withdrawal and compared abstinence symptoms during withdrawal from one of the two drugs only vs both. The results indicate that simultaneous withdrawal from alcohol and nicotine produces physical symptoms that are more severe and last longer than those experienced during withdrawal from one of the two drugs alone. In animals experiencing withdrawal after chronic ethanol treatment, acute nicotine exposure was sufficient to prevent abstinence symptoms. Similarly, symptoms were prevented when alcohol was injected acutely in mice undergoing nicotine withdrawal. These experiments provide evidence for the involvement of the nicotinic cholinergic system in alcohol withdrawal. Furthermore, the outcomes of intracranial microinfusions of mecamylamine, a nonselective nicotinic receptor antagonist, highlight a major role for the nicotinic receptors expressed in medial habenula and interpeduncular nucleus during withdrawal. Overall, the data support the notion that modulating the nicotinic cholinergic system might help to maintain long-term abstinence from alcohol.

Pharmacologic Inhibition Of 5-Lipoxygenase Improves Memory, Rescues Synaptic Dysfunction, and Ameliorates Tau Pathology In A Transgenic Model Of Tauopathy
Giannopoulos PF, Chu J, Sperow M, Li J-G, Yu WH, Kirby LG, Abood M, Praticò. Biol Psychiatry. 2015; 78(10): 693-701.
5-Lipoxygenase (5-LO) is a protein widely distributed in the central nervous system where it modulates amyloidosis and memory impairments in transgenic mouse models of Alzheimer's disease. However, no data are available as to whether 5-LO is elevated in human tauopathy or if it directly influences tau pathology in a relevant model of the disease. The authors assayed 5-LO levels in brain samples from patients with tauopathy and transgenic tau mice, and they evaluated the effect of 5-LO pharmacologic inhibition on the phenotype of these mice.The 5-LO protein is upregulated in human tauopathy and transgenic tau mice brains. Pharmacologic blockade of 5-LO in tau mice resulted in significant memory improvement, rescue of synaptic integrity and dysfunction, and reduction of tau pathology via a cdk5-dependent mechanism. These results establish a key role of 5-LO in the development of the tau pathology phenotype and demonstrate it to be a novel viable therapeutic target for the pharmacologic treatment of human tauopathy.

Involvement Of Endogenous Enkephalins And B-Endorphin In Feeding and Diet-Induced Obesity Mendez IA, Ostlund SB, Maidment NT, Murphy NP. Neuropsychopharmacology. 2015; 40(9): 2103-2112.
Studies implicate opioid transmission in hedonic and metabolic control of feeding, although roles for specific endogenous opioid peptides have barely been addressed. Here, the authors studied palatable liquid consumption in proenkephalin knockout (PENK KO) and β-endorphin-deficient (BEND KO) mice, and how the body weight of these mice changed during consumption of an energy-dense highly palatable cafeteria diet. When given access to sucrose solution, PENK KOs exhibited fewer bouts of licking than wild types, even though the length of bouts was similar to that of wild types, a pattern that suggests diminished food motivation. Conversely, BEND KOs did not differ from wild types in the number of licking bouts, even though these bouts were shorter in length, suggesting that they experienced the sucrose as being less palatable. In addition, licking responses in BEND, but not PENK, KO mice were insensitive to shifts in sucrose concentration or hunger. PENK, but not BEND, KOs exhibited lower baseline body weights compared with wild types on chow diet and attenuated weight gain when fed cafeteria diet. Based on this and related findings, the authors suggest endogenous enkephalins primarily set a background motivational tone regulating feeding behavior, whereas β-endorphin underlies orosensory reward in high need states or when the stimulus is especially valuable. Overall, these studies emphasize complex interplays between endogenous opioid peptides targeting μ-receptors, such as enkephalins and endorphins, underlying the regulation of feeding and body weight that might explain the poor efficacy of drugs that generally target μ-opioid receptors in the long-term control of appetite and body weight.

Cocaine Decreases Metabotropic Glutamate Receptor MGluR1 Currents In Dopamine Neurons By Activating MGluR5 Kramer PF, Williams JT. Neuropsychopharmacology. 2015; 40(10): 2418-2424.
Midbrain dopamine neurons are important mediators of reward and movement and are sensitive to cocaine-induced plasticity. After even a single injection of cocaine, there is an increase in AMPA-dependent synaptic transmission. The present study examines cocaine-induced plasticity of mGluR-dependent currents in dopamine neurons in the substantia nigra. Activation of mGluR1 and mGluR5 resulted in a mixture of inward and outward currents mediated by a nonselective cation conductance and a calcium-activated potassium conductance (SK), respectively. A single injection of cocaine

decreased the current activated by mGluR1 in dopamine neurons, and it had no effect on the size of the mGluR5-mediated current. When the injection of cocaine was preceded by treatment of the animals with a blocker of mGluR5 receptors (MPEP), cocaine no longer decreased the mGluR1 current. Thus, the activation of mGluR5 was required for the cocaine-mediated suppression of mGluR1-mediated currents in dopamine neurons. The results support the hypothesis that mGluR5 coordinates a reduction in mGluR1 functional activity after cocaine treatment.

Failure To Recognize Novelty After Extended Methamphetamine Self-Administration Results From Loss Of Long-Term Depression In the Perirhinal Cortex Scofield MD, Trantham-Davidson H, Schwendt M, Leong K-C, Peters J, See RE, Reichel CM. Neuropsychopharmacology. 2015; 40(11): 2526-2535.
Exposure to methamphetamine (meth) can produce lasting memory impairments in humans and rodents. The authors recently demonstrated that extended access meth self-administration results in novel object recognition (NOR) memory deficits in rats. Recognition of novelty depends upon intact perirhinal (pRh) cortex function, which is compromised by meth-induced downregulation of GluN2B-containing N-methyl-D-aspartate (NMDA) receptors. NMDA receptors containing this subunit have a critical role in pRh long-term depression (LTD), one of the primary physiological processes thought to underlie object recognition memory. The authors hypothesized that meth-induced downregulation of GluN2B receptors would compromise pRh LTD, leading to loss of NOR memory. They found that meth self-administration resulted in an inability to induce pRh LTD following 1 Hz stimulation, an effect that was reversed with bath application of the NMDA receptor partial agonist D-cycloserine (DCS). In addition, pRh microinfusion of DCS restored meth-induced memory deficits. Furthermore, blockade of GluN2B-containing NMDA receptors with Ro 25-6981 prevented DCS restoration of pRh LTD in meth subjects. Thus, targeting pRh LTD may be a promising strategy to treat meth-induced cognitive impairment.

Receptor Reserve Moderates Mesolimbic Responses To Opioids In A Humanized Mouse Model Of The OPRM1 A118G Polymorphism Robinson JE, Vardy E, DiBerto JF, Chefer VI, White KL, Fish EW, Chen M, Gigante E, Krouse MC, Sun H, Thorsell A, Roth BL, Heilig M, Malanga CJ. Neuropsychopharmacology. 2015; 40(11): 2614-2622.
The OPRM1 A118G polymorphism is the most widely studied μ-opioid receptor (MOR) variant. Although its involvement in acute alcohol effects is well characterized, less is known about the extent to which it alters responses to opioids. Prior work has shown that both electrophysiological and analgesic responses to morphine but not to fentanyl are moderated by OPRM1 A118G variation, but the mechanism behind this dissociation is not known. Here the authors found that humanized mice carrying the 118GG allele (h/mOPRM1-118GG) were less sensitive than h/mOPRM1-118AA littermates to the rewarding effects of morphine and hydrocodone but not those of other opioids measured with intracranial self-stimulation. Reduced morphine reward in 118GG mice was associated with decreased dopamine release in the nucleus accumbens and reduced effects on GABA release in the ventral tegmental area that were not due to changes in drug potency or efficacy in vitro or receptor-binding affinity. Fewer MOR-binding sites were observed in h/mOPRM1-118GG mice, and pharmacological reduction of MOR availability unmasked genotypic differences in fentanyl sensitivity. These findings suggest that the OPRM1 A118G polymorphism decreases sensitivity to low-potency agonists by decreasing receptor reserve without significantly altering receptor function.

The Roles Of Dopamine and A1-Adrenergic Receptors In Cocaine Preferences In Female and Male Rats Perry AN, Westenbroek C, Jagannathan L, Becker JB. Neuropsychopharmacology. 2015; 40(12): 2696-2704.
Cocaine dependence is characterized by compulsive drug taking and reduced involvement in social, occupational, or recreational activities. Unraveling the diverse mechanisms contributing to the loss-of-interest in these 'non-drug' pursuits is essential for understanding the neurobiology of addiction and could provide additional targets for treating addiction. The study objectives were to examine changes in cocaine-induced dopamine (DA) overflow in the nucleus accumbens (NAc) over the course of self-administration and determine the roles of α1- and β-adrenergic receptors (AR) in the loss-of-interest in food rewards following the development of an addicted phenotype in male and female rats. Subjects were given access to cocaine and palatable food pellets in a choice self-administration paradigm to identify 'addicted' cocaine-preferring (CP) individuals and resistant pellet-preferring (PP) individuals based on their patterns of self-administration over 7 weeks. Cocaine-induced DA overflow in the NAc was examined with microdialysis early and late during self-administration (weeks 2 and 7). Subjects were treated in counter-balanced order with propranolol (β-AR antagonist), terazosin (α1-AR antagonist), or vehicle for an additional 3 weeks of self-administration. CP rats displayed increased motivation for cocaine and attenuated motivation for pellets following the development of cocaine preferences. In females, the estrous cycle affected pellet, but not cocaine, self-administration. CP rats displayed attenuated cocaine-induced DA overflow in the NAc. Propranolol enhanced cocaine reinforcement and reduced pellet intake, whereas terazosin enhanced motivation for pellets and reversed preferences in a subset of CP rats. The implications of these results for the treatment of addiction are discussed.

Stable Oncogenic Silencing In Vivo By Programmable and Targeted De Novo DNA Methylation In Breast Cancer Stolzenburg S, Beltran AS, Swift-Scanlan T, Rivenbark AG, Rashwan R, Blancafort P. Oncogene. 2015; 34(43): 5427-5435.
With the recent comprehensive mapping of cancer genomes, there is now a need for functional approaches to edit the aberrant epigenetic state of key cancer drivers to reprogram the epi-pathology of the disease. In this study the authors utilized a programmable DNA-binding methyltransferase to induce targeted incorporation of DNA methylation (DNAme) in the SOX2 oncogene in breast cancer through a six zinc finger (ZF) protein linked to DNA methyltransferase 3A (ZF-DNMT3A). The authors demonstrated long-lasting oncogenic repression, which was maintained even after suppression of ZF-DNMT3A expression in tumor cells. The de novo DNAme was faithfully propagated and maintained through cell generations even after the suppression of the expression of the chimeric methyltransferase in the tumor cells. Xenograft studies in NUDE mice demonstrated stable SOX2 repression and long-term breast tumor growth inhibition, which lasted for >100 days post implantation of the tumor cells in mice. This was accompanied with a faithful maintenance of DNAme in the breast cancer implants. In contrast, downregulation of SOX2 by ZF domains engineered with the Krueppel-associated box repressor domain resulted in a transient and reversible suppression of oncogenic gene expression. These results indicated that targeted de novo DNAme of the SOX2 oncogenic promoter was sufficient to induce long-lasting epigenetic silencing, which was not only maintained during cell division but also significantly delayed the tumorigenic phenotype of cancer cells in vivo, even in the absence of treatment. Here, the authors outline a genome-based targeting approach to long-lasting tumor growth inhibition with potential applicability to many other oncogenic drivers that are currently refractory to drug design.

Kalirin-9 and Kalirin-12 Play Essential Roles In Dendritic Outgrowth and Branching
Yan Y, Eipper BA, Mains RE. Cereb Cortex. 2015; 25(10): 3487-3501.
Proteins derived from the Kalrn gene, encoding 2 Rho guanine nucleotide exchange factor (GEF) domains, affect dendritic and axonal morphogenesis. The roles of endogenous Kalirin-9 (Kal9) and Kalirin-12 (Kal12), the Kalrn isoforms expressed before synaptogenesis, have not been studied in neurite growth and maturation during early development. The Caenorhabditis elegans and Drosophila melanogaster orthologues of Kalrn encode proteins equivalent to Kal9 but, lacking a kinase domain, neither organism expresses a protein equivalent to Kal12. Both in vivo and in vitro analyses of cortical neurons from total Kalrn knockout mice, lacking all major Kalirin isoforms, revealed a simplified dendritic arbor and reduced neurite length. Using isoform-specific shRNAs to reduce Kal9 or Kal12 expression in hippocampal cultures resulted in stunted dendritic outgrowth and branching in vitro, without affecting axonal polarity. Exposing hippocampal cultures to inhibitors of the first GEF domain of Kalirin (ITX3, Z62954982) blunted neurite outgrowth and branching, confirming its essential role, without altering the morphology of neurons not expressing Kalrn. In addition, exogenous expression of the active kinase domain unique to Kal12 increased neurite number and length, whereas that of the inactive kinase domain decreased neurite growth. Our results demonstrate that both endogenous Kal9 and endogenous Kal12 contribute to dendritic maturation in early development.

Silent Synapses Speak Up: Updates Of the Neural Rejuvenation Hypothesis Of Drug Addiction Huang YH, Schlüter OM, Dong Y. Neuroscientist. 2015; 21(5): 451-459.
A transient but prominent increase in the level of "silent synapses"--a signature of immature glutamatergic synapses that contain only NMDA receptors without stably expressed AMPA receptors--has been identified in the nucleus accumbens (NAc) following exposure to cocaine. As the NAc is a critical forebrain region implicated in forming addiction-associated behaviors, the initial discoveries have raised speculations about whether and how these drug-induced synapses mature and potentially contribute to addiction-related behaviors. Here, the authors summarize recent progress in recognizing the pathway-specific regulations of silent synapse maturation, and its diverse impacts on behavior. They provide an update of the guiding hypothesis--the "neural rejuvenation hypothesis"--with recently emerged evidence of silent synapses in cocaine craving and relapse.

Morphine Promotes Astrocyte-Preferential Differentiation Of Mouse Hippocampal Progenitor Cells Via PKCε-Dependent ERK Activation and TRBP Phosphorylation
Xu C, Zheng H, Loh HH, Law P-Y. Stem Cells. 2015; 33(9): 2762-2772.
Previously the authors have shown that morphine regulates adult neurogenesis by modulating miR-181a maturation and subsequent hippocampal neural progenitor cell (NPC) lineages. Using NPCs cultured from PKCε or β-arrestin2 knockout mice and the MAPK/ERK kinase inhibitor U0126, the authors demonstrate that regulation of NPC differentiation via the miR-181a/Prox1/Notch1 pathway exhibits ligand-dependent selectivity. In NPCs, morphine and fentanyl activate ERK via the PKCε- and β-arrestin-dependent pathways, respectively. After fentanyl exposure, the activated phospho-ERK translocates to the nucleus. Conversely, after morphine treatment, phospho-ERK remains in the cytosol and is capable of phosphorylating TAR RNA-binding protein (TRBP), a cofactor of Dicer. This augments Dicer activity and promotes the maturation of miR-181a. Furthermore, using NPCs transfected with wild-type TRBP, SΔA, and SΔD TRBP mutants, the authors confirmed the crucial role of TRBP phosphorylation in Dicer activity, miR-181a maturation, and finally the morphine-induced astrocyte-preferential differentiation of NPCs. Thus, morphine modulates the

lineage-specific differentiation of NPCs by PKCε-dependent ERK activation with subsequent TRBP phosphorylation and miR-181a maturation.

Blocking Infralimbic Basic Fibroblast Growth Factor (bFGF Or FGF2) Facilitates Extinction Of Drug Seeking After Cocaine Self-Administration Hafenbreidel M, Twining RC, Rafa Todd C, Mueller D. Neuropsychopharmacology. 2015; 40(13): 2907-2915.
Drug exposure results in structural and functional changes in brain regions that regulate reward and these changes may underlie the persistence of compulsive drug seeking and relapse. Neurotrophic factors, such as basic fibroblast growth factor (bFGF or FGF2), are necessary for neuronal survival, growth, and differentiation, and may contribute to these drug-induced changes. Following cocaine exposure, bFGF is increased in addiction-related brain regions, including the infralimbic medial prefrontal cortex (IL-mPFC). The IL-mPFC is necessary for extinction, but whether drug-induced overexpression of bFGF in this region affects extinction of drug seeking is unknown. Thus, the authors determined whether blocking bFGF in IL-mPFC would facilitate extinction following cocaine self-administration. Rats were trained to lever press for intravenous infusions of cocaine before extinction. Blocking bFGF in IL-mPFC before four extinction sessions resulted in facilitated extinction. In contrast, blocking bFGF alone was not sufficient to facilitate extinction, as blocking bFGF and returning rats to their home cage had no effect on subsequent extinction. Furthermore, bFGF protein expression increased in IL-mPFC following cocaine self-administration, an effect reversed by extinction. These results suggest that cocaine-induced overexpression of bFGF inhibits extinction, as blocking bFGF during extinction permits rapid extinction. Therefore, targeted reductions in bFGF during therapeutic interventions could enhance treatment outcomes for addiction.

Genome-wide Specificity Of DNA Binding, Gene Regulation, and Chromatin Remodeling By TALE- and CRISPR/Cas9-based Transcriptional Activators Polstein LR, Perez-Pinera P, Kocak DD, Vockley CM, Bledsoe P, Song L, Safi A, Crawford GE, Reddy TE, Gersbach CA. Genome Res. 2015; 25(8): 1158-1169.
Genome engineering technologies based on the CRISPR/Cas9 and TALE systems are enabling new approaches in science and biotechnology. However, the specificity of these tools in complex genomes and the role of chromatin structure in determining DNA binding are not well understood. The authors analyzed the genome-wide effects of TALE- and CRISPR-based transcriptional activators in human cells using ChIP-seq to assess DNA-binding specificity and RNA-seq to measure the specificity of perturbing the transcriptome. Additionally, DNase-seq was used to assess genome-wide chromatin remodeling that occurs as a result of their action. Their results show that these transcription factors are highly specific in both DNA binding and gene regulation and are able to open targeted regions of closed chromatin independent of gene activation. Collectively, these results underscore the potential for these technologies to make precise changes to gene expression for gene and cell therapies or fundamental studies of gene function.

Response Of The Ubiquitin-Proteasome System To Memory Retrieval After Extended-Access Cocaine Or Saline Self-Administration Werner CT, Milovanovic M, Christian DT, Loweth JA, Wolf ME. Neuropsychopharmacology. 2015; 40(13): 3006-3014.
The ubiquitin-proteasome system (UPS) has been implicated in the retrieval-induced destabilization of cocaine- and fear-related memories in Pavlovian paradigms. However, nothing is known about its role in memory retrieval after self-administration of cocaine, an operant paradigm, or how the length of withdrawal from cocaine may influence retrieval mechanisms. Here, the authors examined

UPS activity after an extended-access cocaine self-administration regimen that leads to withdrawal-dependent incubation of cue-induced cocaine craving. Controls self-administered saline. In initial experiments, memory retrieval was elicited via a cue-induced seeking/retrieval test on withdrawal day (WD) 50-60, when craving has incubated. The authors found that retrieval of cocaine- and saline-associated memories produced similar increases in polyubiquitinated proteins in the nucleus accumbens (NAc), compared with rats that did not undergo a seeking/retrieval test. Measures of proteasome catalytic activity confirmed similar activation of the UPS after retrieval of saline and cocaine memories. However, in a subsequent experiment in which testing was conducted on WD1, proteasome activity in the NAc was greater after retrieval of cocaine memory than saline memory. Analysis of other brain regions confirmed that effects of cocaine memory retrieval on proteasome activity, relative to saline memory retrieval, depend on withdrawal time. These results, combined with prior studies, suggest that the relationship between UPS activity and memory retrieval depends on training paradigm, brain region, and time elapsed between training and retrieval. The observation that mechanisms underlying cocaine memory retrieval change depending on the age of the memory has implications for development of memory destabilization therapies for cue-induced relapse in cocaine addicts.

A CHRNA5 Smoking Risk Variant Decreases the Aversive Effects Of Nicotine In Humans

Jensen KP, DeVito EE, Herman AI, Valentine GW, Gelernter J, Sofuoglu M. Neuropsychopharmacology. 2015; 40(12): 2813-2821.

Genome-wide association studies have implicated the CHRNA5-CHRNA3-CHRNB4 gene cluster in risk for heavy smoking and several smoking-related disorders. The heavy smoking risk allele might reduce the aversive effects of nicotine, but this hypothesis has not been tested in humans. The authors evaluated the effects of a candidate causal variant in CHRNA5, rs16969968, on the acute response to nicotine in European American (EA) and African American (AA) smokers (n=192; 50% AA; 73% male). Following overnight abstinence from nicotine, participants completed a protocol that included an intravenous (IV) dose of saline and two escalating IV doses of nicotine. The outcomes evaluated were the aversive, pleasurable, and stimulatory ratings of nicotine's effects, cardiovascular reactivity to nicotine, withdrawal severity, and cognitive performance before and after the nicotine administration session. The heavy smoking risk allele (rs16969968*A; frequency=28% (EA) and 6% (AA)) was associated with lower ratings of aversive effects ($P<5 \times 10(-8)$) with marked specificity. This effect was evident in EA and AA subjects analyzed as separate groups and was most robust at the highest nicotine dose. Rs16969968*A was also associated with greater improvement on a measure of cognitive control (Stroop Task) following nicotine administration. These findings support differential aversive response to nicotine as one likely mechanism for the association of CHRNA5-CHRNA3-CHRNB4 with heavy smoking.

Peptidomics For The Discovery And Characterization Of Neuropeptides and Hormones

Romanova EV, Sweedler JV. Trends Pharmacol Sci. 2015; 36(9): 579-586.

The discovery of neuropeptides as signaling molecules with paracrine or hormonal regulatory functions has led to trailblazing advances in physiology and fostered the characterization of numerous neuropeptide-binding G protein-coupled receptors (GPCRs) as potential drug targets. The impact on human health has been tremendous: approximately 30% of commercial drugs act via the GPCR pathway. However, about 25% of the GPCRs encoded by the mammalian genome still lack their pharmacological identity. Searching for the orphan GPCR endogenous ligands that are likely to be neuropeptides has proved to be a formidable task. Here the authors describe the mass spectrometry (MS)-based technologies and experimental strategies that have been successful in

achieving high-throughput characterization of endogenous peptides in nervous and endocrine systems.

Systemic AAV9 Gene Transfer In Adult GM1 Gangliosidosis Mice Reduces Lysosomal Storage In CNS and Extends Lifespan Weismann CM, Ferreira J, Keeler AM, Su Q, Qui L, Shaffer SA, Xu Z, Gao G, Sena-Esteves M. Hum Mol Genet. 2015; 24(15): 4353-4364.
GM1 gangliosidosis (GM1) is an autosomal recessive lysosomal storage disease where GLB1 gene mutations result in a reduction or absence of lysosomal acid β-galactosidase (βgal) activity. βgal deficiency leads to accumulation of GM1-ganglioside in the central nervous system (CNS). GM1 is characterized by progressive neurological decline resulting in generalized paralysis, extreme emaciation and death. In this study, the authors assessed the therapeutic efficacy of an adeno-associated virus (AAV) 9-mβgal vector infused systemically in adult GM1 mice (βGal(-/-)) at 1 × 10(11) or 3 × 10(11) vector genomes (vg). Biochemical analysis of AAV9-treated GM1 mice showed high βGal activity in liver and serum. Moderate βGal levels throughout CNS resulted in a 36-76% reduction in GM1-ganglioside content in the brain and 75-86% in the spinal cord. Histological analyses of the CNS of animals treated with 3 × 10(11) vg dose revealed increased presence of βgal and clearance of lysosomal storage throughout cortex, hippocampus, brainstem and spinal cord. Storage reduction in these regions was accompanied by a marked decrease in astrogliosis. AAV9 treatment resulted in improved performance in multiple tests of motor function and behavior. Also the majority of GM1 mice in the 3 × 10(11) vg cohort retained ambulation and rearing despite reaching the humane endpoint due to weight loss. Importantly, the median survival of AAV9 treatment groups (316-576 days) was significantly increased over controls (250-264 days). This study shows that moderate widespread expression of βgal in the CNS of GM1 gangliosidosis mice is sufficient to achieve significant biochemical impact with phenotypic amelioration and extension in lifespan.

Interactions Of The Antiviral Factor Interferon Gamma-Inducible Protein 16 (IFI16) Mediate Immune Signaling And Herpes Simplex Virus-1 Immunosuppression Diner BA, Lum KK, Javitt A, Cristea IM. Mol Cell Proteomics. 2015; 14(9): 2341-2356.
The interferon-inducible protein IFI16 has emerged as a critical antiviral factor and sensor of viral DNA. IFI16 binds nuclear viral DNA, triggering expression of antiviral cytokines during infection with herpesviruses. The knowledge of the mechanisms and protein interactions through which IFI16 exerts its antiviral functions remains limited. Here, the authors provide the first characterization of endogenous IFI16 interactions following infection with the prominent human pathogen herpes simplex virus 1 (HSV-1). By integrating proteomics and virology approaches, they identified and validated IFI16 interactions with both viral and host proteins that are involved in HSV-1 immunosuppressive mechanisms and host antiviral responses. The authors discover that during early HSV-1 infection, IFI16 is recruited to sub-nuclear puncta and subsequently targeted for degradation. They observed that the HSV-1 E3 ubiquitin ligase ICP0 is necessary, but not sufficient, for the proteasom e-mediated degradation of IFI16 following infection. They substantiate that this ICP0-mediated mechanism suppresses IFI16-dependent immune responses. Utilizing an HSV-1 strain that lacks ICP0 ubiquitin ligase activity provided a system for studying IFI16-dependent cytokine responses to HSV-1, as IFI16 levels were maintained throughout infection. The authors next defined temporal IFI16 interactions during this immune signaling response. They discovered and validated interactions with the viral protein ICP8 and cellular ND10 nuclear body components, sites at which HSV-1 DNA is present during infection. These interactions may be critical for IFI16

to bind to nuclear viral DNA. Altogether, our results provide critical insights into both viral inhibition of IFI16 and interactions that can contribute to IFI16 antiviral functions.

Engineering Humoral Immunity As Prophylaxis Or Therapy Deal CE, Balazs AB. Curr Opin Immunol. 2015; 35: 113-122.
In this review, the authors will discuss the field of engineered humoral immunity with an emphasis on recent work using viral vectors to produce antibodies in vivo. As an alternative to passive transfer of monoclonal antibody protein, a transgene encoding an antibody is delivered to cells via vector transduction, resulting in expression and secretion by the host cell. This review will summarize the evidence in support of this strategy as an alternative to traditional vaccines against infection and as novel therapeutics for a variety of diseases. Historically, humoral immunity has been engineered through vaccination and passive transfer of monoclonal antibodies. However, recent work suggests that vectors can be used to deliver transgenes encoding broadly neutralizing antibodies to non-hematopoietic tissues and can mediate long-term expression that is capable of preventing or treating infectious diseases. The production of engineered monoclonal antibodies allows for precise targeting and elimination of aberrant self-proteins that are characteristic of certain neurodegenerative disease. This approach has also been successfully used to combat cancer and addiction in several animal models. Despite the wide array of expression platforms that have been described, adeno-associated virus vectors have emerged as the frontrunner for rapid clinical translation.Recent advances in vector-mediated antibody expression have demonstrated the potential for such interventions to prevent infection and treat disease. As such, it offers an alternative to immunogen-based vaccine design and a novel therapeutic intervention by enabling precise manipulation of humoral immunity. Success translating these approaches to patients may enable the development of effective prevention against previously intractable pathogens that evade immunity such as HIV, influenza, malaria or HCV and may also enable new treatment options for neurodegenerative diseases such as Alzheimer's disease.

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; 78(7): 474-484.
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.We 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. We 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 $p = 8.9 \times 10(-5)$): rs9478495, rs3778150, rs9384169, and rs562859. Rs3778150, located in OPRM1 intron 1, was significantly replicated ($p = 6.3 \times 10(-5)$). Meta-analysis across all case-control cohorts resulted in $p = 4.3 \times 10(-8)$: 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 ($p = 1.48 \times 10(-6)$ 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).Our 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.

Metabolic Interplay Between Astrocytes and Neurons Regulates Endocannabinoid Action
Viader A, Blankman JL, Zhong P, Liu X, Schlosburg JE, Joslyn CM, Liu Q-S, Tomarchio AJ, Lichtman AH, Selley DE, Sim-Selley LJ, Cravatt BF. Cell Rep. 2015; 12(5): 798-808.
The endocannabinoid 2-arachidonoylglycerol (2-AG) is a retrograde lipid messenger that modulates synaptic function, neurophysiology, and behavior. 2-AG signaling is terminated by enzymatic hydrolysis-a reaction that is principally performed by monoacylglycerol lipase (MAGL). MAGL is broadly expressed throughout the nervous system, and the contributions of different brain cell types to the regulation of 2-AG activity in vivo remain poorly understood. Here, the authors genetically dissect the cellular anatomy of MAGL-mediated 2-AG metabolism in the brain and show that neurons and astrocytes coordinately regulate 2-AG content and endocannabinoid-dependent forms of synaptic plasticity and behavior. They also find that astrocytic MAGL is mainly responsible for converting 2-AG to neuroinflammatory prostaglandins via a mechanism that may involve transcellular shuttling of lipid substrates. Astrocytic-neuronal interplay thus provides distributed oversight of 2-AG metabolism and function and, through doing so, protects the nervous system from excessive CB1 receptor activation and promotes endocannabinoid crosstalk with other lipid transmitter systems.

Single-nucleotide-resolution Mapping Of M6A and M6Am Throughout the Transcriptome
Linder B, Grozhik AV, Olarerin-George AO, Meydan C, Mason CE, Jaffrey SR. Nat Methods. 2015; 12(8): 767-772.
N(6)-methyladenosine (m6A) is the most abundant modified base in eukaryotic mRNA and has been linked to diverse effects on mRNA fate. Current mapping approaches localize m6A residues to transcript regions 100-200 nt long but cannot identify precise m6A positions on a transcriptome-wide level. Here the authors developed m6A individual-nucleotide-resolution cross-linking and immunoprecipitation (miCLIP) and used it to demonstrate that antibodies to m6A can induce specific mutational signatures at m6A residues after ultraviolet light-induced antibody-RNA cross-linking and reverse transcription. They found that these antibodies similarly induced mutational signatures at N(6),2'-O-dimethyladenosine (m6Am), a modification found at the first nucleotide of certain mRNAs. Using these signatures, the authors mapped m6A and m6Am at single-nucleotide resolution in human and mouse mRNA and identified small nucleolar RNAs (snoRNAs) as a new class of m6A-containing non-coding RNAs (ncRNAs).

CRH Engagement Of the Locus Coeruleus Noradrenergic System Mediates Stress-Induced Anxiety McCall JG, Al-Hasani R, Siuda ER, Hong DY, Norris AJ, Ford CP, Bruchas MR. Neuron. 2015; 87(3): 605-620.
The locus coeruleus noradrenergic (LC-NE) system is one of the first systems engaged following a stressful event. While numerous groups have demonstrated that LC-NE neurons are activated by many different stressors, the underlying neural circuitry and the role of this activity in generating stress-induced anxiety has not been elucidated. Using a combination of in vivo chemogenetics, optogenetics, and retrograde tracing, the authors determine that increased tonic activity of the LC-

NE system is necessary and sufficient for stress-induced anxiety and aversion. Selective inhibition of LC-NE neurons during stress prevents subsequent anxiety-like behavior. Exogenously increasing tonic, but not phasic, activity of LC-NE neurons is alone sufficient for anxiety-like and aversive behavior. Furthermore, endogenous corticotropin-releasing hormone(+) (CRH(+)) LC inputs from the amygdala increase tonic LC activity, inducing anxiety-like behaviors. These studies position the LC-NE system as a critical mediator of acute stress-induced anxiety and offer a potential intervention for preventing stress-related affective disorders.

Coding the Direct/indirect Pathways By D1 and D2 Receptors Is Not Valid For Accumbens Projections Kupchik YM, Brown RM, Heinsbroek JA, Lobo MK, Schwartz DJ, Kalivas PW. Nat Neurosci. 2015; 18(9): 1230-1232.
It is widely accepted that D1 dopamine receptor-expressing striatal neurons convey their information directly to the output nuclei of the basal ganglia, whereas D2-expressing neurons do so indirectly via pallidal neurons. Combining optogenetics and electrophysiology, the authors found that this architecture does not apply to mouse nucleus accumbens projections to the ventral pallidum. Thus, current thinking attributing D1 and D2 selectivity to accumbens projections akin to dorsal striatal pathways needs to be reconsidered.

Synthetic Biology Approaches To Engineer T Cells Wu C-Y, Rupp LJ, Roybal KT, Lim WA. Curr Opin Immunol. 2015; 35: 123-130.
There is rapidly growing interest in learning how to engineer immune cells, such as T lymphocytes, because of the potential of these engineered cells to be used for therapeutic applications such as the recognition and killing of cancer cells. At the same time, our knowhow and capability to logically engineer cellular behavior is growing rapidly with the development of synthetic biology. Here the authors describe how synthetic biology approaches are being used to rationally alter the behavior of T cells to optimize them for therapeutic functions. They also describe future developments that will be important in order to construct safe and precise T cell therapeutics.

Rare, Low Frequency and Common Coding Variants In CHRNA5 and their Contribution To Nicotine Dependence In European and African Americans Olfson E, Saccone NL, Johnson EO, Chen L-S, Culverhouse R, Doheny K, Foltz SM, Fox L, Gogarten SM, Hartz S, Hetrick K, Laurie CC, Marosy B, Amin N, Arnett D, Barr RG, Bartz TM, Bertelsen S, Borecki IB, Brown MR, Chasman DI, van Duijn CM, Feitosa MF, Fox ER, Franceschini N, Franco OH, Grove ML, Guo X, Hofman A, Kardia SLR, Morrison AC, Musani SK, Psaty BM, Rao DC, Reiner AP, Rice K, Ridker PM, Rose LM, Schick UM, Schwander K, Uitterlinden AG, Vojinovic D, Wang J-C, Ware EB, Wilson G, Yao J, Zhao W, Breslau N, Hatsukami D, Stitzel JA, Rice J, Goate A, Bierut LJ. Mol Psychiatry. 2015.
The common nonsynonymous variant rs16969968 in the α5 nicotinic receptor subunit gene (CHRNA5) is the strongest genetic risk factor for nicotine dependence in European Americans and contributes to risk in African Americans. To comprehensively examine whether other CHRNA5 coding variation influences nicotine dependence risk, the authors performed targeted sequencing on 1582 nicotine-dependent cases (Fagerström Test for Nicotine Dependence score⩾4) and 1238 non-dependent controls, with independent replication of common and low frequency variants using 12 studies with exome chip data. Nicotine dependence was examined using logistic regression with individual common variants (minor allele frequency (MAF)⩾0.05), aggregate low frequency variants (0.05>MAF⩾0.005) and aggregate rare variants (MAF<0.005). Meta-analysis of primary results was performed with replication studies containing 12 174 heavy and 11 290 light smokers.

Next-generation sequencing with 180 × coverage identified 24 nonsynonymous variants and 2 frameshift deletions in CHRNA5, including 9 novel variants in the 2820 subjects. Meta-analysis confirmed the risk effect of the only common variant (rs16969968, European ancestry: odds ratio (OR)=1.3, P=3.5 × 10(-11); African ancestry: OR=1.3, P=0.01) and demonstrated that three low frequency variants contributed an independent risk (aggregate term, European ancestry: OR=1.3, P=0.005; African ancestry: OR=1.4, P=0.0006). The remaining 22 rare coding variants were associated with increased risk of nicotine dependence in the European American primary sample (OR=12.9, P=0.01) and in the same risk direction in African Americans (OR=1.5, P=0.37). These results indicate that common, low frequency and rare CHRNA5 coding variants are independently associated with nicotine dependence risk. These newly identified variants likely influence the risk for smoking-related diseases such as lung cancer.Molecular Psychiatry advance online publication, 4 August 2015; doi:10.1038/mp.2015.105.

Depression Of Serotonin Synaptic Transmission By the Dopamine Precursor L-DOPA Gantz SC, Levitt ES, Llamosas N, Neve KA, Williams JT. Cell Rep. 2015; 12(6): 944-954.
Imbalance between the dopamine and serotonin (5-HT) neurotransmitter systems has been implicated in the comorbidity of Parkinson's disease (PD) and psychiatric disorders. L-DOPA, the leading treatment of PD, facilitates the production and release of dopamine. This study assessed the action of L-DOPA on monoamine synaptic transmission in mouse brain slices. Application of L-DOPA augmented the D2-receptor-mediated inhibitory postsynaptic current (IPSC) in dopamine neurons of the substantia nigra. This augmentation was largely due to dopamine release from 5-HT terminals. Selective optogenetic stimulation of 5-HT terminals evoked dopamine release, producing D2-receptor-mediated IPSCs following treatment with L-DOPA. In the dorsal raphe, L-DOPA produced a long-lasting depression of the 5-HT1A-receptor-mediated IPSC in 5-HT neurons. When D2 receptors were expressed in the dorsal raphe, application of L-DOPA resulted in a D2-receptor-mediated IPSC. Thus, treatment with L-DOPA caused ectopic dopamine release from 5-HT terminals and a loss of 5-HT-mediated synaptic transmission.

Quantitative Assessment Of RNA-protein Interactions With High-throughput Sequencing-RNA Affinity Profiling Ozer A, Tome JM, Friedman RC, Gheba D, Schroth GP, Lis JT. Nat Protoc. 2015; 10(8): 1212-1233.
Because RNA-protein interactions have a central role in a wide array of biological processes, methods that enable a quantitative assessment of these interactions in a high-throughput manner are in great demand. Recently, the authors developed the high-throughput sequencing-RNA affinity profiling (HiTS-RAP) assay that couples sequencing on an Illumina GAIIx genome analyzer with the quantitative assessment of protein-RNA interactions. This assay is able to analyze interactions between one or possibly several proteins with millions of different RNAs in a single experiment. They have successfully used HiTS-RAP to analyze interactions of the EGFP and negative elongation factor subunit E (NELF-E) proteins with their corresponding canonical and mutant RNA aptamers. Here the authors provide a detailed protocol for HiTS-RAP that can be completed in about a month (8 d hands-on time). This includes the preparation and testing of recombinant proteins and DNA templates, clustering DNA templates on a flowcell, HiTS and protein binding with a GAIIx instrument, and finally data analysis. The authors also highlight aspects of HiTS-RAP that can be further improved and points of comparison between HiTS-RAP and two other recently developed methods, quantitative analysis of RNA on a massively parallel array (RNA-MaP) and RNA Bind-n-Seq (RBNS), for quantitative analysis of RNA-protein interactions.

Boosting Vaccine Efficacy the Natural (killer) Way Rydyznski CE, Waggoner SN. Trends Immunol. 2015; 36(9): 536-546.
Coordination of the innate and adaptive immune systems is paramount to the development of protective humoral and cellular immunity following vaccination. Natural killer (NK) cells are front-line soldiers of the innate immune system, and recent studies have revealed functions for NK cells in long-lived immune memory and the regulation of adaptive immune responses. These findings suggest that NK cells may play important roles in the development of efficacious vaccines, as well as, in some contexts, failed immunizations. Here, the authors review the current understanding of the immunomodulatory and memory differentiation capabilities of NK cells. They examine the context dependency of the mechanisms and the nature of NK cell-mediated modulation of the immune response, and discuss how these insights may impact immunization strategies and the development of next-generation vaccines.

Blocking The ZZ Domain Of Sequestosome1/p62 Suppresses Myeloma Growth and Osteoclast Formation In Vitro and Induces Dramatic Bone Formation In Myeloma-bearing Bones In Vivo Teramachi J, Silbermann R, Yang P, Zhao W, Mohammad KS, Guo J, Anderson JL, Zhou D, Feng R, Myint K-Z, Maertz N, Beumer JH, Eiseman JL, Windle JJ, Xie X-Q, Roodman GD, Kurihara N. Leukemia. 2015.
The authors reported that p62 (sequestosome 1) serves as a signaling hub in bone marrow stromal cells (BMSCs) for the formation of signaling complexes, including NFκB, p38MAPK and JNK, that are involved in the increased osteoclastogenesis and multiple myeloma (MM) cell growth induced by BMSCs that are key contributors to multiple myeloma bone disease (MMBD), and demonstrated that the ZZ domain of p62 (p62-ZZ) is required for BMSC enhancement of MMBD. The authors recently identified a novel p62-ZZ inhibitor, XRK3F2, which inhibits MM cell growth and BMSC growth enhancement of human MM cells. In the current study, they evaluate the relative specificity of XRK3F2 for p62-ZZ, characterize XRK3F2's capacity to inhibit growth of primary MM cells and human MM cell lines, and test the in vivo effects of XRK3F2 in the immunocompetent 5TGM1 MM model. The authors found that XRK3F2 induces dramatic cortical bone formation that is restricted to MM containing bones and blocked the effects and upregulation of tumor necrosis factor alpha (TNFα), an osteoblast (OB) differentiation inhibitor that is increased in the MM bone marrow microenvironment and utilizes signaling complexes formed on p62-ZZ, in BMSC. Interestingly, XRK3F2 had no effect on non-MM bearing bone. These results demonstrate that targeting p62 in MM models has profound effects on MMBD.Leukemia advance online publication, 2 October 2015; doi:10.1038/leu.2015.229.

Loss Of Striatonigral GABAergic Presynaptic Inhibition Enables Motor Sensitization In Parkinsonian Mice Borgkvist A, Avegno EM, Wong MY, Kheirbek MA, Sonders MS, Hen R, Sulzer D. Neuron. 2015; 87(5): 976-988.
Degeneration of dopamine (DA) neurons in Parkinson's disease (PD) causes hypokinesia, but DA replacement therapy can elicit exaggerated voluntary and involuntary behaviors that have been attributed to enhanced DA receptor sensitivity in striatal projection neurons. Here the authors reveal that in hemiparkinsonian mice, striatal D1 receptor-expressing medium spiny neurons (MSNs) directly projecting to the substantia nigra reticulata (SNr) lose tonic presynaptic inhibition by GABAB receptors. The absence of presynaptic GABAB response potentiates evoked GABA release from MSN efferents to the SNr and drives motor sensitization. This alternative mechanism of sensitization suggests a synaptic target for PD pharmacotherapy.

Distinct Subpopulations Of Nucleus Accumbens Dynorphin Neurons Drive Aversion and Reward Al-Hasani R, McCall JG, Shin G, Gomez AM, Schmitz GP, Bernardi JM, Pyo C-O, Park SI, Marcinkiewcz CM, Crowley NA, Krashes MJ, Lowell BB, Kash TL, Rogers JA, Bruchas MR. Neuron. 2015; 87(5): 1063-1077.
The nucleus accumbens (NAc) and the dynorphinergic system are widely implicated in motivated behaviors. Prior studies have shown that activation of the dynorphin-kappa opioid receptor (KOR) system leads to aversive, dysphoria-like behavior. However, the endogenous sources of dynorphin in these circuits remain unknown. The authors investigated whether dynorphinergic neuronal firing in the NAc is sufficient to induce aversive behaviors. They found that photostimulation of dynorphinergic cells in the ventral NAc shell elicits robust conditioned and real-time aversive behavior via KOR activation, and in contrast, photostimulation of dorsal NAc shell dynorphin cells induced a KOR-mediated place preference and was positively reinforcing. These results show previously unknown discrete subregions of dynorphin-containing cells in the NAc shell that selectively drive opposing behaviors. Understanding the discrete regional specificity by which NAc dynorphinerigic cells regulate preference and aversion provides insight into motivated behaviors that are dysregulated in stress, reward, and psychiatric disease.

Cell-to-Cell Transmission Of HIV-1 Is Required To Trigger Pyroptotic Death Of Lymphoid-Tissue-Derived CD4 T Cells Galloway NLK, Doitsh G, Monroe KM, Yang Z, Muñoz-Arias I, Levy DN, Greene WC. Cell Rep. 2015; 12(10): 1555-1563.
The progressive depletion of CD4 T cells underlies clinical progression to AIDS in untreated HIV-infected subjects. Most dying CD4 T cells correspond to resting nonpermissive cells residing in lymphoid tissues. Death is due to an innate immune response against the incomplete cytosolic viral DNA intermediates accumulating in these cells. The viral DNA is detected by the IFI16 sensor, leading to inflammasome assembly, caspase-1 activation, and the induction of pyroptosis, a highly inflammatory form of programmed cell death. We now show that cell-to-cell transmission of HIV is obligatorily required for activation of this death pathway. Cell-free HIV-1 virions, even when added in large quantities, fail to activate pyroptosis. These findings underscore the infected CD4 T cells as the major killing units promoting progression to AIDS and highlight a previously unappreciated role for the virological synapse in HIV pathogenesis.

5-HT1A Autoreceptors In the Dorsal Raphe Nucleus Convey Vulnerability To Compulsive Cocaine Seeking You I-J, Wright SR, Garcia-Garcia AL, Tapper AR, Gardner PD, Koob GF, David LE, Bohn LM, Wee S. Neuropsychopharmacology. 2015.
Cocaine addiction and depression are comorbid disorders. Although it is well recognized that 5-hydroxytryptamine (5-HT; serotonin) plays a central role in depression, our understanding of its role in addiction is notably lacking. The 5-HT system in the brain is carefully controlled by a combined process of regulating 5-HT neuron firing through 5-HT autoreceptors, neurotransmitter release, enzymatic degradation, and reuptake by transporters. This study tests the hypothesis that activation of 5-HT1A autoreceptors, which would lessen 5-HT neuron firing, contributes to cocaine-seeking behaviors. Using 5-HT neuron-specific reduction of 5-HT1A autoreceptor gene expression in mice, the authors demonstrate that 5-HT1A autoreceptors are necessary for cocaine conditioned place preference. In addition, using designer receptors exclusively activated by designer drugs (DREADDs) technology, they found that stimulation of the serotonergic dorsal raphe nucleus (DRN) afferents to the nucleus accumbens (NAc) abolishes cocaine reward and promotes antidepressive-like behaviors. Finally, using a rat model of compulsive-like cocaine self-administration, the authors found that inhibition of dorsal raphe 5-HT1A autoreceptors attenuates

cocaine self-administration in rats with 6 h extended access, but not 1 h access to the drug. Therefore, their findings suggest an important role for 5-HT1A autoreceptors, and thus DRNNAc 5-HT neuronal activity, in the etiology and vulnerability to cocaine reward and addiction. Moreover, their findings support a strategy for antagonizing 5-HT1A autoreceptors for treating cocaine addiction.Neuropsychopharmacology advance online publication, 7 October 2015; doi:10.1038/npp.2015.268.

Functional Maturation Of GABA Synapses During Postnatal Development Of the Monkey Dorsolateral Prefrontal Cortex Gonzalez-Burgos G, Miyamae T, Pafundo DE, Yoshino H, Rotaru DC, Hoftman G, Datta D, Zhang Y, Hammond M, Sampson AR, Fish KN, Bard Ermentrout G, Lewis DA. Cereb Cortex. 2015; 25(11): 4076-4093.
Development of inhibition onto pyramidal cells may be crucial for the emergence of cortical network activity, including gamma oscillations. In primate dorsolateral prefrontal cortex (DLPFC), inhibitory synaptogenesis starts in utero and inhibitory synapse density reaches adult levels before birth. However, in DLPFC, the expression levels of γ-aminobutyric acid (GABA) synapse-related gene products changes markedly during development until young adult age, suggesting a highly protracted maturation of GABA synapse function. Therefore, the authors examined the development of GABA synapses by recording GABAAR-mediated inhibitory postsynaptic currents (GABAAR-IPSCs) from pyramidal cells in the DLPFC of neonatal, prepubertal, peripubertal, and adult macaque monkeys. They found that the decay of GABAAR-IPSCs, possibly including those from parvalbumin-positive GABA neurons, shortened by prepubertal age, while their amplitude increased until the peripubertal period. Interestingly, both GABAAR-mediated quantal response size, estimated by miniature GABAAR-IPSCs, and the density of GABAAR synaptic appositions, measured with immunofluorescence microscopy, were stable with age. Simulations in a computational model network with constant GABA synapse density showed that the developmental changes in GABAAR-IPSC properties had a significant impact on oscillatory activity and predicted that, whereas DLPFC circuits can generate gamma frequency oscillations by prepubertal age, mature levels of gamma band power are attained at late stages of development.

Metabotropic Glutamate Receptor and Fragile X Signaling In A Female Model Of Escalated Aggression Been LE, Moore KM, Kennedy BC, Meisel RL. Biol Psychiatry. 2015.
Escalated aggression is a behavioral sign of numerous psychiatric disorders characterized by a loss of control. The neurobiology underlying escalated aggression is unknown and is particularly understudied in females. Research in our laboratory demonstrated that repeated aggressive experience in female hamsters resulted in an escalated response to future aggressive encounters and an increase in dendritic spine density on nucleus accumbens (NAc) neurons. The authors hypothesized that the activation of group I metabotropic glutamate receptor signaling though the fragile X mental retardation protein (FMRP) pathway may underlie synaptic plasticity associated with aggression escalation.Female hamsters were given five daily aggression tests with or without prior treatment with the metabotropic glutamate receptor 5 (mGluR5) antagonist 2-methyl-6-(phenylethynyl)-pyridine. Following aggression testing, messenger RNA expression and protein levels were measured in the nucleus accumbens for postsynaptic density protein 95 (PSD-95) and SAP90/PSD-95-associated protein 3, as well as the levels of phosphorylated FMRP.Experience-dependent escalation of aggression in female hamsters depends on activation of mGluR5 receptors. Furthermore, aggressive experience decreases phosphorylation of FMRP in the NAc, which is coupled to a long-term increase in the expression of the synaptic scaffolding proteins PSD-95 and SAP90/PSD-95-associated protein 3. Finally, the experience-dependent increase in PSD-95 is

prevented by antagonism of the mGluR5 receptor.Activation of the FMRP pathway by group I metabotropic glutamate receptors is involved in regulating synaptic plasticity following aggressive experience. The NAc is a novel target for preclinical studies of the treatment of escalated aggression, with the added benefit that emerging therapeutic approaches are likely to be effective in treating pathologic aggression in both female and male subjects.

The Basolateral Amygdala In Reward Learning and Addiction Wassum KM, Izquierdo A. Neurosci Biobehav Rev. 2015; 57: 271-283.
Sophisticated behavioral paradigms partnered with the emergence of increasingly selective techniques to target the basolateral amygdala (BLA) have resulted in an enhanced understanding of the role of this nucleus in learning and using reward information. Due to the wide variety of behavioral approaches many questions remain on the circumscribed role of BLA in appetitive behavior. In this review, the authors integrate conclusions of BLA function in reward-related behavior using traditional interference techniques (lesion, pharmacological inactivation) with those using newer methodological approaches in experimental animals that allow in vivo manipulation of cell type-specific populations and neural recordings. Secondly, from a review of appetitive behavioral tasks in rodents and monkeys and recent computational models of reward procurement, the authors derive evidence for BLA as a neural integrator of reward value, history, and cost parameters. Taken together, BLA codes specific and temporally dynamic outcome representations in a distributed network to orchestrate adaptive responses. The authors provide evidence that experiences with opiates and psychostimulants alter these outcome representations in BLA, resulting in long-term modified action.

How Is the Effectiveness Of Immune Surveillance Impacted By the Spatial Distribution Of Spreading Infections? Kadolsky UD, Yates AJ. Philos Trans R Soc Lond B Biol Sci. 2015; 370(1675).
What effect does the spatial distribution of infected cells have on the efficiency of their removal by immune cells, such as cytotoxic T lymphocytes (CTL)? If infected cells spread in clusters, CTL may initially be slow to locate them but subsequently kill more rapidly than in diffuse infections. The authors address this question using stochastic, spatially explicit models of CTL interacting with different patterns of infection. Rather than the effector: target ratio, the authors show that the relevant quantity is the ratio of a CTL's expected time to locate its next target (search time) to the average time it spends conjugated with a target that it is killing (handling time). For inefficient (slow) CTL, when the search time is always limiting, the critical density of CTL (that required to control 50% of infections, C(*)) is independent of the spatial distribution and derives from simple mass-action kinetics. For more efficient CTL such that handling time becomes limiting, mass-action underestimates C(*), and the more clustered an infection the greater is C(*). If CTL migrate chemotactically towards targets the converse holds-C(*) falls, and clustered infections are controlled most efficiently. Real infections are likely to spread patchily; this combined with even weak chemotaxis means that sterilizing immunity may be achieved with substantially lower numbers of CTL than standard models predict.

Thyroid Hormone Signaling: Contribution To Neural Function, Cognition, and Relationship To Nicotine Leach PT, Gould TJ. Neurosci Biobehav Rev. 2015; 57: 252-263.
Cigarette smoking is common despite its adverse effects on health, such as cardiovascular disease and stroke. Understanding the mechanisms that contribute to the addictive properties of nicotine makes it possible to target them to prevent the initiation of smoking behavior and/or increase the

chance of successful quit attempts. While highly addictive, nicotine is not generally considered to be as reinforcing as other drugs of abuse. There are likely other mechanisms at work that contribute to the addictive liability of nicotine. Nicotine modulates aspects of the endocrine system, including the thyroid, which is critical for normal cognitive functioning. It is possible that nicotine's effects on thyroid function may alter learning and memory, and this may underlie some of its addictive potential. Here, the authors review the literature on thyroid function and cognition, with a focus on how nicotine alters thyroid hormone signaling and the potential impact on cognition. Changes in cognition are a major symptom of nicotine addiction. Current anti-smoking therapies have modest success at best. If some of the cognitive effects of nicotine are mediated through the thyroid hormone system, then thyroid hormone agonists may be novel treatments for smoking cessation therapies. The content of this review is important because it clarifies the relationship between smoking and thyroid function, which has been ill-defined in the past. This review is timely because the reduction in smoking rates we have seen in recent decades, due to public awareness campaigns and public smoking bans, has leveled off in recent years. Therefore, novel treatment approaches are needed to help reduce smoking rates further.

Perirhinal Cortex MGlu5 Receptor Activation Reduces Relapse To Methamphetamine Seeking By Restoring Novelty Salience Peters J, Scofield MD, Ghee SM, Heinsbroek JA, Reichel CM. Neuropsychopharmacology. 2015.
Rats that have self-administered methamphetamine (meth) under long access, but not short access, conditions do not recognize novel objects. The perirhinal cortex is critical for novelty detection, and perirhinal metabotropic glutamate 5 receptors (mGlu5) are downregulated after long-access meth. The novel positive allosteric modulator (PAM) 1-(4-(2,4-difluorophenyl) piperazin-1-yl)-2-((4-fluorobenzyl)oxy)-ethanone, or DPFE, demonstrates improved solubility compared with other mGlu5 PAMs, thus allowing brain-site-specific pharmacological studies. Infusion of DPFE into perirhinal cortex restored novel object recognition in long-access meth rats. To investigate the impact of these cognitive enhancing effects on relapse, the authors tested the effects of DPFE infusions into perirhinal cortex on meth-seeking under two different test conditions. In the standard cue relapse test, perirhinal DPFE infusions did not alter meth-seeking in the presence of meth cues. However, in a novel cue relapse test, wherein animals were allowed to allocate responding between a novel cue and meth-conditioned cue, perirhinal DPFE infusions shifted the pattern of responding in long-access rats toward a profile resembling short-access rats, which respond equally for novel and meth cues. Perirhinal mGlu5 are thus a promising pharmacological target for the restoration of cognitive function in meth addicts. Targeting these receptors may also reduce relapse, particularly in situations where novel stimuli compete with conditioned stimuli for control over meth seeking.Neuropsychopharmacology advance online publication, 21 October 2015; doi:10.1038/npp.2015.283.

Nano-enabled Delivery Of Diverse Payloads Across Complex Biological Barriers Ross KA, Brenza TM, Binnebose AM, Phanse Y, Kanthasamy AG, Gendelman HE, Salem AK, Bartholomay LC, Bellaire BH, Narasimhan B. J Control Release. 2015; 219: 548-559.
Complex biological barriers are major obstacles for preventing and treating disease. Nanocarriers are designed to overcome such obstacles by enhancing drug delivery through physiochemical barriers and improving therapeutic indices. This review critically examines both biological barriers and nanocarrier payloads for a variety of drug delivery applications. A spectrum of nanocarriers is discussed that have been successfully developed for improving tissue penetration for preventing or treating a range of infectious, inflammatory, and degenerative diseases.

Towards Detection and Diagnosis Of Ebola Virus Disease At Point-of-care Kaushik A, Tiwari S, Dev Jayant R, Marty A, Nair M. Biosens Bioelectron. 2016; 75: 254-272.
Ebola outbreak-2014 (mainly Zaire strain related Ebola virus) has been declared most widely spread deadly persistent epidemic due to unavailability of rapid diagnostic, detection, and therapeutics. Ebola virus disease (EVD), a severe viral hemorrhagic fever syndrome caused by Ebola virus (EBOV) is transmitted by direct contact with the body fluids of infected person and objects contaminated with virus or infected animals. World Health Organization (WHO) has declared EVD epidemic as public health emergency of international concern with severe global economic burden. At fatal EBOV infection stage, patients usually die before the antibody response. Currently, rapid blood tests to diagnose EBOV infection include the antigen or antibodies capture using ELISA and RNA detection using RT/Q-PCR within 3-10 days after the onset of symptoms. Moreover, few nanotechnology-based colorimetric and paper-based immunoassay methods have been recently reported to detect Ebola virus. Unfortunately, these methods are limited to laboratory only. As state-of-the art (SoA) diagnostics time to confirm Ebola infection, varies from 6h to about 3 days, it causes delay in therapeutic approaches. Thus developing a cost-effective, rapid, sensitive, and selective sensor to detect EVD at point-of-care (POC) is certainly worth exploring to establish rapid diagnostics to decide therapeutics. This review highlights SoA of Ebola diagnostics and also a call to develop rapid, selective and sensitive POC detection of EBOV for global health care. We propose that adopting miniaturized electrochemical EBOV immunosensing can detect virus level at pM concentration within ~40min compared to 3 days of ELISA test at nM levels.

SPG7 Is An Essential and Conserved Component Of The Mitochondrial Permeability Transition Pore Shanmughapriya S, Rajan S, Hoffman NE, Higgins AM, Tomar D, Nemani N, Hines KJ, Smith DJ, Eguchi A, Vallem S, Shaikh F, Cheung M, Leonard NJ, Stolakis RS, Wolfers MP, Ibetti J, Chuprun JK, Jog NR, Houser SR, Koch WJ, Elrod JW, Madesh M. Mol Cell. 2015; 60(1): 47-62.
Mitochondrial permeability transition is a phenomenon in which the mitochondrial permeability transition pore (PTP) abruptly opens, resulting in mitochondrial membrane potential ($\Delta\Psi m$) dissipation, loss of ATP production, and cell death. Several genetic candidates have been proposed to form the PTP complex, however, the core component is unknown. The authors identified a necessary and conserved role for spastic paraplegia 7 (SPG7) in Ca(2+)- and ROS-induced PTP opening using RNAi-based screening. Loss of SPG7 resulted in higher mitochondrial Ca(2+) retention, similar to cyclophilin D (CypD, PPIF) knockdown with sustained $\Delta\Psi m$ during both Ca(2+) and ROS stress. Biochemical analyses revealed that the PTP is a heterooligomeric complex composed of VDAC, SPG7, and CypD. Silencing or disruption of SPG7-CypD binding prevented Ca(2+)- and ROS-induced $\Delta\Psi m$ depolarization and cell death. This study identifies an ubiquitously expressed IMM integral protein, SPG7, as a core component of the PTP at the OMM and IMM contact site.

Transcriptional Control Of Synaptic Remodeling Through Regulated Expression Of An Immunoglobulin Superfamily Protein He S, Philbrook A, McWhirter R, Gabel CV, Taub DG, Carter MH, Hanna IM, Francis MM, Miller 3rd, DM. Curr Biol. 2015; 25(19): 2541-2548.
Neural circuits are actively remodeled during brain development, but the molecular mechanisms that trigger circuit refinement are poorly understood. Here, the authors describe a transcriptional program in C. elegans that regulates expression of an Ig domain protein, OIG-1, to control the timing of synaptic remodeling. DD GABAergic neurons reverse polarity during larval development by exchanging the locations of pre- and postsynaptic components. In newly born larvae, DDs

receive cholinergic inputs in the dorsal nerve cord. These inputs are switched to the ventral side by the end of the first larval (L1) stage. VD class GABAergic neurons are generated in the late L1 and are postsynaptic to cholinergic neurons in the dorsal nerve cord but do not remodel. The authors investigated remodeling of the postsynaptic apparatus in DD and VD neurons using targeted expression of the acetylcholine receptor (AChR) subunit, ACR-12::GFP. They determined that OIG-1 antagonizes the relocation of ACR-12 from the dorsal side in L1 DD neurons. During the L1/L2 transition, OIG-1 is downregulated in DD neurons by the transcription factor IRX-1/Iroquois, allowing the repositioning of synaptic inputs to the ventral side. In VD class neurons, which normally do not remodel, the transcription factor UNC-55/COUP-TF turns off IRX-1, thus maintaining high levels of OIG-1 to block the removal of dorsally located ACR-12 receptors. OIG-1 is secreted from GABA neurons, but its anti-plasticity function is cell autonomous and may not require secretion. This study provides a novel mechanism by which synaptic remodeling is set in motion through regulated expression of an Ig domain protein.

Mechanism For Selective Synaptic Wiring Of Rod Photoreceptors Into the Retinal Circuitry and Its Role In Vision Cao Y, Sarria I, Fehlhaber KE, Kamasawa N, Orlandi C, James KN, Hazen JL, Gardner MR, Farzan M, Lee A, Baker S, Baldwin K, Sampath AP, Martemyanov KA. Neuron. 2015; 87(6): 1248-1260.
In the retina, rod and cone photoreceptors form distinct connections with different classes of downstream bipolar cells. However, the molecular mechanisms responsible for their selective connectivity are unknown. Here the authors identify a cell-adhesion protein, ELFN1, to be essential for the formation of synapses between rods and rod ON-bipolar cells in the primary rod pathway. ELFN1 is expressed selectively in rods where it is targeted to the axonal terminals by the synaptic release machinery. At the synapse, ELFN1 binds in trans to mGluR6, the postsynaptic receptor on rod ON-bipolar cells. Elimination of ELFN1 in mice prevents the formation of synaptic contacts involving rods, but not cones, allowing a dissection of the contributions of primary and secondary rod pathways to retinal circuit function and vision. The authors conclude that ELFN1 is necessary for the selective wiring of rods into the primary rod pathway and is required for high sensitivity of vision.

IFITM Proteins Restrict HIV-1 Infection By Antagonizing the Envelope Glycoprotein Yu J, Li M, Wilkins J, Ding S, Swartz TH, Esposito AM, Zheng Y-M, Freed EO, Liang C, Chen BK, Liu S-L. Cell Rep. 2015; 13(1): 145-156.
The interferon-induced transmembrane (IFITM) proteins have been recently shown to restrict HIV-1 and other viruses. Here, the authors provide evidence that IFITM proteins, particularly IFITM2 and IFITM3, specifically antagonize the HIV-1 envelope glycoprotein (Env), thereby inhibiting viral infection. IFITM proteins interact with HIV-1 Env in viral producer cells, leading to impaired Env processing and virion incorporation. Notably, the level of IFITM incorporation into HIV-1 virions does not strictly correlate with the extent of inhibition. Prolonged passage of HIV-1 in IFITM-expressing T lymphocytes leads to emergence of Env mutants that overcome IFITM restriction. The ability of IFITMs to inhibit cell-to-cell infection can be extended to HIV-1 primary isolates, HIV-2 and SIVs; however, the extent of inhibition appears to be virus-strain dependent. Overall, our study uncovers a mechanism by which IFITM proteins specifically antagonize HIV-1 Env to restrict HIV-1 infection and provides insight into the specialized role of IFITMs in HIV infection.

BIRC2/cIAP1 Is A Negative Regulator Of HIV-1 Transcription and Can Be Targeted By Smac Mimetics To Promote Reversal Of Viral Latency Pache L, Dutra MS, Spivak AM, Marlett JM, Murry JP, Hwang Y, Maestre AM, Manganaro L, Vamos M, Teriete P, Martins LJ, König R, Simon V, Bosque A, Fernandez-Sesma A, Cosford NDP, Bushman FD, Young JAT, Planelles V, Chanda SK. Cell Host Microbe. 2015; 18(3): 345-353.
Combination antiretroviral therapy (ART) is able to suppress HIV-1 replication to undetectable levels. However, the persistence of latent viral reservoirs allows for a rebound of viral load upon cessation of therapy. Thus, therapeutic strategies to eradicate the viral latent reservoir are critically needed. Employing a targeted RNAi screen, the authors identified the ubiquitin ligase BIRC2 (cIAP1), a repressor of the noncanonical NF-κB pathway, as a potent negative regulator of LTR-dependent HIV-1 transcription. Depletion of BIRC2 through treatment with small molecule antagonists known as Smac mimetics enhanced HIV-1 transcription, leading to a reversal of latency in a JLat latency model system. Critically, treatment of resting CD4+ T cells isolated from ART-suppressed patients with the histone deacetylase inhibitor (HDACi) panobinostat together with Smac mimetics resulted in synergistic activation of the latent reservoir. These data implicate Smac mimetics as useful agents for shock-and-kill strategies to eliminate the latent HIV reservoir.

Cellular Evidence For Efference Copy In Drosophila Visuomotor Processing Kim AJ, Fitzgerald JK, Maimon G. Nat Neurosci. 2015; 18(9): 1247-1255.
Each time a locomoting fly turns, the visual image sweeps over the retina and generates a motion stimulus. Classic behavioral experiments suggested that flies use active neural-circuit mechanisms to suppress the perception of self-generated visual motion during intended turns. Direct electrophysiological evidence, however, has been lacking. The authors found that visual neurons in Drosophila receive motor-related inputs during rapid flight turns. These inputs arrived with a sign and latency appropriate for suppressing each targeted cell's visual response to the turn. Precise measurements of behavioral and neuronal response latencies supported the idea that motor-related inputs to optic flow-processing cells represent internal predictions of the expected visual drive induced by voluntary turns. Motor-related inputs to small object-selective visual neurons could reflect either proprioceptive feedback from the turn or internally generated signals. These results in Drosophila echo the suppression of visual perception during rapid eye movements in primates, demonstrating common functional principles of sensorimotor processing across phyla.

NMR Structure and Dynamics Of the Agonist Dynorphin Peptide Bound To the Human Kappa Opioid Receptor O'Connor C, White KL, Doncescu N, Didenko T, Roth BL, Czaplicki G, Stevens RC, Wüthrich K, Milon A. Proc Natl Acad Sci U S A. 2015; 112(38): 11852-11857.
The structure of the dynorphin (1-13) peptide (dynorphin) bound to the human kappa opioid receptor (KOR) has been determined by liquid-state NMR spectroscopy. (1)H and (15)N chemical shift variations indicated that free and bound peptide is in fast exchange in solutions containing 1 mM dynorphin and 0.01 mM KOR. Radioligand binding indicated an intermediate-affinity interaction, with a Kd of ~200 nM. Transferred nuclear Overhauser enhancement spectroscopy was used to determine the structure of bound dynorphin. The N-terminal opioid signature, YGGF, was observed to be flexibly disordered, the central part of the peptide from L5 to R9 to form a helical turn, and the C-terminal segment from P10 to K13 to be flexibly disordered in this intermediate-affinity bound state. Combining molecular modeling with NMR provided an initial framework for understanding multistep activation of a G protein-coupled receptor by its cognate peptide ligand.

Chromatin Remodeling Factor Brg1 Supports the Early Maintenance and Late Responsiveness Of Nestin-Lineage Adult Neural Stem and Progenitor Cells Petrik David, Latchney SE, Masiulis I, Yun S, Zhang Z, Wu JI, Eisch AJ. Stem Cells. 2015.
Insights from embryonic development suggest chromatin remodeling is important in adult neural stem cells (aNSCs) maintenance and self-renewal, but this concept has not been fully explored in the adult brain. To assess the role of chromatin remodeling in adult neurogenesis, the authors inducibly deleted Brg1-the core subunit of SWI/SNF-like Brg1/Brm-associated factor chromatin remodeling complexes-in nestin-expressing aNSCs and their progeny in vivo and in culture. This resulted in abnormal adult neurogenesis in the hippocampus, which initially reduced hippocampal aNSCs and progenitor maintenance, and later reduced its responsiveness to physiological stimulation. Mechanistically, deletion of Brg1 appeared to impair cell cycle progression, which is partially due to elevated p53 pathway and p21 expression. Knockdown of p53 rescued the neurosphere growth defects caused by Brg1 deletion. These results show that epigenetic chromatin remodeling (via a Brg1 and p53/p21-dependent process) determines the aNSCs and progenitor maintenance and responsiveness of neurogenesis. Stem Cells 2015.

Regulator Of G-Protein Signaling 7 Regulates Reward Behavior By Controlling Opioid Signaling In the Striatum Sutton LP, Ostrovskaya O, Dao M, Xie K, Orland C, Smith RWS, Martemyanov KA. Biol Psychiatry. 2015.
Morphine mediates its euphoric and analgesic effects by acting on the μ-opioid receptor (MOR). MOR belongs to the family of G-protein coupled receptors whose signaling efficiency is controlled by the regulator of G-protein signaling (RGS) proteins. Our understanding of the molecular diversity of RGS proteins that control MOR signaling, their circuit specific actions, and underlying cellular mechanisms is very limited. The authors used genetic approaches to ablate regulator of G-protein signaling 7 (RGS7) both globally and in specific neuronal populations. They used conditioned place preference and self-administration paradigms to examine reward-related behavior and a battery of tests to assess analgesia, tolerance, and physical dependence to morphine. Electrophysiology approaches were applied to investigate the impact of RGS7 on morphine-induced alterations in neuronal excitability and plasticity of glutamatergic synapses. At least three animals were used for each assessment.Elimination of RGS7 enhanced reward, increased analgesia, delayed tolerance, and heightened withdrawal in response to morphine administration. RGS7 in striatal neurons was selectively responsible for determining the sensitivity of rewarding and reinforcing behaviors to morphine without affecting analgesia, tolerance, and withdrawal. In contrast, deletion of RGS7 in dopaminergic neurons did not influence morphine reward. RGS7 exerted its effects by controlling morphine-induced changes in excitability of medium spiny neurons in nucleus accumbens and gating the compositional plasticity of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid and N-methyl-D-aspartate receptors.This study identifies RGS7 as a novel regulator of MOR signaling by dissecting its circuit specific actions and pinpointing its role in regulating morphine reward by controlling the activity of nucleus accumbens neurons.

Sex Differences and Stress Across the Lifespan Bale TL, Epperson CN. Nat Neurosci. 2015; 18(10): 1413-1420.
Sex differences in stress responses can be found at all stages of life and are related to both the organizational and activational effects of gonadal hormones and to genes on the sex chromosomes. As stress dysregulation is the most common feature across neuropsychiatric diseases, sex differences in how these pathways develop and mature may predict sex-specific periods of vulnerability to disruption and increased disease risk or resilience across the lifespan. The aging

brain is also at risk to the effects of stress, where the rapid decline of gonadal hormones in women combined with cellular aging processes promote sex biases in stress dysregulation. In this Review, the authors discuss potential underlying mechanisms driving sex differences in stress responses and their relevance to disease. Although stress is involved in a much broader range of diseases than neuropsychiatric ones, we highlight here this area and its examples across the lifespan.

Viral-genetic Tracing Of the Input-output Organization Of A Central Noradrenaline Circuit Schwarz LA, Miyamichi K, Gao XJ, Beier KT, Weissbourd B, DeLoach K, Ren J, Ibanes S, Malenka RC, Kremer EJ, Luo L. Nature. 2015; 524(7563): 88-92.
Deciphering how neural circuits are anatomically organized with regard to input and output is instrumental in understanding how the brain processes information. For example, locus coeruleus noradrenaline (also known as norepinephrine) (LC-NE) neurons receive input from and send output to broad regions of the brain and spinal cord, and regulate diverse functions including arousal, attention, mood and sensory gating. However, it is unclear how LC-NE neurons divide up their brain-wide projection patterns and whether different LC-NE neurons receive differential input. Here the authors developed a set of viral-genetic tools to quantitatively analyse the input-output relationship of neural circuits, and applied these tools to dissect the LC-NE circuit in mice. Rabies-virus-based input mapping indicated that LC-NE neurons receive convergent synaptic input from many regions previously identified as sending axons to the locus coeruleus, as well as from newly identified presynaptic partners, including cerebellar Purkinje cells. The 'tracing the relationship between input and output' method (or TRIO method) enables trans-synaptic input tracing from specific subsets of neurons based on their projection and cell type. The authors found that LC-NE neurons projecting to diverse output regions receive mostly similar input. Projection-based viral labelling revealed that LC-NE neurons projecting to one output region also project to all brain regions we examined. Thus, the LC-NE circuit overall integrates information from, and broadcasts to, many brain regions, consistent with its primary role in regulating brain states. At the same time, we uncovered several levels of specificity in certain LC-NE sub-circuits. These tools for mapping output architecture and input-output relationship are applicable to other neuronal circuits and organisms. More broadly, our viral-genetic approaches provide an efficient intersectional means to target neuronal populations based on cell type and projection pattern.

RGS9-2--controlled Adaptations In The Striatum Determine the Onset Of Action and Efficacy Of Antidepressants In Neuropathic Pain States Mitsi V, Terzi D, Purushothaman I, Manouras L, Gaspari S, Neve RL, Stratinaki M, Feng J, Shen L, Zachariou V. Proc Natl Acad Sci U S A. 2015; 112(36): E5088-5097.
The striatal protein Regulator of G-protein signaling 9-2 (RGS9-2) plays a key modulatory role in opioid, monoamine, and other G-protein-coupled receptor responses. Here, the authors use the murine spared-nerve injury model of neuropathic pain to investigate the mechanism by which RGS9-2 in the nucleus accumbens (NAc), a brain region involved in mood, reward, and motivation, modulates the actions of tricyclic antidepressants (TCAs). Prevention of RGS9-2 action in the NAc increases the efficacy of the TCA desipramine and dramatically accelerates its onset of action. By controlling the activation of effector molecules by G protein α and βγ subunits, RGS9-2 affects several protein interactions, phosphoprotein levels, and the function of the epigenetic modifier histone deacetylase 5, which are important for TCA responsiveness. Furthermore, information from RNA-sequencing analysis reveals that RGS9-2 in the NAc affects the expression of many genes known to be involved in nociception, analgesia, and antidepressant drug actions. Our findings

provide novel information on NAc-specific cellular mechanisms that mediate the actions of TCAs in neuropathic pain states.

Contemporary Approaches To Neural Circuit Manipulation and Mapping: Focus On Reward and Addiction Saunders, Benjamin T; Richard, Jocelyn M; Janak, Patricia H. Philos Trans R Soc Lond B Biol Sci. 2015; 370(1677): 20140210.
Tying complex psychological processes to precisely defined neural circuits is a major goal of systems and behavioural neuroscience. This is critical for understanding adaptive behaviour, and also how neural systems are altered in states of psychopathology, such as addiction. Efforts to relate psychological processes relevant to addiction to activity within defined neural circuits have been complicated by neural heterogeneity. Recent advances in technology allow for manipulation and mapping of genetically and anatomically defined neurons, which when used in concert with sophisticated behavioural models, have the potential to provide great insight into neural circuit bases of behaviour. Here the authors discuss contemporary approaches for understanding reward and addiction, with a focus on midbrain dopamine and cortico-striato-pallidal circuits.

Endogenous Glucagon-like Peptide-1 Suppresses High-Fat Food Intake By Reducing Synaptic Drive Onto Mesolimbic Dopamine Neurons Wang X-F, Liu J-J, Xia J, Liu J, Mirabella V, Pang ZP. Cell Rep. 2015; 12(5): 726-733.
Glucagon-like peptide-1 (GLP-1) and its analogs act as appetite suppressants and have been proven to be clinically efficacious in reducing body weight in obese individuals. Central GLP-1 is expressed in a small population of brainstem cells located in the nucleus tractus solitarius (NTS), which project to a wide range of brain areas. However, it remains unclear how endogenous GLP-1 released in the brain contributes to appetite regulation. Using chemogenetic tools, the authors discovered that central GLP-1 acts on the midbrain ventral tegmental area (VTA) and suppresses high-fat food intake. They used integrated pathway tracing and synaptic physiology to further demonstrate that activation of GLP-1 receptors specifically reduces the excitatory synaptic strength of dopamine (DA) neurons within the VTA that project to the nucleus accumbens (NAc) medial shell. These data suggest that GLP-1 released from NTS neurons can reduce highly palatable food intake by suppressing mesolimbic DA signaling.

Blood-Derived CD4 T Cells Naturally Resist Pyroptosis During Abortive HIV-1 Infection Muñoz-Arias I, Doitsh G, Yang Z, Sowinski S, Ruelas D, Greene WC. Cell Host Microbe. 2015; 18(4): 463-470.
Progression to AIDS is driven by CD4 T cell depletion, mostly involving pyroptosis elicited by abortive HIV infection of CD4 T cells in lymphoid tissues. Inefficient reverse transcription in these cells leads to cytoplasmic accumulation of viral DNAs that are detected by the DNA sensor IFI16, resulting in inflammasome assembly, caspase-1 activation, and pyroptosis. Unexpectedly, the authors found that peripheral blood-derived CD4 T cells naturally resist pyroptosis. This resistance is partly due to their deeper resting state, resulting in fewer HIV-1 reverse transcripts and lower IFI16 expression. However, when co-cultured with lymphoid-derived cells, blood-derived CD4 T cells become sensitized to pyroptosis, likely recapitulating interactions occurring within lymphoid tissues. Sensitization correlates with higher levels of activated NF-κB, IFI16 expression, and reverse transcription. Blood-derived lymphocytes purified from co-cultures lose sensitivity to pyroptosis. These differences highlight how the lymphoid tissue microenvironment encountered by trafficking CD4 T lymphocytes dynamically shapes their biological response to HIV.

Interactions Of Iron, Dopamine and Neuromelanin Pathways In Brain Aging and Parkinson's Disease Zucca FA, Segura-Aguilar J, Ferrari E,Muñoz P, Paris I, Sulzer D, Sarna T, Casella L, Zecca L. Prog Neurobiol. 2015.
There are several interrelated mechanisms involving iron, dopamine, and neuromelanin in neurons. Neuromelanin accumulates during aging and is the catecholamine-derived pigment of the dopamine neurons of the substantia nigra and norepinephrine neurons of the locus coeruleus, the two neuronal populations most targeted in Parkinson's disease. Many cellular redox reactions rely on iron, however an altered distribution of reactive iron is cytotoxic. In fact, increased levels of iron in the brain of Parkinson's disease patients are present. Dopamine accumulation can induce neuronal death; however, excess dopamine can be removed by converting it into a stable compound like neuromelanin, and this process rescues the cell. Interestingly, the main iron compound in dopamine and norepinephrine neurons is the neuromelanin-iron complex, since neuromelanin is an effective metal chelator. Neuromelanin serves to trap iron and provide neuronal protection from oxidative stress. This equilibrium between iron, dopamine, and neuromelanin is crucial for cell homeostasis and in some cellular circumstances can be disrupted. Indeed, when neuromelanin-containing organelles accumulate high load of toxins and iron during aging a neurodegenerative process can be triggered. In addition, neuromelanin released by degenerating neurons activates microglia and the latter cause neurons death with further release of neuromelanin, then starting a self-propelling mechanism of neuroinflammation and neurodegeneration. Considering the above issues, age-related accumulation of neuromelanin in dopamine neurons shows an interesting link between aging and neurodegeneration.

Anhedonia, Reduced Cocaine Reward, and Dopamine Dysfunction In A Rat Model Of Posttraumatic Stress Disorder Enman NM, Arthur K, Ward SJ, Perrine SA, Unterwald EM. Biol Psychiatry. 2015; 78(12): 871-879.
Posttraumatic stress disorder (PTSD) co-occurs with substance use disorders at high rates, but the neurobiological basis of this relationship is largely unknown. PTSD and drug addiction each involve dysregulation of brain reward circuitry; therefore, the identification of pathology of the mesolimbic dopamine system may aid in understanding their functional relationship. Dopamine reward dysfunction also may be relevant to the mechanisms underlying the PTSD symptoms of anhedonia and emotional numbing. Single-prolonged stress (SPS) was used as a rat model of PTSD, and a series of behavioral and neuropharmacologic assays were applied to assess the impact of SPS on reward, cocaine intake, and components of the striatal dopamine system. Exposure to SPS increased anhedonia-like behaviors and decreased the rewarding properties of cocaine compared with control handling. Altered cocaine intake during extended access self-administration sessions was observed in rats exposed to SPS, further suggesting a difference in the reinforcing properties of cocaine following severe stress. SPS reduced tissue content of dopamine and its metabolites in the striatum, as well as altered striatal dopamine transporter and D2, but not D1, receptor densities.These results support a role for altered dopaminergic transmission in reduced reward function in PTSD. Pathology of the dopamine system and the degradation of reward processes may contribute to PTSD symptomology and have implications for co-occurring psychiatric disorders such as substance abuse or depression.

Action Potentials and Amphetamine Release Antipsychotic Drug From Dopamine Neuron Synaptic VMAT Vesicles Tucker KR, Block ER, Levitan ES. Proc Natl Acad Sci U S A. 2015; 112(32): E4485-4494.
Based on lysotracker red imaging in cultured hippocampal neurons, antipsychotic drugs (APDs) were proposed to accumulate in synaptic vesicles by acidic trapping and to be released in response to action potentials. Because many APDs are dopamine (DA) D2 receptor (D2R) antagonists, such a mechanism would be particularly interesting if it operated in midbrain DA neurons. Here, the APD cyamemazine (CYAM) is visualized directly by two-photon microscopy in substantia nigra and striatum brain slices. CYAM accumulated slowly into puncta based on vacuolar H(+)-ATPase activity and dispersed rapidly upon dissipating organelle pH gradients. Thus, CYAM is subject to acidic trapping and released upon deprotonation. In the striatum, Ca(2+)-dependent reduction of the CYAM punctate signal was induced by depolarization or action potentials. Striatal CYAM overlapped with the dopamine transporter (DAT). Furthermore, parachloroamphetamine (pCA), acting via vesicular monoamine transporter (VMAT), and a charged VMAT, substrate 1-methyl-4-phenylpyridinium (MPP(+)), reduced striatal CYAM. In vivo CYAM administration and in vitro experiments confirmed that clinically relevant CYAM concentrations result in vesicular accumulation and pCA-dependent release. These results show that some CYAM is in DA neuron VMAT vesicles and suggests a new drug interaction in which amphetamine induces CYAM deprotonation and release as a consequence of the H(+) countertransport by VMAT that accompanies vesicular uptake, but not by inducing exchange or acting as a weak base. Therefore, in the striatum, APDs are released with DA in response to action potentials and an amphetamine. This synaptic corelease is expected to enhance APD antagonism of D2Rs where and when dopaminergic transmission occurs.

The Dorsal Agranular Insular Cortex Regulates the Cued Reinstatement Of Cocaine-Seeking, But Not Food-Seeking, Behavior In Rats Cosme CV, Gutman AL, LaLumiere RT. Neuropsychopharmacology. 2015; 40(10): 2425-2433.
Prior studies suggest that the insular cortex (IC), and particularly its posterior region (the PIc), is involved in nicotine craving and relapse in humans and rodents. The present experiments were conducted to determine whether the IC and its different subregions regulate relapse to cocaine-seeking behavior in rats. To address this issue, male Sprague-Dawley rats underwent cocaine self-administration followed by extinction training and reinstatement tests. Before each reinstatement, the PIc or the more anterior dorsal agranular IC (AId) was inactivated to determine their roles in the reinstatement to cocaine seeking. In contrast to the nicotine findings, PIc inactivation had no effect on cue-induced reinstatement for cocaine seeking. However, AId inactivation reduced cued reinstatement while having no effect on cocaine-prime reinstatement. AId inactivation had no effect on reinstatement of food-seeking behavior induced by cues, a food-prime, or cues+food-prime. Based on previous work hypothesizing a role for corticotropin-releasing factor (CRF) in the IC during craving and relapse, a subsequent experiment found that CRF receptor-1 (CRF1) blockade in the AId similarly reduced cued reinstatement. These results suggest that the AId, along with CRF1 receptors in this region, regulates reinstatement to cocaine seeking, but not food seeking, depending on the type of reinstatement, whereas PIc activity does not influence cue-induced reinstatement.

H2S: A Novel Gasotransmitter That Signals By Sulfhydration Paul BD, Snyder SH. Trends Biochem Sci. 2015; 40(11): 687-700.
Hydrogen sulfide (H2S) is a member of the growing family of gasotransmitters. Once regarded as a noxious molecule predominantly present in the atmosphere, H2S is now known to be synthesized

endogenously in mammals. H2S participates in a myriad of physiological processes ranging from regulation of blood pressure to neuroprotection. Its chemical nature precludes H2S from being stored in vesicles and acting on receptor proteins in the fashion of other chemical messengers. Thus, novel cellular mechanisms have evolved to mediate its effects. This review focuses on sulfhydration (or persulfidation), which appears to be the principal post-translational modification elicited by H2S.

The Mitochondrial Permeability Transition Pore: Channel Formation By F-ATP Synthase, Integration In Signal Transduction, and Role In Pathophysiology Bernardi P, Rasola A, Forte M, Lippe G. Physiol Rev. 2015; 95(4): 1111-1155.
The mitochondrial permeability transition (PT) is a permeability increase of the inner mitochondrial membrane mediated by a channel, the permeability transition pore (PTP). After a brief historical introduction, we cover the key regulatory features of the PTP and provide a critical assessment of putative protein components that have been tested by genetic analysis. The discovery that under conditions of oxidative stress the F-ATP synthases of mammals, yeast, and Drosophila can be turned into Ca(2+)-dependent channels, whose electrophysiological properties match those of the corresponding PTPs, opens new perspectives to the field. The authors discuss structural and functional features of F-ATP synthases that may provide clues to its transition from an energy-conserving into an energy-dissipating device as well as recent advances on signal transduction to the PTP and on its role in cellular pathophysiology.

Retroviruses Use CD169-mediated Trans-infection Of Permissive Lymphocytes To Establish Infection Sewald X, Ladinsky MS, Uchil PD, Beloor J, Pi R, Herrmann C, Motamedi N, Murooka TT, Brehm MA, Greiner DL, Shultz LD, Mempel TR, Bjorkman PJ, Kumar P, Mothes W. Science. 2015; 350(6260): 563-567.
Dendritic cells can capture and transfer retroviruses in vitro across synaptic cell-cell contacts to uninfected cells, a process called trans-infection. Whether trans-infection contributes to retroviral spread in vivo remains unknown. Here, the authors visualize how retroviruses disseminate in secondary lymphoid tissues of living mice. They demonstrate that murine leukemia virus (MLV) and human immunodeficiency virus (HIV) are first captured by sinus-lining macrophages. CD169/Siglec-1, an I-type lectin that recognizes gangliosides, captures the virus. MLV-laden macrophages then form long-lived synaptic contacts to trans-infect B-1 cells. Infected B-1 cells subsequently migrate into the lymph node to spread the infection through virological synapses. Robust infection in lymph nodes and spleen requires CD169, suggesting that a combination of fluid-based movement followed by CD169-dependent trans-infection can contribute to viral spread.

Alteration In 5-hydroxymethylcytosine-mediated Epigenetic Regulation Leads To Purkinje Cell Vulnerability In ATM Deficiency Jiang D, Zhang Y, Hart RP, Chen J, Herrup K, Li J. Brain. 2015; 138(Pt 12): 3520-3536.
A long-standing mystery surrounding ataxia-telangiectasia is why it is mainly cerebellar neurons, Purkinje cells in particular, that appear vulnerable to ATM deficiency. Here the authors present data showing that 5-hydroxymethylcytosine (5hmC), a newly recognized epigenetic marker found at high levels in neurons, is substantially reduced in human ataxia-telangiectasia and Atm(-/-) mouse cerebellar Purkinje cells. The authors further show that TET1, an enzyme that converts 5-methylcytosine (5mC) to 5hmC, responds to DNA damage and manipulation of TET1 activity directly affects the DNA damage signalling and ATM-deficient neuronal cell cycle re-entry and death. Quantitative genome-wide analysis of 5hmC-containing sequences shows that in ATM

deficiency there is a cerebellum- and Purkinje cell-specific shift in 5hmC enrichment in both regulatory elements and repeated sequences. Finally, they verify that TET1-mediated 5hmC production is linked to the degenerative process of Purkinje cells and behavioural deficits in Atm(-/-) mice. Taken together, the selective loss of 5hmC plays a critical role in driving Purkinje cell vulnerability in ATM deficiency.

Perinatal Deiodinase 2 Expression In Hepatocytes Defines Epigenetic Susceptibility To Liver Steatosis and Obesity Fonseca TL, Fernandes GW, McAninch EA, Bocco BMLC, Abdalla SM, Ribeiro MO, Mohácsik P, Fekete C, Li D, Xing X, Wang T, Gereben B, Bianco AC. Proc Natl Acad Sci U S A. 2015; 112(45): 14018-14023.
Thyroid hormone binds to nuclear receptors and regulates gene transcription. Here the authors report that in mice, at around the first day of life, there is a transient surge in hepatocyte type 2 deiodinase (D2) that activates the prohormone thyroxine to the active hormone triiodothyronine, modifying the expression of ~165 genes involved in broad aspects of hepatocyte function, including lipid metabolism. Hepatocyte-specific D2 inactivation (ALB-D2KO) is followed by a delay in neonatal expression of key lipid-related genes and a persistent reduction in peroxisome proliferator-activated receptor-γ expression. Notably, the absence of a neonatal D2 peak significantly modifies the baseline and long-term hepatic transcriptional response to a high-fat diet (HFD). Overall, changes in the expression of approximately 400 genes represent the HFD response in control animals toward the synthesis of fatty acids and triglycerides, whereas in ALB-D2KO animals, the response is limited to a very different set of only approximately 200 genes associated with reverse cholesterol transport and lipase activity. A whole genome methylation profile coupled to multiple analytical platforms indicate that 10-20% of these differences can be related to the presence of differentially methylated local regions mapped to sites of active/suppressed chromatin, thus qualifying as epigenetic modifications occurring as a result of neonatal D2 inactivation. The resulting phenotype of the adult ALB-D2KO mouse is dramatic, with greatly reduced susceptibility to diet-induced steatosis, hypertriglyceridemia, and obesity.

Parent-of-Origin Effects Of The APOB Gene On Adiposity In Young Adults Hochner H, Allard C, Granot-Hershkovitz E, Chen J, Sitlani CM, Sazdovska S, Lumley T, McKnight B, Rice K, Enquobahrie DA, Meigs JB, Kwok P, Hivert M-F, Borecki IB, Gomez F, Wang T, van Duijn C, Amin N, Rotter JI, Stamatoyannopoulos J, Meiner V, Manor O, Dupuis J, Friedlander Y, Siscovick DS. PLoS Genet. 2015; 11(10): e1005573.
Loci identified in genome-wide association studies (GWAS) of cardio-metabolic traits account for a small proportion of the traits' heritability. To date, most association studies have not considered parent-of-origin effects (POEs). Here the authors report investigation of POEs on adiposity and glycemic traits in young adults. The Jerusalem Perinatal Family Follow-Up Study (JPS), comprising 1250 young adults and their mothers was used for discovery. Focusing on 18 genes identified by previous GWAS as associated with cardio-metabolic traits, the authors used linear regression to examine the associations of maternally- and paternally-derived offspring minor alleles with body mass index (BMI), waist circumference (WC), fasting glucose and insulin. They replicated and meta-analyzed JPS findings in individuals of European ancestry aged ≤50 belonging to pedigrees from the Framingham Heart Study, Family Heart Study and Erasmus Rucphen Family study (total N≅4800). The authors considered p<2.7x10-4 statistically significant to account for multiple testing. They identified a common coding variant in the 4th exon of APOB (rs1367117) with a significant maternally-derived effect on BMI (β = 0.8; 95%CI:0.4,1.1; p = 3.1x10-5) and WC (β = 2.7; 95%CI:1.7,3.7; p = 2.1x10-7). The corresponding paternally-derived effects were non-

significant (p>0.6). Suggestive maternally-derived associations of rs1367117 were observed with fasting glucose (β = 0.9; 95%CI:0.3,1.5; p = 4.0x10-3) and insulin (ln-transformed, β = 0.06; 95%CI:0.03,0.1; p = 7.4x10-4). Bioinformatic annotation for rs1367117 revealed a variety of regulatory functions in this region in liver and adipose tissues and a 50% methylation pattern in liver only, consistent with allelic-specific methylation, which may indicate tissue-specific POE. These findings demonstrate a maternal-specific association between a common APOB variant and adiposity, an association that was not previously detected in GWAS. These results provide evidence for the role of regulatory mechanisms, POEs specifically, in adiposity. In addition this study highlights the benefit of utilizing family studies for deciphering the genetic architecture of complex traits.

Different Motif Requirements For The Localization Zipcode Element Of B-actin MRNA Binding By HuD and ZBP1 Kim HH, Lee SJ, Gardiner AS, Perrone-Bizzozero NI, Yoo S. Nucleic Acids Res. 2015; 43(15): 7432-7446.
Interactions of RNA-binding proteins (RBPs) with their target transcripts are essential for regulating gene expression at the posttranscriptional level including mRNA export/localization, stability, and translation. ZBP1 and HuD are RBPs that play pivotal roles in mRNA transport and local translational control in neuronal processes. While HuD possesses three RNA recognition motifs (RRMs), ZBP1 contains two RRMs and four K homology (KH) domains that either increase target specificity or provide a multi-target binding capability. Here the authors used isolated cis-element sequences of the target mRNA to examine directly protein-RNA interactions in cell-free systems. They found that both ZBP1 and HuD bind the zipcode element in rat β-actin mRNA's 3' UTR. Differences between HuD and ZBP1 were observed in their binding preference to the element. HuD showed a binding preference for U-rich sequence. In contrast, ZBP1 binding to the zipcode RNA depended more on the structural level, as it required the proper spatial organization of a stem-loop that is mainly determined by the U-rich element juxtaposed to the 3' end of a 5'-ACACCC-3' motif. On the basis of this work, the authors propose that ZBP1 and HuD bind to overlapping sites in the β-actin zipcode, but they recognize different features of this target sequence.

The Psychology and Neuroscience Of Curiosity Kidd C, Hayden BY. Neuron. 2015; 88(3): 449-460.
Curiosity is a basic element of our cognition, but its biological function, mechanisms, and neural underpinning remain poorly understood. It is nonetheless a motivator for learning, influential in decision-making, and crucial for healthy development. One factor limiting our understanding of it is the lack of a widely agreed upon delineation of what is and is not curiosity. Another factor is the dearth of standardized laboratory tasks that manipulate curiosity in the lab. Despite these barriers, recent years have seen a major growth of interest in both the neuroscience and psychology of curiosity. In this Perspective, the authors advocate for the importance of the field, provide a selective overview of its current state, and describe tasks that are used to study curiosity and information-seeking. The authors propose that, rather than worry about defining curiosity, it is more helpful to consider the motivations for information-seeking behavior and to study it in its ethological context.

Molecular Histochemistry Identifies Peptidomic Organization and Reorganization Along Striatal Projection Units Hishimoto A, Nomaru H, Ye K, Nishi A, Lim J, Aguilan JT, Nieves E, Kang G, Angeletti RH, Hiroi N. Biol Psychiatry. 2015.
Matrix-assisted laser desorption ionization (MALDI) imaging mass spectrometry (IMS) (MALDI-IMS) provides a technical means for simultaneous analysis of precise anatomic localization and regulation of peptides. The authors explored the technical capability of matrix-assisted laser desorption ionization mass spectrometry for characterization of peptidomic regulation by an addictive substance along two distinct projection systems in the mouse striatum. The spatial expression patterns of substance P and proenkephalin, marker neuropeptides of two distinct striatal projection neurons, were negatively correlated at baseline. The authors detected 768 mass/charge (m/z) peaks whose expression levels were mostly negatively and positively correlated with expression levels of substance P and proenkephalin A (amino acids 218-228), respectively, within the dorsal striatum. After nicotine administration, there was a positive shift in correlation of mass/charge peak expression levels with substance P and proenkephalin A (218-228). The authors' exploratory analyses demonstrate the technical capacity of MALDI-IMS for comprehensive identification of peptidomic regulation patterns along histochemically distinguishable striatal projection pathways.

Coordination Of M(6)A MRNA Methylation and Gene Transcription By ZFP217 Regulates Pluripotency and Reprogramming Aguilo F, Zhang F, Sancho A, Fidalgo M, Di Cecilia S, Vashisht A, Lee D-F, Chen C-H, Rengasamy M, Andino B, Jahouh F, Roman A, Krig SR, Wang R, Zhang W, Wohlschlegel JA, Wang J, Walsh MJ. Cell Stem Cell. 2015; 17(6): 689-704.
Epigenetic and epitranscriptomic networks have important functions in maintaining the pluripotency of embryonic stem cells (ESCs) and somatic cell reprogramming. However, the mechanisms integrating the actions of these distinct networks are only partially understood. Here the authors show that the chromatin-associated zinc finger protein 217 (ZFP217) coordinates epigenetic and epitranscriptomic regulation. ZFP217 interacts with several epigenetic regulators, activates the transcription of key pluripotency genes, and modulates N6-methyladenosine (m(6)A) deposition on their transcripts by sequestering the enzyme m(6)A methyltransferase-like 3 (METTL3). Consistently, Zfp217 depletion compromises ESC self-renewal and somatic cell reprogramming, globally increases m(6)A RNA levels, and enhances m(6)A modification of the Nanog, Sox2, Klf4, and c-Myc mRNAs, promoting their degradation. ZFP217 binds its own target gene mRNAs, which are also METTL3 associated, and is enriched at promoters of m(6)A-modified transcripts. Collectively, these findings shed light on how a transcription factor can tightly couple gene transcription to m(6)A RNA modification to ensure ESC identity.

Epigenetic Effects Of Cannabis Exposure Szutorisz H, Hurd YL. Biol Psychiatry. 2015.
The past decade has witnessed a number of societal and political changes that have raised critical questions about the long-term impact of marijuana (Cannabis sativa) that are especially important given the prevalence of its abuse and that potential long-term effects still largely lack scientific data. Disturbances of the epigenome have generally been hypothesized as the molecular machinery underlying the persistent, often tissue-specific transcriptional and behavioral effects of cannabinoids that have been observed within one's lifetime and even into the subsequent generation. Here, the authors provide an overview of the current published scientific literature that has examined epigenetic effects of cannabinoids. Though mechanistic insights about the epigenome remain sparse, accumulating data in humans and animal models have begun to reveal aberrant epigenetic modifications in brain and the periphery linked to cannabis exposure. Expansion of such knowledge

and causal molecular relationships could help provide novel targets for future therapeutic interventions.

APP and APLP2 Interact With the Synaptic Release Machinery and Facilitate Transmitter Release At Hippocampal Synapses Fanutza T, Del Prete D, Ford MJ, Castillo PE, D'Adamio L. Elife. 2015; 4.
The Amyloid precursor protein (APP), whose mutations cause familial Alzheimer's disease, interacts with the synaptic release machinery suggesting a role in neurotransmission. Here the authors mapped this interaction to the NH2-terminal region of the APP intracellular domain. A peptide encompassing this binding domain -named JCasp- is naturally produced by a γ-secretase/ caspase double-cut of APP. JCasp interferes with the APP-presynaptic proteins interaction and, if linked to a cell-penetrating peptide, reduces glutamate release in acute hippocampal slices from wild-type but not APP deficient mice, indicating that JCasp inhibits APP function. The APP-like protein-2 (APLP2) also binds the synaptic release machinery. Deletion of APP and APLP2 produces synaptic deficits similar to those caused by JCasp. These data support the notion that APP and APLP2 facilitate transmitter release, likely through the interaction with the neurotransmitter release machinery. Given the link of APP to Alzheimer's disease, alterations of this synaptic role of APP could contribute to dementia.

Extracellular Thiol Isomerases and Their Role In Thrombus Formation Schulman S, Bendapudi P, Sharda A, Chen V,Bellido-Martin L, Jasuja R, Furie BC, Flaumenhaft R, Furie B. Antioxid Redox Signal. 2015.
The mammalian endoplasmic reticulum (ER) houses a large family of twenty thioredoxin-like proteins of which protein disulfide isomerase (PDI) is the archetypal member. Although the PDI family is best known for its role in oxidative protein folding of secretory proteins in the ER, these thioredoxin-like proteins fulfill ever-expanding roles, both within the secretory pathway and beyond. Secreted PDI family proteins have now been shown to serve a critical role in platelet thrombus formation and fibrin generation. Utilizing intravital microscopy to visualize thrombus formation in mice, the authors have demonstrated the presence of extracellular PDI antigen during thrombus formation following injury of the vascular wall. Inhibition of PDI abrogates thrombus formation in vivo (16, 26, 46, 55). These observations have been extended to other PDI family members, including ERp57 (39, 116, 118, 123) and ERp5 (77). The vascular thiol isomerases are those PDI family members secreted from platelets and/or endothelium (40): PDI, ERp57, ERp5, ERp72, ERp44, ERp29, and TMX3. The authors focus here on PDI (16, 46, 55), ERp57 (39, 116, 118, 123), and ERp5 (77), which have been implicated in thrombus formation in vivo. It would appear that a system of thiol isomerase redox catalysts has been hijacked from the ER to regulate thrombus formation in the vasculature. How this redox system is trafficked to and regulated at the cell surface, the identity of extracellular substrates, why so many thiol isomerases are required, and which thiol isomerase functions are necessary are critical unanswered questions in understanding the role of thiol isomerases in thrombus formation.

Synaptic Interactions and Inhibitory Regulation In Auditory Cortex Askew CE, Metherate R. Biol Psychol. 2015.
This Special Issue focuses on the auditory-evoked mismatch negativity (MMN), an electrophysiological index of change, and its reduction in schizophrenia. The following brief review is an attempt to complement the behavioral and clinical contributions to the Special Issue by providing basic information on synaptic interactions and processing in auditory cortex. A key

observation in previous studies is that the MMN involves activation of cortical N-methyl-d-aspartate (NMDA) receptors. Yet, NMDA receptor activation is regulated by a number of synaptic events, which also may contribute to the MMN reduction in schizophrenia. Accordingly, this review will focus on synaptic interactions, notably inhibitory regulation of NMDA receptor-mediated activity, in auditory cortex.

Mesolimbic Dopamine Signals the Value Of Work Hamid AA, Pettibone JR, Mabrouk OS, Hetrick VL, Schmidt R, Vander Weele CM, Kennedy RT, Aragona BJ, Berke JD. Nat Neurosci. 2015.
Dopamine cell firing can encode errors in reward prediction, providing a learning signal to guide future behavior. Yet dopamine is also a key modulator of motivation, invigorating current behavior. Existing theories propose that fast (phasic) dopamine fluctuations support learning, whereas much slower (tonic) dopamine changes are involved in motivation. The authors examined dopamine release in the nucleus accumbens across multiple time scales, using complementary microdialysis and voltammetric methods during adaptive decision-making. They found that minute-by-minute dopamine levels covaried with reward rate and motivational vigor. Second-by-second dopamine release encoded an estimate of temporally discounted future reward (a value function). Changing dopamine immediately altered willingness to work and reinforced preceding action choices by encoding temporal-difference reward prediction errors. These results indicate that dopamine conveys a single, rapidly evolving decision variable, the available reward for investment of effort, which is employed for both learning and motivational functions.

Brain Circuits Encoding Reward From Pain Relief Navratilova E, Atcherley CW, Porreca F. Trends Neurosci. 2015.
Relief from pain in humans is rewarding and pleasurable. Primary rewards, or reward-predictive cues, are encoded in brain reward/motivational circuits. While considerable advances have been made in our understanding of reward circuits underlying positive reinforcement, less is known about the circuits underlying the hedonic and reinforcing actions of pain relief. The authors review findings from electrophysiological, neuroimaging, and behavioral studies supporting the concept that the rewarding effect of pain relief requires opioid signaling in the anterior cingulate cortex (ACC), activation of midbrain dopamine neurons, and the release of dopamine in the nucleus accumbens (NAc). Understanding of circuits that govern the reward of pain relief may allow the discovery of more effective and satisfying therapies for patients with acute or chronic pain.

Sweet and Bitter Taste In the Brain Of Awake Behaving Animals Peng Y, Gillis-Smith S, Jin H, Tränkner D, Ryba NJP, Zuker CS. Nature. 2015; 527(7579): 512-515.
Taste is responsible for evaluating the nutritious content of food, guiding essential appetitive behaviours, preventing the ingestion of toxic substances, and helping to ensure the maintenance of a healthy diet. Sweet and bitter are two of the most salient sensory percepts for humans and other animals; sweet taste allows the identification of energy-rich nutrients whereas bitter warns against the intake of potentially noxious chemicals. In mammals, information from taste receptor cells in the tongue is transmitted through multiple neural stations to the primary gustatory cortex in the brain. Recent imaging studies have shown that sweet and bitter are represented in the primary gustatory cortex by neurons organized in a spatial map, with each taste quality encoded by distinct cortical fields. Here the authors demonstrate that by manipulating the brain fields representing sweet and bitter taste they directly control an animal's internal representation, sensory perception, and behavioural actions. These results substantiate the segregation of taste qualities in the cortex,

expose the innate nature of appetitive and aversive taste responses, and illustrate the ability of gustatory cortex to recapitulate complex behaviours in the absence of sensory input.

G Protein-Gated K+ Channel Ablation In Forebrain Pyramidal Neurons Selectively Impairs Fear Learning Victoria NC, Marron Fernandez de Velasco E, Ostrovskaya O, Metzger S, Xia Z, Kotecki L, Benneyworth MA, Zink AN, Martemyanov KA, Wickman K. Biol Psychiatry. 2015. Cognitive dysfunction occurs in many debilitating conditions including Alzheimer's disease, Down syndrome, schizophrenia, and mood disorders. The dorsal hippocampus is a critical locus of cognitive processes linked to spatial and contextual learning. G protein-gated inwardly rectifying potassium ion (GIRK/Kir3) channels, which mediate the postsynaptic inhibitory effect of many neurotransmitters, have been implicated in hippocampal-dependent cognition. Available evidence, however, derives primarily from constitutive gain-of-function models that lack cellular specificity.The authors used constitutive and neuron-specific gene ablation models targeting an integral subunit of neuronal GIRK channels (GIRK2) to probe the impact of GIRK channels on associative learning and memory.Constitutive Girk2(-/-) mice exhibited a striking deficit in hippocampal-dependent (contextual) and hippocampal-independent (cue) fear conditioning. Mice lacking GIRK2 in gamma-aminobutyric acid neurons (GAD-Cre:Girk2(flox/flox) mice) exhibited a clear deficit in GIRK-dependent signaling in dorsal hippocampal gamma-aminobutyric acid neurons but no evident behavioral phenotype. Mice lacking GIRK2 in forebrain pyramidal neurons (CaMKII-Cre(+):Girk2(flox/flox) mice) exhibited diminished GIRK-dependent signaling in dorsal, but not ventral, hippocampal pyramidal neurons. CaMKII-Cre(+):Girk2(flox/flox) mice also displayed a selective impairment in contextual fear conditioning, as both cue fear and spatial learning were intact in these mice. Finally, loss of GIRK2 in forebrain pyramidal neurons correlated with enhanced long-term depression and blunted depotentiation of long-term potentiation at the Schaffer collateral/cornu ammonis 1 synapse in the dorsal hippocampus. These data suggest that GIRK channels in dorsal hippocampal pyramidal neurons are necessary for normal learning involving aversive stimuli and support the contention that dysregulation of GIRK-dependent signaling may underlie cognitive dysfunction in some disorders.

EPIDEMIOLOGY RESEARCH

Association Of Substance Dependence Phenotypes In the COGA Sample Wetherill L, Agrawal A, Kapoor M, Bertelsen S, Bierut LJ, Brooks A, Dick D, Hesselbrock M, Hesselbrock V, Koller DL, Le N, Nurnberger Jr, JI, Salvatore JE, Schuckit M, Tischfield JA, Wang Jen-Chyong, Xuei X, Edenberg HJ, Porjesz B, Bucholz K, Goate AM, Foroud T. Addict Biol. 2015; 20(3): 617-627. Alcohol and drug use disorders are individually heritable (50%). Twin studies indicate that alcohol and substance use disorders share common genetic influences, and therefore may represent a more heritable form of addiction and thus be more powerful for genetic studies. This study utilized data from 2322 subjects from 118 European-American families in the Collaborative Study on the Genetics of Alcoholism sample to conduct genome-wide association analysis of a binary and a continuous index of general substance dependence liability. The binary phenotype (ANYDEP) was based on meeting lifetime criteria for any DSM-IV dependence on alcohol, cannabis, cocaine or opioids. The quantitative trait (QUANTDEP) was constructed from factor analysis based on endorsement across the seven DSM-IV criteria for each of the four substances. Heritability was estimated to be 54% for ANYDEP and 86% for QUANTDEP. One single-nucleotide polymorphism (SNP), rs2952621 in the uncharacterized gene LOC151121 on chromosome 2, was associated with ANYDEP (P = 10(-8)), with support from surrounding imputed SNPs and replication in an independent sample [Study of Addiction: Genetics and Environment (SAGE); P = 0.02]. One SNP, rs2567261 in ARHGAP28 (Rho GTPase-activating protein 28), was associated with QUANTDEP (P = 3.8 × 10(-8)), and supported by imputed SNPs in the region, but did not replicate in an independent sample (SAGE; P =0.29). The results of this study provide evidence that there are common variants that contribute to the risk for a general liability to substance dependence.

Should Pathological Gambling and Obesity Be Considered Addictive Disorders? A Factor Analytic Study In A Nationally Representative Sample Blanco C, GarcÃa-Anaya M, Wall M, de Los Cobos J, Carlos P, Swierad E, Wang S, Petry NM. Drug Alcohol Depend. 2015; 150: 129-134. Pathological gambling (PG) is now aligned with substance use disorders in the DSM-5 as the first officially recognized behavioral addiction. There is growing interest in examining obesity as an addictive disorder as well. The goal of this study was to investigate whether epidemiological data provide support for the consideration of PG and obesity as addictive disorders. Factor analysis of data from a large, nationally representative sample of US adults (N=43,093), using nicotine dependence, alcohol dependence, drug dependence, PG and obesity as indicators. It was hypothesized that nicotine dependence, alcohol dependence and drug use dependence would load on a single factor. It was further hypothesized that if PG and obesity were addictive disorders, they would load on the same factor as substance use disorders, whereas failure to load on the addictive factor would not support their conceptualization as addictive disorders. A model with one factor including nicotine dependence, alcohol dependence, drug dependence and PG, but not obesity, provided a very good fit to the data, as indicated by CFI=0.99, TLI=0.99 and RMSEA=0.01 and loadings of all indicators >0.4. Data from this study support the inclusion of PG in a latent factor with substance use disorders but do not lend support to the consideration of obesity, as defined by BMI, as an addictive disorder. Future research should investigate whether certain subtypes of obesity are best conceptualized as addictive disorders and the shared biological and environmental factors that account for the common and specific features of addictive disorders.

Perceived Cannabis Use Norms and Cannabis Use Among Adolescents In The United States Wu LT, Swartz MS, Brady KT, Hoyle RH, NIDA AAPI Workgroup. J Psychiatr Res. 2015; 64: 79-87.
Due to changes in cannabis policies, concerns about cannabis use (CU) in adolescents have increased. The population of nonwhite groups is growing quickly in the United States. The authors examined perceived CU norms and their association with CU and CU disorder (CUD) for White, Black, Hispanic, Native-American, Asian-American, Native Hawaiian/Pacific Islander (NH/PI), and mixed-race adolescents. Data were from adolescents (12-17 years) in the 2004-2012 National Surveys on Drug Use and Health (N = 163,837). Substance use and CUD were assessed by computer-assisted, self-interviewing methods. Blacks, Hispanics, Native-Americans, and mixed-race adolescents had greater odds of past-year CU and CUD than Whites. Among past-year cannabis users (CUs), Hispanics and Native-Americans had greater odds of having a CUD than Whites. Asian-Americans had the highest prevalence of perceived parental or close friends' CU disapproval. Native-Americans and mixed-race adolescents had lower odds than Whites of perceiving CU disapproval from parents or close friends. In adjusted analyses, adolescents' disapproval of CU, as well as perceived disapproval by parents or close friends, were associated with a decreased odds of CU in each racial/ethnic group, except for NHs/PIs. Adolescents' disapproval of CU was associated with a decreased odds of CUD among CUs for Whites (personal, parental, and close friends disapproval), Hispanics (personal, parental, and close friends' disapproval), and mixed-race adolescents (personal, close friends' disapproval). Racial/ethnic differences in adolescent CU prevalence were somewhat consistent with adolescents' reports of CU norm patterns. Longitudinal research on CU health effects should oversample nonwhite adolescents to assure an adequate sample for analysis and reporting.

Detecting Initiation Or Risk For Initiation Of Substance Use Before High School During Pediatric Well-child Check-ups Ridenour TA, Willis D, Bogen DL, Novak S, Scherer J, Reynolds MD, Zhai ZW, Tarter RE. Drug Alcohol Depend. 2015; 150: 54-62.
Youth substance use (SU) is prevalent and costly, affecting mental and physical health. American Academy of Pediatrics and Affordable Care Act call for SU screening and prevention. The Youth Risk Index (©) (YRI) was tested as a screening tool for having initiated and propensity to initiate SU before high school (which forecasts SU disorder). YRI was hypothesized to have good to excellent psychometrics, feasibility and stakeholder acceptability for use during well-child check-ups. A high-risk longitudinal design with two cross-sectional replication samples, ages 9-13 was used. Analyses included receiver operating characteristics and regression analyses. A one-year longitudinal sample (N=640) was used for YRI derivation. Replication samples were a cross-sectional sample (N=345) and well-child check-up patients (N=105) for testing feasibility, validity and acceptability as a screening tool. YRI has excellent test-retest reliability and good sensitivity and specificity for concurrent and one-year-later SU (odds ratios=7.44, CI=4.3-13.0) and conduct problems (odds ratios=7.33, CI=3.9-13.7). Results were replicated in both cross-sectional samples. Well-child patients, parents and pediatric staff rated YRI screening as important, acceptable, and a needed service. Identifying at-risk youth prior to age 13 could reap years of opportunity to intervene before onset of SU disorder. Most results pertained to YRI & association with concurrent or recent past risky behaviors; further replication ought to specify its predictive validity, especially adolescent-onset risky behaviors. YRI well identifies youth at risk for SU and conduct problems prior to high school, is feasible and valid for screening during well-child check-ups, and is acceptable to stakeholders.

Early Emerging Nicotine Dependence Symptoms In Adolescence Predict Daily Smoking In Young Adulthood Dierker L, Hedeker D, Rose J, Selya A, Mermelstein R. Drug Alcohol Depend. 2015; 151: 267-271.
The present study evaluated the predictive validity of individual early emerging nicotine dependence symptoms in adolescence on smoking behavior in young adulthood. A total of 492 adolescents who, at baseline, had not smoked more than 100 cigarettes in their lifetime and 123 adolescents who smoked more than 100 cigarettes lifetime, and who participated in the 6-year follow-up assessment were included in the present analyses. Predictive validity of 10 nicotine dependence items administered at baseline was evaluated at the 6 year follow-up when the sample had entered young adulthood (mean age=21.6). Among adolescents who had smoked fewer than 100 cigarettes, experiencing higher levels of overall nicotine dependence as well as individual symptoms at baseline longitudinally predicted an increase in risk for daily smoking in young adulthood, after controlling for baseline smoking and other tobacco use. For adolescents who had smoked more than 100 cigarettes at baseline, level of nicotine dependence and individual symptom endorsement did not predict smoking behavior in young adulthood. These findings add to accumulating evidence that early emerging dependence symptoms reported at low levels of smoking exposure signal a greater propensity for continued smoking behavior. Screening for these early emerging symptoms among novice adolescent smokers represents an important and unused tool in tobacco control efforts aimed at preventing the development of chronic smoking patterns.

A Dimensional Liability Model Of Age Differences In Mental Disorder Prevalence: Evidence From A National Sample Hoertel N, McMahon K, Olfson M, Wall MM, RodrÃguez-FernÃ¡ndez JM, Lemogne C, Limosin F, Blanco C. J Psychiatr Res. 2015; 64: 107-113.
Recent theories have proposed a metastructure that organizes related mental disorders into broad dimensions of psychopathology (i.e., internalizing and externalizing dimensions). Prevalence rates of most mental disorders, when examined independently, are substantially lower in older than in younger adults, which may affect this metastructure. Within a nationally representative sample, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; N = 43,093), the authors developed a dimensional liability model of common psychiatric disorders to clarify whether aging affects specific disorders or general dimensions of psychopathology. Significant age differences existed across age groups (18-24, 25-34, 35-44, 45-54, 55-64, 65-75 and 75+), such that older adults showed lower prevalence rates of most disorders compared to younger adults. They next investigated patterns of disorder comorbidity for past-year psychiatric disorders and found that a distress-fear-externalizing liability model fit the data well. This model was age-group invariant and indicated that the observed lower prevalence of mental disorders with advancing age originates from lower average means on externalizing and internalizing liability dimensions. This unifying dimensional liability model of age and mental disorder comorbidity can help inform the role of aging on mental disorder prevalence for research and intervention efforts, and service planning for the impending crisis in geriatric mental health.

Towards A Comprehensive Developmental Model Of Pathological Gambling Blanco C, Hanania J, Petry NM, Wall MM, Wang S, Jin CJ, Kendler KS. Addiction. 2015; 110(8): 1340-1351.
The aim of this study was to develop a comprehensive etiological model of pathological gambling (PG) for men and women based on Kendler development model for major depression, which groups 22 risk factors into five developmental tiers (childhood, early adolescence, late adolescence, adulthood, last year). The authors hypothesized that: (1) all risk factors would be associated significantly with PG; (2) the effect of risk factors in earlier developmental tiers would be

accounted for by later tiers; and (3) there would be few gender differences. Separate models were built for life-time gambling and for 12-month PG among those with life-time gambling. Data drawn from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) in the United States. Respondents to NESARC wave 1 (n = 43 093).Odds ratios (OR) and adjusted OR (AOR) were used to determine the risk factors in multiple models. After mutually adjusting for other risk factors, family history of substance use disorders (SUD) or depression, impulsivity, childhood-onset anxiety, number of Axis I and II disorders, history of SUD, nicotine dependence, social deviance in adulthood, and past-year history of SUD, nicotine dependence and independent stressful life events predicted life-time gambling. Past history of PG, number of personality disorders and past year nicotine dependence were associated significantly with 12-month PG (all P < 0.05). There were no significant gender interactions for 12-month PG.A modification of Kendler's model for major depression provides a foundation for the development of a comprehensive developmental model of pathological gambling. Life-time history of gambling and 12-month pathological gambling appear to be determined by risk factors in several developmental levels, with the effect of earlier development tiers accounted for by later ones.

Are Genetic Variants For Tobacco Smoking Associated With Cannabis Involvement? Agrawal A, Lynskey MT, Kapoor M, Bucholz KK, Edenberg HJ, Schuckit M, Brooks A, Hesselbrock V, Kramer J, Saccone N, Tischfield J, Bierut LJ. Drug Alcohol Depend. 2015; 150: 183-187.
Cannabis users are highly likely to also be tobacco cigarette smokers and a proportion of this comorbidity is attributable to shared genetic influences. Three large meta-analyses of genomewide association studies (GWAS) of tobacco smoking have identified multiple genomewide significant ($p<5 \times 10(-8)$) single nucleotide polymorphisms (SNPs). The authors examine whether these SNPs are associated with tobacco smoking and with cannabis involvement in an independent sample. Eleven SNPs associated with cigarettes per day (CPD), ever versus never smoking and current smoking/smoking cessation at $p<5 \times 10(-8)$ were selected from three published meta-analyses. Association analyses were conducted with similar tobacco smoking measures in 2716 European-American subjects from the Study of Addictions Genes and Environment (SAGE) and with lifetime and current cannabis use and DSM-IV cannabis abuse/dependence. Cannabis use and tobacco smoking correlated at 0.54. Rs16969968 in CHRNA5 (and its proxy, rs1051730 in CHRNA3) and rs1451240, a proxy for rs13280604 in CHRNB3, were associated with CPD after Bonferroni correction ($p<0.006$). rs1451240 was also associated with DSM-IV cannabis abuse/dependence. Rs6265 in BDNF was associated with smoking initiation, as in the original meta-analysis and also with lifetime cannabis use. Associations with cannabis involvement were no longer significant upon adjustment for the tobacco smoking measures. The modest associations between cannabis involvement and SNPs for tobacco smoking were not independent of the comorbidity between tobacco and cannabis involvement. Larger samples of individuals might be required to articulate the specific genetic architecture of cannabis involvement.

Racial/ethnic Differences In Trends In Heroin Use and Heroin-related Risk Behaviors Among Nonmedical Prescription Opioid Users Martins SS, Santaella-Tenorio J, Marshall BDL, Maldonado A, Cerda M. Drug Alcohol Depend. 2015; 151: 278-183.
This study examines changing patterns of past-year heroin use and heroin-related risk behaviors among individuals with nonmedical use of prescription opioids (NMUPO) by racial/ethnic groups in the United States. The authors used data from the National Survey on Drug Use and Health (NSDUH) from 2002 to 2005 and 2008 to 2011, resulting in a total sample of N = 448,597. Past-year heroin use increased among individuals with NMUPO and increases varied by frequency of

past year NMUPO and race/ethnicity. Those with NMUPO in the 2008-2011 period had almost twice the odds of heroin use as those with NMUPO in the 2002-2005 period (OR = 1.89, 95%CI: 1.50, 2.39), with higher increases in non-Hispanic (NH) Whites and Hispanics. In 2008-2011, the risk of past year heroin use, ever injecting heroin, past-year heroin abuse or dependence, and the perception of availability of heroin increased as the frequency of NMUPO increased across respondents of all race/ethnicities. Individuals with NMUPO, particularly non-Hispanic Whites, are at high risk of heroin use and heroin-related risk behaviors. These results suggest that frequent nonmedical users of prescription opioids, regardless of race/ethnicity, should be the focus of novel public health efforts to prevent and mitigate the harms of heroin use.

The Association Between Speed Of Transition From Initiation To Subsequent Use Of Cannabis and Later Problematic Cannabis Use, Abuse and Dependence Hines LA, Morley KI, Strang J, Agrawal A, Nelson EC, Statham D, Martin NG, Lynskey MT. Addiction. 2015; 110(8): 1311-1320.
The aims of this study were to test whether speed of transition from initiation use to subsequent use of cannabis is associated with likelihood of later cannabis dependence and other outcomes, and whether transition speed is attributable to genetic or environmental factors. This is a Cross-sectional interview study. A total of 2239 twins and siblings who reported using cannabis at least twice [mean age at time of survey = 32.0, 95% confidence interval (CI) = 31.9 - 32.1, range = 22-45].Time between initiation and subsequent cannabis use (within 1week; within 3 months; between 3 and 12 months; more than 1 year later), later use of cannabis and symptoms of DSM-IV cannabis abuse/dependence. Multinomial regression analyses (comparison group: more than 1 year later) adjusted the association between speed of transition and the outcomes of cannabis daily use, abuse/dependence and treatment-seeking after controlling for socio-demographic, childhood, mental health, peer and licit drug factors. Twin modelling estimated the proportion of variance in transition speed attributable to genetic (A), common environment (C) and unique environmental (E) factors. Subsequent use of cannabis within 1week of initiation was associated with daily use [odds ratio (OR) = 2.64, 95% CI = 1.75-3.99], abuse and/or dependence (OR= 3.25, 95% CI = 2.31-4.56) and treatment-seeking for cannabis problems (OR = 1.89, 95% CI = 1.03-3.46). Subsequent use within 3 months was associated with abuse and/or dependence (OR = 1.61, 95% CI = 1.18-2.19). The majority of the variation of the speed of transition was accounted for by unique environment factors (0.75).Rapid transition from initiation to subsequent use of cannabis is associated with increased likelihood of subsequent daily cannabis use and abuse/dependence.

Nonmedical Prescription Opioid Use In Childhood and Early Adolescence Predicts Transitions To Heroin Use In Young Adulthood: A National Study Cerda M, Santaella J, Marshall BDL, Kim JH, Martins SS. J Pediatr. 2015; 167(3): 605-12.e1-2.
The aims of this study were to examine the relationship between nonmedical use of prescription opioids and heroin initiation from childhood to young adulthood, and to test whether certain ages, racial/ethnic, and income groups were at higher risk for this transition. Among a nationally representative sample of US adolescents assessed in the 2004-2011 National Surveys on Drug Use and Health cross-sectional surveys (n = 223,534 respondents aged 12-21 years), discrete-time hazard models were used to estimate the age-specific hazards of heroin initiation associated with prior history of nonmedical use of prescription opioids. Interactions were estimated between prior history of nonmedical use of prescription opioids and age of nonmedical use of prescription opioid initiation, race/ethnicity, and income. A prior history of nonmedical use of prescription opioids was strongly associated with heroin initiation (hazard ratio 13.12, 95% CI 10.73, 16.04). Those initiating

nonmedical use of prescription opioids at ages 10-12 years had the highest risk of transitioning to heroin use; the association did not vary by race/ethnicity or income group. Prior use of nonmedical use of prescription opioids is a strong predictor of heroin use onset in adolescence and young adulthood, regardless of the user race/ethnicity or income group. Primary prevention of nonmedical use of prescription opioids in late childhood may prevent the onset of more severe types of drug use such as heroin at later ages. Moreover, because the peak period of heroin initiation occurs at ages 17-18 years, secondary efforts to prevent heroin use may be most effective if they focus on young adolescents who already initiated nonmedical use of prescription opioids.

Mental Disorders and Risk Of Suicide Attempt: A National Prospective Study Hoertel N, Franco S, Wall MM, Oquendo MA, Kerridge BT, Limosin F, Blanco C. Mol Psychiatry. 2015; 20(6): 718-726.
Most mental disorders, when examined independently, are associated with an elevated risk for suicide attempt. However, mental disorders often co-occur, and that co-occurrence is well explained by models where specific mental disorders are understood as manifestations of latent dimensions of psychopathology. To date, it remains unclear whether the risk of suicide attempt is due to specific mental disorders, to specific dimensions of psychopathology (that is, internalizing and externalizing dimensions), to a general psychopathology factor or to a combination of these explanations. In a large nationally representative prospective survey, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), we used structural equation modeling to examine the shared and specific effects of Axis I and Axis II disorders on the occurrence of suicide attempts in the general population and among individuals with a lifetime history of suicidal ideation. Effects of mental disorders on the risk of suicide attempt were exerted almost exclusively through a general psychopathology factor representing the shared effect across all mental disorders. Effects of remitted psychiatric disorders on the risk of suicide attempt were fully mediated by current mental disorders. Similar patterns of associations were found in individuals with suicidal ideation. These results held when using different approaches to modeling psychiatric comorbidity. These findings underscore the importance of adopting dimensional approaches to comorbidity in the study of suicidal behavior. Because mental disorders increase the risk of suicide attempt through a general psychopathology liability, this dimension should be considered as an important therapeutic target to substantially advance suicide prevention.

Developmental Changes In Genetic and Shared Environmental Contributions To Smoking Initiation and Subsequent Smoking Quantity In Adolescence and Young Adulthood Bares CB, Kendler KS, Maes HH. Twin Res Hum Genet. 2015; 18(5): 497-506.
Few studies examining the genetic architecture of cigarette smoking have focused on adolescents or examined developmental changes in additive genetic, shared environment, and unique environmental influences on liability to initiate cigarette smoking and quantity of cigarettes smoked. The aim of this study was to add to the literature on liability to initiate and use cigarettes during adolescence using a nationally representative sample. Data for this study came from adolescent and young adult twin pairs (aged 14-33 years) from the National Longitudinal Study of Adolescent to Adult Health. The authors ran a series of developmental causal-contingent-common pathway models to examine whether additive genetic, shared, and unique environmental influences on liability to the initiation of cigarette use are shared with those on smoking quantity, and whether their contributions change across development. They found evidence for a developmental shift in genetic and shared environmental contributions to cigarette use. Early in adolescence, genetic and environmental influences work independently on liability to cigarette smoking initiation and

quantity of cigarettes smoked, but liability to these behaviors becomes correlated as individuals' age into young adulthood. These findings provide insight into the causal processes underlying the liability to smoke cigarettes. With age, there is greater overlap in the genetic and environmental factors that influence the initiation of cigarette smoking and quantity of cigarettes smoked.

Earlier Adolescent Substance Use Onset Predicts Stronger Connectivity Between Reward and Cognitive Control Brain Networks Weissman DG, Schriber RA, Fassbender C, Atherton O, Krafft C, Robins RW, Hastings PD, Guyer AE. Dev Cogn Neurosci. 2015.
Early adolescent onset of substance use is a robust predictor of future substance use disorders. The authors examined the relation between age of substance use initiation and resting state functional connectivity (RSFC) of the core reward processing (nucleus accumbens; NAcc) to cognitive control (prefrontal cortex; PFC) brain networks. Adolescents in a longitudinal study of Mexican-origin youth reported their substance use annually from ages 10 to 16 years. At age 16, 69 adolescents participated in a resting state functional magnetic resonance imaging scan. Seed-based correlational analyses were conducted using regions of interest in bilateral NAcc. The earlier that adolescents initiated substance use, the stronger the connectivity between bilateral NAcc and right dorsolateral PFC, right dorsomedial PFC, right pre-supplementary motor area, right inferior parietal lobule, and left medial temporal gyrus. The regions that demonstrated significant positive linear relationships between the number of adolescent years using substances and connectivity with NAcc are nodes in the right frontoparietal network, which is central to cognitive control. The coupling of reward and cognitive control networks may be a mechanism through which earlier onset of substance use is related to brain function over time, a trajectory that may be implicated in subsequent substance use disorders.

Chronic Adolescent Marijuana Use As A Risk Factor For Physical and Mental Health Problems In Young Adult Men Bechtold J, Simpson T, White HR, Pardini D. Psychol Addict Behav. 2015; 29(3): 552-563.
Some evidence suggests that youth who use marijuana heavily during adolescence may be particularly prone to health problems in later adulthood (e.g., respiratory illnesses, psychotic symptoms). However, relatively few longitudinal studies have prospectively examined the long-term physical and mental health consequences associated with chronic adolescent marijuana use. The present study used data from a longitudinal sample of Black and White young men to determine whether different developmental patterns of marijuana use, assessed annually from early adolescence to the mid-20s, were associated with adverse physical (e.g., asthma, high blood pressure) and mental (e.g., psychosis, anxiety disorders) health outcomes in the mid-30s. Analyses also examined whether chronic marijuana use was more strongly associated with later health problems in Black men relative to White men. Findings from latent class growth curve analysis identified 4 distinct subgroups of marijuana users: early onset chronic users, late increasing users, adolescence-limited users, and low/nonusers. Results indicated that the 4 marijuana use trajectory groups were not significantly different in terms of their physical and mental health problems assessed in the mid-30s. The associations between marijuana group membership and later health problems did not vary significantly by race. Findings are discussed in the context of a larger body of work investigating the potential long-term health consequences of early onset chronic marijuana use, as well as the complications inherent in studying the possible link between marijuana use and health effects.

Bulimic Behaviors and Early Substance Use: Findings From A Cotwin-Control Study Munn-Chernoff MA, Grant JD, Bucholz KK, Agrawal A, Lynskey MT, Madden PAF, Heath AC, Duncan AE. Alcohol Clin Exp Res. 2015; 39(9): 1740-1748.
Bulimic behaviors (i.e., binge eating and compensatory behaviors) and substance use frequently co-occur. However, the etiology underlying this association is poorly understood. This study evaluated the association between bulimic behaviors and early substance use, controlling for genetic and shared environmental factors. Participants were 3,540 young adult women from the Missouri Adolescent Female Twin Study. A telephone adaptation of the Semi-Structured Assessment for the Genetics of Alcoholism interview assessed DSM-IV bulimic behaviors, substance use, and other psychological characteristics. Lifetime bulimic behaviors were examined in twin pairs concordant and discordant for early substance use. Logistic regressions were adjusted for the nonindependence of twin data, zygosity, age, body mass index, early menarche (onset before age 12), and early sex (first consensual sexual intercourse before age 15).In the entire study population, women who reported early use of alcohol or nicotine were more likely to engage in bulimic behaviors after adjusting for covariates. In 53 pairs of monozygotic twins discordant for alcohol experimentation before age 15, the twin who reported early alcohol experimentation had 3.21 (95% confidence interval = 1.54 to 6.67) times higher odds of reporting bulimic behaviors than the cotwin who did not report early alcohol experimentation, even after adjustment for covariates. Findings suggest that early alcohol experimentation may contribute to the development of bulimic behaviors via mechanisms extending beyond shared vulnerability, including individual-specific environmental experiences or causal pathways.

Heroin-related Overdose: The Unexplored Influences Of Markets, Marketing and Source-types In the United States Mars SG, Fessel JN, Bourgois P, Montero F, Karandinos G, Ciccarone D. Soc Sci Med. 2015; 140: 44-53.
Heroin overdose, more accurately termed heroin-related overdose due to the frequent involvement of other drugs, is the leading cause of mortality among regular heroin users. (Degenhardt et al., 2010) Heroin injectors are at greater risk of hospital admission for heroin-related overdose (HOD) in the eastern United States where Colombian-sourced powder heroin is sold than in the western US where black tar heroin predominates. (Unick et. al., 2014) This paper examines under-researched influences on HOD, both fatal and non-fatal, using data from a qualitative study of injecting drug users of black tar heroin in San Francisco and powder heroin in Philadelphia Data were collected through in-depth, semi-structured interviews carried out in 2012 that were conducted against a background of longer-term participant-observation, ethnographic studies of drug users and dealers in Philadelphia (2007-12) and of users in San Francisco (1994-2007, 2012). These findings suggest three types of previously unconsidered influences on overdose risk that arise both from structural socio-economic factors and from the physical properties of the heroin source-types: 1) retail market structure including information flow between users; 2) marketing techniques such as branding, free samples and pricing and 3) differences in the physical characteristics of the two major heroin source forms and how they affect injecting techniques and vascular health. Although chosen for their contrasting source-forms, we found that the two cities have contrasting dominant models of drug retailing: San Francisco respondents tended to buy through private dealers and Philadelphia respondents frequented an open-air street market where heroin is branded and free samples are distributed, although each city included both types of drug sales. These market structures and marketing techniques shape the availability of information regarding heroin potency and its dissemination among users who tend to seek out the strongest heroin available on a given day. The physical characteristics of these two source-types, the way they are prepared for injecting and their

effects on vein health also differ markedly. The purpose of this paper is to examine some of the unexplored factors that may lead to heroin-related overdose in the United States and to generate hypotheses for further study.

Association Of Electronic Cigarette Use With Initiation Of Combustible Tobacco Product Smoking In Early Adolescence Leventhal AM, Strong DR, Kirkpatrick MG, Unger JB, Sussman S, Riggs NR, Stone MD, Khoddam R, Samet JM, Audrain-McGovern J. JAMA. 2015; 314(7): 700-707.
Exposure to nicotine in electronic cigarettes (e-cigarettes) is becoming increasingly common among adolescents who report never having smoked combustible tobacco. The aim of the study was to evaluate whether e-cigarette use among 14-year-old adolescents who have never tried combustible tobacco is associated with risk of initiating use of 3 combustible tobacco products (ie, cigarettes, cigars, and hookah). Longitudinal repeated assessment of a school-based cohort at baseline (fall 2013, 9th grade, mean age = 14.1 years) and at a 6-month follow-up (spring 2014, 9th grade) and a 12-month follow-up (fall 2014, 10th grade). Ten public high schools in Los Angeles, California, were recruited through convenience sampling. Participants were students who reported never using combustible tobacco at baseline and completed follow-up assessments at 6 or 12 months (N = 2530). At each time point, students completed self-report surveys during in-classroom data collections. Student self-report of whether he or she ever used e-cigarettes (yes or no) at baseline. Six- and 12-month follow-up reports on use of any of the following tobacco products within the prior 6 months: (1) any combustible tobacco product (yes or no); (2) combustible cigarettes (yes or no), (3) cigars (yes or no); (4) hookah (yes or no); and (5) number of combustible tobacco products (range: 0-3). Past 6-month use of any combustible tobacco product was more frequent in baseline e-cigarette ever users (n = 222) than never users (n = 2308) at the 6-month follow-up (30.7% vs 8.1%, respectively; difference between groups in prevalence rates, 22.7% [95% CI, 16.4%-28.9%]) and at the 12-month follow-up (25.2% vs 9.3%, respectively; difference between groups, 15.9% [95% CI, 10.0%-21.8%]). Baseline e-cigarette use was associated with greater likelihood of use of any combustible tobacco product averaged across the 2 follow-up periods in the unadjusted analyses (odds ratio [OR], 4.27 [95% CI, 3.19-5.71]) and in the analyses adjusted for sociodemographic, environmental, and intrapersonal risk factors for smoking (OR, 2.73 [95% CI, 2.00-3.73]). Product-specific analyses showed that baseline e-cigarette use was positively associated with combustible cigarette (OR, 2.65 [95% CI, 1.73-4.05]), cigar (OR, 4.85 [95% CI, 3.38-6.96]), and hookah (OR, 3.25 [95% CI, 2.29-4.62]) use and with the number of different combustible products used (OR, 4.26 [95% CI, 3.16-5.74]) averaged across the 2 follow-up periods. Among high school students in Los Angeles, those who had ever used e-cigarettes at baseline compared with nonusers were more likely to report initiation of combustible tobacco use over the next year. Further research is needed to understand whether this association may be causal.

Differences Between African-American and European-American Women In the Association Of Childhood Sexual Abuse With Initiation Of Marijuana Use and Progression To Problem Use Sartor CE, Agrawal A, Grant JD, Duncan AE, Madden PAF, Lynskey MT, Heath AC, Bucholz KK. J Stud Alcohol Drugs. 2015; 76(4): 569-577.
Childhood sexual abuse (CSA) is associated with elevated risk of early marijuana use and cannabis use disorder (CUD). Both the prevalence of CSA and the course of marijuana use differ between African Americans and European Americans. The current study aimed to determine whether these differences manifest in racial/ ethnic distinctions in the association of CSA with early and problem use of marijuana. Data were derived from female participants in a female twin study and a high-risk

family study of substance use (n = 4,193, 21% African-American). Cox proportional hazard regression analyses using CSA to predict initiation of marijuana use and progression to CUD symptom(s) were conducted separately by race/ethnicity. Sibling status on the marijuana outcome was used to adjust for familial influences. CSA was associated with both stages of marijuana use in African-American and European-American women. The association was consistent over the risk period (hazard ratio [HR] = 1.57, 95% confidence interval [CI] [1.37, 1.79] for initiation; HR = 1.51, 95% CI [1.21, 1.88] for CUD symptom onset) in European-American women. In African-American women, the HRs for initiation were 2.52 (95% CI [1.52, 4.18]) before age 15, 1.82 (95% CI [1.36, 2.44]) at ages 15-17, and nonsignificant after age 17. In the CUD symptom model, CSA predicted onset only at age 21 and older (HR = 2.17, 95% CI [1.31, 3.59]).The association of CSA with initiation of marijuana use and progression to problem use is stable over time in European-American women, but in African-American women, it varies by developmental period. Findings suggest the importance of considering race/ethnicity in prevention efforts with this high-risk population.

Effects Of Quitting Cannabis On Respiratory Symptoms Hancox RJ, Shin HH, Gray AR, Poulton R, Sears MR. Eur Respir J. 2015; 46(1): 80-87.
Smoking cannabis is associated with symptoms of bronchitis. Little is known about the persistence of symptoms after stopping cannabis use. The authors assessed associations between changes in cannabis use and respiratory symptoms in a population-based cohort of 1037 young adults. Participants were asked about cannabis and tobacco use at ages 18, 21, 26, 32 and 38 years. Symptoms of morning cough, sputum production, wheeze, dyspnea on exertion and asthma diagnoses were ascertained at the same ages. Frequent cannabis use was defined as ≥ 52 occasions over the previous year. Associations between frequent cannabis use and respiratory symptoms were analyzed using generalized estimating equations with adjustments for tobacco smoking, asthma, sex and age. Frequent cannabis use was associated with morning cough (OR 1.97, p<0.001), sputum production (OR 2.31, p<0.001) and wheeze (OR 1.55, p<0.001). Reducing or quitting cannabis use was associated with reductions in the prevalence of cough, sputum and wheeze to levels similar to nonusers. Frequent cannabis use is associated with symptoms of bronchitis in young adults. Reducing cannabis use often leads to a resolution of these symptoms.

Deep Sequencing Of Three Loci Implicated In Large-Scale Genome-Wide Association Study Smoking Meta-Analyses Clark SL, McClay JL, Adkins DE, Aberg KA, Kumar G, Nerella S, Xie L, Collins AL, Crowley JJ, Quakenbush CR, Hillard CE, Gao G, Shabalin AA, Peterson RE, Copeland WE, Silberg JL, Maes H, Sullivan PF, Costello EJ, van den Oord EJ. Nicotine Tob Res. 2015.
Genome-wide association study meta-analyses have robustly implicated three loci that affect susceptibility for smoking: CHRNA5\CHRNA3\CHRNB4, CHRNB3\CHRNA6 and EGLN2\CYP2A6. Functional follow-up studies of these loci are needed to provide insight into biological mechanisms. However, these efforts have been hampered by a lack of knowledge about the specific causal variant(s) involved. In this study, the authors prioritized variants in terms of the likelihood they account for the reported associations. They employed targeted capture of the CHRNA5\CHRNA3\CHRNB4, CHRNB3\CHRNA6, and EGLN2\CYP2A6 loci and flanking regions followed by next-generation deep sequencing (mean coverage 78Ã—) to capture genomic variation in 363 individuals. The authors performed single locus tests to determine if any single variant accounts for the association, and examined if sets of (rare) variants that overlapped with biologically meaningful annotations account for the associations. In total, they investigated 963

variants, of which 71.1% were rare (minor allele frequency < 0.01), 6.02% were insertion/deletions, and 51.7% were catalogued in dbSNP141. The single variant results showed that no variant fully accounts for the association in any region. In the variant set results, CHRNB4 accounts for most of the signal with significant sets consisting of directly damaging variants. CHRNA6 explains most of the signal in the CHRNB3\CHRNA6 locus with significant sets indicating a regulatory role for CHRNA6. Significant sets in CYP2A6 involved directly damaging variants while the significant variant sets suggested a regulatory role for EGLN2. The authors found that multiple variants implicating multiple processes explain the signal. Some variants can be prioritized for functional follow-up.

Prevalence and Correlates Of Co-ingestion Of Prescription Tranquilizers and Other Psychoactive Substances By U.S. High School Seniors: Results From A National Survey
Schepis TS, West BT, Teter CJ, McCabe SE. Addict Behav. 2016; 52: 8-12.
Nonmedical tranquilizer use (NMTU) is a concerning and understudied phenomenon in adolescents, despite being the second most prevalent form of nonmedical use in this population. Thus, this work aimed to examine the sociodemographic and substance use correlates of past-year co-ingestion of a prescription tranquilizer and another substance among adolescents. Data were from the Monitoring the Future study, a nationally representative survey of U.S. high school students. Data from 11,444 seniors (12th graders) completing form 1 of the survey were used. The participants represented a population that was 52.7% female, 61.8% White, and had a modal age of 18. Weighted frequencies and Rao-Scott chi-square analyses were computed to describe the target population and examine associations of interest. An estimated 5.3% of the population engaged in past-year NMTU during this time period, with an estimated 72.6% of those users engaged in past-year co-ingestion of a tranquilizer and another substance. Marijuana and alcohol were the most commonly co-ingested substances. Those engaged in co-ingestion were more likely than past-year nonmedical users without co-ingestion to be engaged in other substance or nonmedical use (including past year nonmedical Xanax® (alprazolam) use), have an earlier onset of NMTU, and endorse recreational motives. Adolescent nonmedical tranquilizer users engaged in co-ingestion may be a particularly vulnerable population, with higher rates of other substance use, other nonmedical use and problematic NMTU characteristics than nonmedical users without co-ingestion. Identification of and intervention with adolescent co-ingestion users are important avenues for future research and clinical practice.

Associations Of Adolescent Cannabis Use With Academic Performance and Mental Health: A Longitudinal Study Of Upper Middle Class Youth Meier MH, Hill ML, Small PJ, Luthar SS. Drug Alcohol Depend. 2015; 156: 207-212.
There is a hypothesis that low socioeconomic status (SES) may explain the link between cannabis use and poorer academic performance and mental health. A key question, therefore, is whether adolescent cannabis use is associated with poorer academic performance and mental health in high SES communities where there is reduced potential for confounding. Youth (n=254) from an upper middle class community were followed prospectively through the four years of high school (from age 14/15 to age 17/18). Past-year frequency of cannabis use was assessed annually. Official school records of academic performance and self-reported mental health symptoms (externalizing and internalizing symptoms) were assessed in grades 9 and 12.Persistent cannabis use across the four years of high school was associated with lower grade-point average (β=-0.18, p=.006), lower Scholastic Aptitude Test (SAT) score (β =-0.13, p=.038), and greater externalizing symptoms (β=0.29, p<.001) in 12th grade, but not with greater internalizing symptoms (β =0.04, p=.53).

Moreover, persistent cannabis use was associated with lower grade-point average (β=-0.13, p=.014) and greater externalizing symptoms (β =0.24, p=.002) in 12th grade, even after controlling for 9th grade levels of these outcomes. Similar associations were observed for persistent alcohol and tobacco use. Effects for persistent cannabis use became non-significant after controlling for persistent alcohol and tobacco use, reflecting the difficulties of disentangling effects of cannabis from effects of alcohol and tobacco. Low SES cannot fully explain associations between cannabis use and poorer academic performance and mental health.

Month-wise Estimates Of Tobacco Smoking During Pregnancy For The United States, 2002-2009 Alshaarawy O, Anthony JC. Matern Child Health J. 2015; 19(5): 1010-1015.
The timing of prenatal exposure to tobacco cigarette smoking can be crucial for the developing fetus. Pushing the field beyond prior pregnancy trimester-focused smoking estimates, The authors estimated month-specific prevalence proportions for tobacco cigarette smoking among pregnant and non-pregnant women of the United States, with consideration of tobacco dependence (TD) as well. In advance, the authors posited that pregnancy onset might prompt smoking cessation in early months, before the end of the 1st trimester, and that TD might account for sustained smoking in later months, especially months 8-9, when there are added reasons to quit. Estimates are from the 2002-2009 National Surveys on Drug Use and Health Restricted-Data Analysis System (R-DAS), with large nationally representative samples of US civilians, including 12-44 year old women (n ~ 70,000) stratified by pregnancy status and month of pregnancy, with multi-item assessment of TD as well as recently active smoking. Age was held constant via the Breslow-Day indirect standardization approach, a methodological detail of potential interest to other research teams conducting online R-DAS analyses. Among 12-44year old women in Month 1 of pregnancy, as well as non-pregnant women, just over one in four was a recently active smoker (26-27%), and approximately one-half of these smokers qualified as a TD case (52%). Corresponding estimates for women in Month 3 were 17.6% and two-thirds, respectively, lending some support for the authors' advance hypotheses. Nonetheless, their a priori TD hypothesis about Months 8-9 seems to be contradicted: an increased concentration of TD among smokers surfaced early in pregnancy. Evidence of a possible ameliorative pregnancy effect on smoking prevalence as well as TD effect on smoking persistence might be seen quite early in pregnancy. Substitution of a month-specific view for the traditional trimester view sheds new light on how pregnancy might shape smoking behavior before the end of trimester 1, with TD seeming to thwart a public health goal of 100% cessation, early in pregnancy.

Girls' Childhood Trajectories Of Disruptive Behavior Predict Adjustment Problems In Early Adolescence van der Molen E, Blokland AAJ, Hipwell AE, Vermeiren RRJM, Doreleijers TAH, Loeber R. J Child Psychol Psychiatry. 2015; 56(7): 766-773.
It is widely recognized that early onset of disruptive behavior is linked to a variety of detrimental outcomes in males, later in life. In contrast, little is known about the association between girl's childhood trajectories of disruptive behavior and adjustment problems in early adolescence. This study used nine waves of data from the ongoing Pittsburgh Girls Study. A semiparametric group-based model was used to identify trajectories of disruptive behavior in 1,513 girls from age 6 to 12 years. Adjustment problems were characterized by depression, self-harm, Post-Traumatic Stress Disorder (PTSD), substance use, interpersonal aggression, sexual behavior, affiliation with delinquent peers, and academic achievement at ages 13 and 14.Three trajectories of childhood disruptive behavior were identified: low, medium, and high. Girls in the high group were at increased risk for depression, self-harm, PTSD, illegal substance use, interpersonal aggression,

early and risky sexual behavior, and lower academic achievement. The likelihood of multiple adjustment problems increased with trajectories reflecting higher levels of disruptive behavior. Girls following the high childhood trajectory of disruptive behavior require early intervention programs to prevent multiple, adverse outcomes in adolescence and further escalation in adulthood.

Selective Nonresponse Bias In Population-based Survey Estimates Of Drug Use Behaviors In The United States McCabe SE, West BT. Soc Psychiatry Psychiatr Epidemiol. 2015.
There is a trend of decreasing response rates in population surveys, and selective nonresponse represents a major source of potential bias in population-based survey estimates of drug use behaviors, especially estimates based on longitudinal designs. This study compared baseline substance use behaviors among initial respondents who did respond (n=34,653) and did not respond (n = 8440) to a 3-year follow-up interview in a prospective study of the general U.S. adult population. Differences in nonresponse rates were assessed as a function of past-year drug use behaviors both before and after adjustment for socio-demographic differences potentially associated with these behaviors, and the effects of interactions of the socio-demographic characteristics with the drug use behaviors were assessed in multivariate logistic regression models for response at the 3-year follow-up. Weighted and unweighted nonresponse rates varied between alcohol users and users of other drugs such as cocaine and marijuana, with rates of nonresponse being higher in the latter drug categories. There were also significant differences in nonresponse rates as a function of frequency of use and demographics. More specifically, being married tends to reduce the probability of non-response, while older age, being male, being Asian or Hispanic, and having lower education all substantially increase the probability of nonresponse at Wave 2, even after controlling for relevant covariates. This study provides the substance abuse field with a methodology that users of longitudinal data can apply to test the sensitivity of their inferences to assumptions about attrition patterns.

Prescription Drug Misuse and Sexual Risk Behaviors Among Young Men Who Have Sex With Men (YMSM) In Philadelphia Kecojevic A, Silva K, Sell RL, Lankenau SE. AIDS Behav. 2015; 19(5): 847-856.
This study examined the relationship between prescription drug misuse and sexual risk behaviors (i.e. unprotected sex, increased number of sex partners) in a sample of young men who have sex with men (YMSM) in Philadelphia. Data come from a cross-sectional study of 18-29 year old YMSM (N = 191) who misused prescription drugs in the past 6 months. Associations were investigated in two regression models: logistic models for unprotected anal intercourse (UAI) and zero-truncated Poisson regression model for number of sex partners. Of 177 participants engaging in anal intercourse in the past 6 months, 57.6% engaged in UAI. After adjusting for socio-demographic variables and illicit drug use, misuse of prescription pain pills and muscle relaxants remained significantly associated with engaging in receptive UAI. No prescription drug class was associated with a high number of sex partners. This study provides additional evidence that some prescription drugs are associated with sexual risk behaviors among YMSM.

Gender Differences In the Structure Of Risk For Alcohol Use Disorder In Adolescence and Young Adulthood Foster KT, Hicks BM, Iacono WG, McGue M. Psychol Med. 2015; 45(14): 3047-3058.
Gender differences in the prevalence of alcohol use disorder (AUD) have motivated the separate study of its risk factors and consequences in men and women. However, leveraging gender as a third variable to help account for the association between risk factors and consequences for AUD

could elucidate etiological mechanisms and clinical outcomes. Using data from a large, community sample followed longitudinally from 17 to 29 years of age, the authors tested for gender differences in psychosocial risk factors and consequences in adolescence and adulthood after controlling for gender differences in the base rates of AUD and psychosocial factors. Psychosocial factors included alcohol use, other drug use, externalizing and internalizing symptoms, deviant peer affiliation, family adversity, academic problems, attitudes and use of substances by a romantic partner, and adult socio-economic status. At both ages of 17 and 29 years, mean levels of psychosocial risks and consequences were higher in men and those with AUD. However, the amount of risk exposure in adolescence was more predictive of AUD in women than men. By adulthood, AUD consequences were larger in women than men and internalizing risk had a stronger relationship with AUD in women at both ages. Despite higher mean levels of risk exposure in men overall, AUD appears to be a more severe disorder in women characterized by higher levels of adolescent risk factors and a greater magnitude of the AUD consequences among women than men. Furthermore, internalizing symptoms appear to be a gender-specific risk factor for AUD in women.

Prescription Drug Misuse and Sexual Behavior Among Young Adults Wells BE, Kelly BC, Rendina HJ, Parsons JT. J Sex Res. 2015; 52(6): 659-668.
Though research indicates a complex link between substance use and sexual risk behavior, there is limited research on the association between sexual risk behavior and prescription drug misuse. In light of alarming increases in prescription drug misuse and the role of demographic characteristics in sexual risk behavior and outcomes, the current study examined demographic differences (gender, sexual identity, age, relationship status, parental class background, and race/ethnicity) in sexual risk behavior, sexual behavior under the influence of prescription drugs, and sexual risk behavior under the influence of prescription drugs in a sample of 402 young adults (ages 18 to 29) who misused prescription drugs. Nearly half of the sexually active young adult prescription drug misusers in this sample reported recent sex under the influence of prescription drugs; more than three-quarters reported recent sex without a condom; and more than one-third reported recent sex without a condom after using prescription drugs. Zero-inflated Poisson regression models indicated that White race, younger age, higher parental class, and being a heterosexual man were all associated with sexual risk behavior, sex under the influence of prescription drugs, and sexual risk under the influence of prescription drugs. Findings have implications for the targeting of prevention and intervention efforts.

Preventing HIV Transmission Among Partners Of HIV-Positive Male Sex Workers In Mexico City: A Modeling Study Monteiro J, Filipe G, Marshall BDL, Escudero D, Sosa-Rubi SG, Gonzalez A, Flanigan T, Operario D, Mayer KH, Lurie MN, Galarraga O. AIDS Behav. 2015; 19(9): 1579-1588.
Mexico has a concentrated HIV epidemic, with male sex workers constituting a key affected population. The authors estimated annual HIV cumulative incidence among male sex workers' partners, and then compared incidence under three hypothetical intervention scenarios: improving condom use; and scaling up HIV treatment as prevention, considering current viral suppression rates (CVS, 60.7%) or full viral suppression among those treated (FVS, 100%). Clinical and behavioral data to inform model parameterization were derived from a sample (n = 79) of male sex workers recruited from street locations and Clinica Condesa, an HIV clinic in Mexico City. The authors estimated annual HIV incidence among male sex workers' partners to be 8.0 % (95Â % CI: 7.3-8.7). Simulation models demonstrated that increasing condom use by 10%, and scaling up HIV treatment initiation by 50 % (from baseline values) would decrease the male sex workers-

attributable annual incidence to 5.2, 4.4% (CVS) and 3.2Â % (FVS), respectively. Scaling up the number of male sex workers on ART and implementing interventions to ensure adherence is urgently required to decrease HIV incidence among male sex workers' partners in Mexico City.

Parental Separation, Parental Alcoholism, and Timing Of First Sexual Intercourse Waldron M, Doran KA, Bucholz KK, Duncan AE, Lynskey MT, Madden PAF, Sartor CE, Heath AC. J Adolesc Health. 2015; 56(5): 550-556.
The authors examined timing of first voluntary sexual intercourse as a joint function of parental separation during childhood and parental history of alcoholism. Data were drawn from a birth cohort of female like-sex twins (n= 569 African ancestry [AA]; n = 3,415 European or other ancestry [EA]). Cox proportional hazards regression was conducted predicting age at first sex from dummy variables coding for parental separation and parental alcoholism. Propensity score analysis was also employed to compare intact and separated families, stratified by predicted probability of separation. Earlier sex was reported by EA twins from separated and alcoholic families, compared to EA twins from intact nonalcoholic families, with effects most pronounced through the age of 14 years. Among AA twins, effects of parental separation and parental alcoholism were largely nonsignificant. Results of propensity score analyses confirmed unique risks from parental separation in EA families, where consistent effects of parental separation were observed across predicted probability of separation. For AA families, there was poor matching on risk factors presumed to predate separation, which limited interpretability of survival-analytic findings. In European American families, parental separation during childhood is an important predictor of early-onset sex, beyond parental alcoholism and other correlated risk factors. To characterize risk for African Americans associated with parental separation, additional research is needed where matching on confounders can be achieved.

CHRNA5 Risk Variant Predicts Delayed Smoking Cessation and Earlier Lung Cancer Diagnosis--A Meta-analysis Chen L-S, Hung RJ, Baker T, Horton A, Culverhouse R, Saccone N, Cheng I, Deng B, Han Y, Hansen HM, Horsman J, Kim C, Lutz SRosenberger A, Aben KK, Andrew AS, Breslau N, Chang S-C,; Dieffenbach AK, Dienemann H, Frederiksen B, Han J, Hatsukami DK, Johnson EO, Pande M, Wrensch MR, McLaughlin J, Skaug V, van der Heijden HF, Wampfler J, Wenzlaff A, Woll P, Zienolddiny S, Bickeboller H, Brenner H, Duell EJ, Haugen A, Heinrich J, Hokanson JE, Hunter DJ, Kiemeney LA, Lazarus P, Le Marchand L, Liu G, Mayordomo J, Risch A, Schwartz A, Teare D, Wu X, Wiencke JK, Yang P, Zhang Z-F, Spitz MR, Kraft P, Amos CI, Bierut LJ. J Natl Cancer Inst. 2015; 107(5): pii: djv100. doi: 0.1093/jnci/djv100.
Recent meta-analyses show strong evidence of associations among genetic variants in CHRNA5 on chromosome 15q25, smoking quantity, and lung cancer. This meta-analysis tests whether the CHRNA5 variant rs16969968 predicts age of smoking cessation and age of lung cancer diagnosis. Meta-analyses examined associations between rs16969968, age of quitting smoking, and age of lung cancer diagnosis in 24 studies of European ancestry (n = 29 072). In each dataset, the authors used Cox regression models to evaluate the association between rs16969968 and the two primary phenotypes (age of smoking cessation among ever smokers and age of lung cancer diagnosis among lung cancer case patients) and the secondary phenotype of smoking duration. Heterogeneity across studies was assessed with the Cochran Q test. All statistical tests were two-sided. The rs16969968 allele (A) was associated with a lower likelihood of smoking cessation (hazard ratio [HR] = 0.95, 95% confidence interval [CI] = 0.91 to 0.98, P = .0042), and the AA genotype was associated with a four-year delay in median age of quitting compared with the GG genotype. Among smokers with lung cancer diagnoses, the rs16969968 genotype (AA) was

associated with a four-year earlier median age of diagnosis compared with the low-risk genotype (GG) (HR = 1.08, 95% CI = 1.04 to 1.12, P = 1.1*10(-5)).These data support the clinical significance of the CHRNA5 variant rs16969968. It predicts delayed smoking cessation and an earlier age of lung cancer diagnosis in this meta-analysis. Given the existing evidence that this CHRNA5 variant predicts favorable response to cessation pharmacotherapy, these findings underscore the potential clinical and public health importance of rs16969968 in CHRNA5 in relation to smoking cessation success and lung cancer risk.

Clinical Risk Factors For In-hospital Adverse Cardiovascular Events After Acute Drug Overdose Manini AF, Hoffman RS, Stimmel B, Vlahov D. Acad Emerg Med. 2015; 22(5): 499-507.
It was recently demonstrated that adverse cardiovascular events (ACVE) complicate a high proportion of hospitalizations for patients with acute drug overdoses. The aim of this study was to derive independent clinical risk factors for ACVE in patients with acute drug overdoses. This prospective cohort study was conducted over 3 years at two urban university hospitals. Patients were adults with acute drug overdoses enrolled from the ED. In-hospital ACVE was defined as any of myocardial injury, shock, ventricular dysrhythmia, or cardiac arrest. There were 1,562 patients meeting inclusion/exclusion criteria (mean age, 41.8 years; female, 46%; suicidal, 38%). ACVE occurred in 82 (5.7%) patients (myocardial injury, 61; shock, 37; dysrhythmia, 23; cardiac arrests, 22) and there were 18 (1.2%) deaths. On univariate analysis, ACVE risk increased with age, lower serum bicarbonate, prolonged QTc interval, prior cardiac disease, and altered mental status. In a multivariable model adjusting for these factors as well as patient sex and hospital site, independent predictors were: QTc > 500 msec (3.8% prevalence, odds ratio [OR] = 27.6), bicarbonate < 20 mEq/L (5.4% prevalence, ORÂ = 4.4), and prior cardiac disease (7.1% prevalence, ORÂ = 9.5). The derived prediction rule had 51.6% sensitivity, 93.7% specificity, and 97.1% negative predictive value, while presence of two or more risk factors had 90.9% positive predictive value. The authors' derived independent clinical risk factors for ACVE in patients with acute drug overdose, which should be validated in future studies as a prediction rule in distinct patient populations and clinical settings.

Responsible and Controlled Use: Older Cannabis Users and Harm Reduction Lau N, Sales P, Averill S, Murphy F, Sato S-O, Murphy S. Int J Drug Policy. 2015; 26(8): 709-718.
Cannabis use is becoming more accepted in mainstream society. In this paper, the authors use Zinberg classic theoretical framework of drug, set, and setting to elucidate how older adult cannabis users managed health, social and legal risks in a context of normalized cannabis use. They present selected findings from their qualitative study of Baby Boomer (born 1946-1964) cannabis users in the San Francisco Bay Area. Data collection consisted of a recorded, in-depth life history interview followed by a questionnaire and health survey. Qualitative interviews were analyzed to discover the factors of cannabis harm reduction from the users' perspectives. Interviewees made harm reduction choices based on preferred cannabis derivatives and routes of administration, as well as why, when, where, and with whom to use. Most interviewees minimized cannabis-related harms so they could maintain social functioning in their everyday lives. Responsible and controlled use was described as moderation of quantity and frequency of cannabis used, using in appropriate settings, and respect for non-users. Users contributed to the normalization of cannabis use through normification. Participants followed rituals or cultural practices, characterized by sanctions that helped define "normal" or "acceptable" cannabis use. Users contributed to cannabis normalization through their harm reduction methods. These cultural practices may prove to be more effective than formal legal

prohibitions in reducing cannabis-related harms. Findings also suggest that users with access to a regulated market (medical cannabis dispensaries) were better equipped to practice harm reduction. More research is needed on both cannabis culture and alternative routes of administration as harm reduction methods.

Depressive Symptoms and Externalizing Behaviors Among Hispanic Immigrant Adolescents: Examining Longitudinal Effects Of Cultural Stress Cano M, Schwartz SJ, Castillo LG, Romero AJ, Huang S, Lorenzo-Blanco EI, Unger JB, Zamboanga BL, Des Rosiers SE, Baezconde-Garbanati L, Lizzi KM, Soto DW, Oshri A, Villamar JA, Pattarroyo M, Szapocznik J. J Adolesc. 2015; 42: 31-39.
This study examined longitudinal effects of cultural stress (a latent factor comprised of bicultural stress, ethnic discrimination, and negative context of reception) on depressive symptoms and a range of externalizing behaviors among recently (≤ 5 years in the U.S. at baseline) immigrated Hispanic adolescents. A sample of 302 adolescents (53% boys; mean age 14.51 years) completed baseline measures of perceived ethnic discrimination, bicultural stress, and perceived negative context of reception; and outcome measures of depressive symptoms, cigarette smoking, alcohol use, aggressive behavior, and rule-breaking behavior six months post-baseline. A path analysis indicated that higher cultural stress scores predicted higher levels of all outcomes. These effects were consistent across genders, but varied by study site. Specifically, higher cultural stress scores increased depressive symptoms among participants in Miami, but not in Los Angeles. Findings suggest that cultural stress is a clinically relevant predictor of depressive symptoms and externalizing behaviors among Hispanic immigrant adolescents.

Motivations For Prescription Drug Misuse Among Young Men Who Have Sex With Men (YMSM) In Philadelphia Kecojevic A, Corliss HL, Lankenau SE. Int J Drug Policy. 2015; 26(8): 764-771.
Prescription drug misuse (i.e. opioids, tranquilizers and stimulants) has become the fastest growing area of substance abuse among young adults. Limited studies focus on prescription drug misuse among young men who have sex with men (YMSM, aged 18-29 years). Furthermore, little is known about YMSM motivations for misuse. The purpose of this study was to explore personal motivations for prescription drug misuse among YMSM, including the possible connection between misuse and sexual behaviors. As part of a larger mixed methods study of 191 YMSM recruited in Philadelphia during 2012-2013, the authors conducted semi-structured qualitative interviews with 25 of these participants to gather additional contextual information about their prescription drug misuse. They conducted thematic analysis of qualitative data. While their results corroborated previous literature on motives for misuse of prescription drugs, their data yielded some distinct motivations specific among YMSM. These motives included social/recreational motives, facilitating sex with other men (including motives such as use of opioids for less painful anal receptive sex), and psychological motives such as depression, stress management, coping with everyday hardships (opioids and tranquilizers) or feeling more energized (stimulants). Prescription drugs were commonly misused within the broader contexts of participants' polysubstance use, adding to the significance of this problem. These findings offer insights into YMSM motivations for prescription drug misuse, and point to the importance of recognizing and addressing them. While substance use is likely related to various psychosocial issues impacting YMSM, it also may lead to significant health consequences. Results support the need to include prescription drugs and polysubstance use in harm reduction messages and treatment approaches aimed at substance using YMSM.

Progression To Regular Heroin Use: Examination Of Patterns, Predictors, and Consequences Woodcock EA, Lundahl LH, Stoltman JJK, Greenwald MK. Addict Behav. 2015; 45: 287-293.
The present study retrospectively evaluated the chronology and predictors of substance use progression in current heroin-using individuals. Out-of-treatment heroin users (urinalysis-verified; N=562) were screened for laboratory-based research studies using questionnaires and urinalysis. Comprehensive substance use histories were collected. Between- and within-substance use progression was analyzed using stepwise linear regression models. The strongest predictor of onset of regular heroin use was age at initial heroin use, accounting for 71.8% of variance. The strongest between-substance predictors of regular heroin use were ages at regular alcohol and tobacco use, accounting for 8.1% of variance. Earlier onset of regular heroin use (≤ 20 years) vs. older onset (≥30 years) was associated with a more rapid progression from initial to regular use, longer duration of heroin use, more lifetime use-related negative consequences, and greater likelihood of injecting heroin. The majority of participants (79.7%) reported substance use progression consistent with the gateway hypothesis. Gateway-inconsistent individuals were more likely to be African-American and to report younger age at initial use, longer duration of heroin use, and more frequent past-month heroin use. These findings demonstrate the predictive validity and clinical relevance of evaluating substance use chronology and the gateway hypothesis pattern of progression.

Cigarette Smoking and The Onset and Persistence Of Depression Among Adults In The United States: 1994-2005 Bakhshaie J, Zvolensky MJ, Goodwin RD. Compr Psychiatry. 2015; 60: 142-148.
The present study investigated the relationship between daily cigarette smoking and risk of onset and persistence of major depressive disorder (MDD) over a 10-year period among adults in the United States and whether successful smoking cessation reduced the risk for MDD. Data were drawn from the Midlife Development in the United States Survey (MIDUS; n=2101) Waves I and II. Logistic regressions were used to investigate the relations between smoking and the onset and persistence of MDD, adjusting for demographic characteristics and substance use problems. Daily smoking in 1994 [OR=1.9 (1.2-3.2)] and persistent daily smoking (in 1994 and 2005) [OR=2.2 (1.3-3.7)] were both associated with a significantly increased likelihood of MDD in 2005. Additionally, abstinence, compared to daily smoking, for more than 10years significantly reduced the risk of MDD in 2005 [OR=0.5 (0.3-0.87)] and persistent MDD in 1994 and 2005; [OR=0.5 (0.3-0.87)].Findings from this study provide new insights into the role of smoking in the onset and persistence of MDD. Namely, among those in mid-adulthood, smoking is associated with greater MDD risk and quitting may help to reduce such risk. These results suggest that there may be merit in targeting smoking to reduce the risk of MDD and the mental health benefits of quitting smoking in the form of reduced risk of MDD could usefully be added to common information listed as reasons to quit.

Predictors Of Participant Engagement and Naloxone Utilization In A Community-based Naloxone Distribution Program Rowe C, Santos G-M, Vittinghoff E, Wheeler E, Davidson P, Coffin PO. Addiction. 2015; 110(8): 1301-1310.
The aims of this study were to describe characteristics of participants and overdose reversals associated with a community-based naloxone distribution program and identify predictors of obtaining naloxone refills and using naloxone for overdose reversal. Bivariate statistical tests were used to compare characteristics of participants who obtained refills and reported overdose reversals versus those who did not. The authors fitted multiple logistic regression models to identify predictors of refills and reversals; zero-inflated multiple Poisson regression models were used to

identify predictors of number of refills and reversals. San Francisco, California, USA. Naloxone program participants registered and reversals reported from 2010 to 2013. Baseline characteristics of participants and reported characteristics of reversals. A total of 2500 participants were registered and 702 reversals were reported from 2010 to 2013. Participants who had witnessed an overdose [adjusted odds ratio (AOR)=2.02, 95% confidence interval (CI)=1.53-2.66; AOR= 2.73, 95% CI =1.73-4.30] or used heroin (AOR= 1.85, 95% CI= 1.44-2.37; AOR= 2.19, 95% CI= 1.54-3.13) or methamphetamine (AOR=1.71, 95% CI=1.37-2.15; AOR=1.61, 95% CI=1.18-2.19) had higher odds of obtaining a refill and reporting a reversal, respectively. African American (AOR= 0.63, 95% CI= 0.45-0.88) and Latino (AOR = 0.65, 95% CI = 0.43-1.00) participants had lower odds of obtaining a naloxone refill, whereas Latino participants who obtained at least one refill reported a higher number of refills [incidence rate ratio (IRR) = 1.33 (1.05-1.69)].Community naloxone distribution programs are capable of reaching sizeable populations of high-risk individuals and facilitating large numbers of overdose reversals. Community members most likely to engage with a naloxone program and use naloxone to reverse an overdose are active drug users.

Investigating Dimensionality and Measurement Bias Of DSM-5 Alcohol Use Disorder In A Representative Sample Of the Largest Metropolitan Area In South America Castaldelli-Maia, JM, Wang Y-P, Borges G, Silveira CM, Siu ER, Viana MC, Andrade AG, Martins SS, Andrade LH. Drug Alcohol Depend. 2015; 152: 123-130.

Given the recent launch of a new diagnostic classification (DSM-5) for alcohol use disorders (AUD), the authors aimed to investigate its dimensionality and possible measurement bias in a non-U.S. The current analyses were restricted to 948 subjects who endorsed drinking at least one drink per week in the past year from a sample of 5037 individuals. Data came from São Paulo Megacity Project (which is part of World Mental Health Surveys) collected between 2005 and 2007. First, exploratory factor analysis (EFA) was carried out to test for the best dimensional structure for DSM-5-AUD criteria. Then, item response theory (IRT) was used to investigate the severity and discrimination properties of each criterion of DSM-5-AUD. Finally, differential criterion functioning (DCF) were investigated by socio-demographics (income, gender, age, employment status, marital status and education). All analyses were performed in Mplus software taking into account complex survey design features. The best EFA model was a one-dimensional model. IRT results showed that the criteria "Time Spent" and "Given Up" have the highest discrimination and severity properties, while the criterion "Larger/Longer" had the lowest value of severity, but an average value of discrimination. Only female gender had DCF both at criterion- and factor-level, rendering measurement bias. This study reinforces the existence of a DSM-5-AUD continuum in the largest metropolitan area of South America, including subgroups that had previously higher rates of alcohol use (lower educational/income levels). Lower DSM-5-AUD scores were found in women.

The Relationship Between Cannabis Involvement and Suicidal Thoughts and Behaviors Delforterie MJ, Lynskey MT, Huizink AC, Creemers HE, Grant JD, Few LR, Glowinski AL, Statham DJ, Trull TJ, Bucholz KK, Madden PAF, Martin NG, Heath AC, Agrawal A. Drug Alcohol Depend. 2015; 150: 98-104.

In the present study, the authors examined the relationship between cannabis involvement and suicidal ideation (SI), plan and attempt, differentiating the latter into planned and unplanned attempt, taking into account other substance involvement and psychopathology. They used two community-based twin samples from the Australian Twin Registry, including 9583 individuals (58.5% female, aged between 27 and 40). The Semi-Structured Assessment of the Genetics of

Alcoholism (SSAGA) was used to assess cannabis involvement which was categorized into: (0) no cannabis use (reference category); (1) cannabis use only; (2) 1-2 cannabis use disorder symptoms; (3) 3 or more symptoms. Separate multinomial logistic regression analyses were conducted for SI and suicide attempt with or without a plan. Twin analyses examined the genetic overlap between cannabis involvement and SI. All levels of cannabis involvement were related to SI, regardless of duration (odds ratios [ORs] =1.28-2.00, $p<0.01$). Cannabis use and endorsing ≥ 3 symptoms were associated with unplanned (SANP; ORs=1.95 and 2.51 respectively, $p<0.05$), but not planned suicide attempts ($p>0.10$). Associations persisted even after controlling for other psychiatric disorders and substance involvement. Overlapping genetic (rG=0.45) and environmental (rE=0.21) factors were responsible for the covariance between cannabis involvement and SI. Cannabis involvement is associated, albeit modestly, with SI and unplanned suicide attempts. Such attempts are difficult to prevent and their association with cannabis use and cannabis use disorder symptoms requires further study, including in different samples and with additional attention to confounders.

Biomedical HIV Prevention Including Pre-exposure Prophylaxis and Opiate Agonist Therapy For Women Who Inject Drugs: State Of Research and Future Directions Page K, Tsui J, Maher L, Choopanya K, Vanichseni S, Mock PA, Celum C, Martin M. J Acquir Immune Defic Syndr. 2015; 69 Suppl 2: S169-175.

Women who inject drugs (WWID) are at higher risk of HIV compared with their male counterparts as a result of multiple factors, including biological, behavioral, and sociostructural factors, yet comparatively little effort has been invested in testing and delivering prevention methods that directly target this group. In this article, the authors discuss the need for expanded prevention interventions for WWID, focusing on 2 safe, effective, and approved, yet underutilized biomedical prevention methods: opiate agonist therapy (OAT) and oral pre-exposure prophylaxis (PrEP). Although both interventions are well researched, they have not been well examined in the context of gender. The authors discuss the drivers of women injectors' higher HIV risk, review the effectiveness of OAT and PrEP interventions among women, and explain why these new HIV prevention tools should be prioritized for WWID. There is substantial potential for impact of OAT and PrEP programs for WWID in the context of broader gender-responsive HIV prevention initiatives. Although awaiting efficacy data on other biomedical approaches in the HIV prevention research "pipeline," the authors propose that the scale-up and implementation of these proven, safe, and effective interventions are needed now.

Childhood Maltreatment and Its Effect On Neurocognitive Functioning: Timing and Chronicity Matter Cowell RA, Cicchetti D, Rogosch FA, Toth SL. Dev Psychopathol. 2015; 27(2): 521-533.

Childhood maltreatment represents a complex stressor, with the developmental timing, duration, frequency, and type of maltreatment varying with each child (Barnett, Manly, & Cicchetti, 1993; Cicchetti & Manly, 2001). Multiple brain regions and neural circuits are disrupted by the experience of child maltreatment (Cicchetti & Toth, in press; DeBellis et al., 2002; McCrory & Viding, 2010; Teicher, Anderson, & Polcari, 2012). These neurobiological compromises indicate the impairment of a number of important cognitive functions, including working memory and inhibitory control. The present study extends prior research by examining the effect of childhood maltreatment on neurocognitive functioning based on developmental timing of maltreatment, including onset, chronicity, and recency, in a sample of 3- to 9-year-old nonmaltreated (n = 136) and maltreated children (n = 223). Maltreated children performed more poorly on inhibitory control and working-memory tasks than did nonmaltreated children. Group differences between maltreated children

based on the timing of maltreatment and the chronicity of maltreatment also were evident. Specifically, children who were maltreated during infancy, and children with a chronic history of maltreatment, exhibited significantly poorer inhibitory control and working-memory performance than did children without a history of maltreatment. The results suggest that maltreatment occurring during infancy, a period of major brain organization, disrupts normative structure and function, and these deficits are further instantiated by the prolonged stress of chronic maltreatment during the early years of life.

Does the Transmissible Liability Index (TLI) Assessed In Late Childhood Predict Suicidal Symptoms At Young Adulthood? Cornelius JR, Kirisci L, Reynolds M, Vanyukov M, Tarter R. Am J Drug Alcohol Abuse. 2015; 41(3): 264-268.
The authors' previous work demonstrated that the Transmissible Liability Index (TLI), an instrument designed as an index of liability for substance use disorder (SUD), is associated with risk of substance use disorder. This longitudinal study assessed whether TLI measured in 10-12-year-olds (late childhood) predicts suicidal behavior from age 12-14 (preadolescence) to age 25 (young adulthood). The authors hypothesized that TLI would predict number and severity of suicide attempts. Subjects were sons of men who had lifetime history of SUD (n= 250), called the High Average Risk (HAR) group, and sons of men with no lifetime history of a SUD (n= 250), called the Low Average Risk (LAR) group. The TLI was delineated at baseline (age 10-12), and age-specific versions were administered at 12-14, 16, 19, 22, and 25 years of age. TLI was significantly associated with number and severity of lifetime suicide attempts. These findings confirm the hypothesis that TLI assessed at late childhood is a predictor of frequency and severity of suicidal behavior from preadolescence to young adulthood.

The Impact Of Childhood Gender Expression On Childhood Sexual Abuse and Psychopathology Among Young Men Who Have Sex With Men Hidalgo MA, Kuhns LM, Kwon S, Mustanski B, Garofalo R. Child Abuse Negl. 2015; 46: 103-112.
Young men who have sex with men (MSM) are a risk group highly vulnerable to HIV infection and psychiatric symptoms are direct predictors of sexual risk behavior in MSM. Childhood sexual abuse (CSA) is associated with psychiatric symptomology in adolescence, and MSM are disproportionately impacted by CSA compared to heterosexuals. Some evidence suggests that childhood gender nonconformity, a natural variation of human gender expression, is more common in MSM than heterosexual males and places MSM at greater risk for CSA. This study examined whether or not childhood gender expression moderated the association between incidents of unwanted, early sexual experiences occurring before age 13 (ESE) and current psychiatric symptomology in a community-based sample of 449 young MSM aged 16-20. Analyses revealed significant bivariate associations between ESE and psychological symptoms, and significant multivariable associations between ESE, gender nonconformity and psychiatric outcomes. Young MSM with childhood gender nonconformity may be disproportionately victimized by CSA thereby increasing their likelihood of developing psychiatric symptoms in adolescence. Early intervention addressing these factors may help reduce lifetime negative sequelae.

Patterns Of Major Depression and Nonmedical Use Of Prescription Opioids In the United States Fink DS, Hu R, Cerda M, Keyes KM, Marshall BDL, Galea S, Martins SS. Drug Alcohol Depend. 2015; 153: 258-264.
Recent epidemiologic studies have shown that nonmedical use of prescription opioids (NMUPO) and major depression frequently co-occur. Comorbid forms of drug use and mental illness such as

NMUPO and depression pose a greater disease burden than either condition alone. However, sociodemographic and substance use differences between individuals with either NMUPO or depression and those with comorbid conditions have not yet been fully investigated. Data came from the 2011 and 2012 National Survey on Drug Use and Health (NSDUH). Adolescents and adults were examined independently because of differences in screening for major depressive episodes (MDE). Weighted multinomial logistic regression investigated differences between persons with either past-year NMUPO (4.0%) or MDE (5.5%) and those with comorbid NMUPO and MDE (0.6%), compared to persons with neither condition. Females were more likely than males to report, either MDE-alone, and comorbid NMUPO and MDE, whereas adult men were marginally more likely to report NMUPO-alone (not significant among adolescents). Polydrug use and alcohol use disorders were more pronounced among those with comorbid NMUPO and MDE than persons with either NMUPO-alone or MDE-alone. Persons with independent and comorbid NMUPO and MDE were more likely to report lower income and unemployment versus employment. This study found that independent and comorbid NMUPO and MDE were disproportionately clustered with burdens of lower socioeconomic position, suggesting that a population-based approach to address NMUPO would target these social determinants of health, whereas a high-risk approach to prevention should be tailored to females experiencing MDE symptoms and polydrug users.

High Dead-space Syringe Use Among People Who Inject Drugs In Tijuana, Mexico Rafful C, Zule W, González-Zúñiga PE, Patricia E, Werb D, Medina-Mora ME, Magis-Rodriguez C, Strathdee SA. Am J Drug Alcohol Abuse. 2015; 41(3): 220-225.
High dead-space syringes (HDSS) are believed to confer an elevated risk of acquiring HIV and other blood-borne infections. The authors identified prevalence and correlates of HDSS use among injection drug users (IDU) in Tijuana, Mexico, where syringe purchase and possession is legal without a prescription. Beginning in 2011, IDU who reported being 18 years or older and injected drugs within the last month were recruited into a prospective study. At baseline and semi-annually, 557 IDU underwent HIV-testing and interviewer-administered surveys. Logistic regression was used to identify correlates of using HDSS. Of 557 IDU, 40% had ever used HDSS, mostly because no other syringe type was available (72%), or because they were easier to get (20%). Controlling for sex and age at first injection, use of HDSS was associated with cocaine as the first drug injected (Adjusted Odds Ratio [AOR]: 2.68; Confidence Interval 95% [CI]: 1.15-6.22), having been stopped or arrested by police (AOR: 1.84; 95% CI: 1.11-3.07), being deported from the US (AOR: 1.64; 95% CI:1.06-2.53), and believing it is illegal to carry syringes (AOR:1.78; 95% CI: 1.01-3.15).Use of HDSS is surprisingly common among IDU in Tijuana. Efforts are needed to expand coverage of low-dead space syringes through existing syringe exchange programs. Education is required to increase awareness of the harms associated with HDSS, and to inform IDU that syringe possession is legal across Mexico.

Abuse and Diversion Of Gabapentin Among Nonmedical Prescription Opioid Users In Appalachian Kentucky Smith RV, Lofwall MR, Havens JR. Am J Psychiatry. 2015; 172(5): 487-488.
In a cohort of 503 adults reporting current, nonmedical use of diverted prescription opioids in Appalachian Kentucky (and not presently in substance abuse treatment; study details are described elsewhere [8]), 15% of participants identified using gabapentin specifically “to get high” in the past 6 months. This represents a 165% increase in use compared with reports from 1 year prior and a 2,950% increase since 2008 within this cohort. Participants reported using gabapentin an average of 25 of the past 30 days and were more likely than nonusers to be abusing immediate-release

oxycodone (64.8% compared with 46.5%; difference in percentages [d]=18.3%; 95% Wald continuity corrected confidence interval [CI]=3.1%–31.5%), buprenorphine (44.4% compared with 26.0%; d=18.4%; 95% CI=4.3%–33.1%), and benzodiazepines (42.6% compared with 21.6%; d=21.0%; 95% CI=7.1%–35.7%) in the prior 30 days "to get high." There were no differences in past 30-day use of heroin, cocaine, and methamphetamine. Females (77.8%; d=17.3%; 95% CI=10.4%–24.6%) and participants reporting chronic medical conditions (48.2%; d=16.3%; 95% CI=1.8%–31.0%) were also significantly more likely to report gabapentin use. The two major sources of gabapentin were physicians (52%) and drug dealers (36%), and street costs were reported to be less than $1.00 per pill. Several volunteers reported use of dosages outside the range of standard medical care. To the authors' knowledge, this is the first prospective report of gabapentin abuse in an epidemiologic study of drug users.

Genetic Overlap Between Alcohol Use Disorder and Bulimic Behaviors In European American and African American Women Munn-Chernoff MA, Grant JD, Agrawal A, Sartor CE, Werner KB, Bucholz KK, Madden PAF, Heath AC, Duncan AE. Drug Alcohol Depend. 2015; 153: 335-340.

Despite substantial evidence that alcohol use disorder (AUD) and bulimic behaviors (i.e., binge eating and compensatory behaviors) co-occur, insufficient information exists regarding a possible shared etiology. Moreover, although numerous twin studies of European ancestry individuals have reported moderate heritability estimates for AUD and bulimic behaviors, with little evidence for shared environmental factors, research on genetic and environmental risk in African American (AA) individuals is lacking. The authors investigated specific and overlapping genetic and environmental influences on AUD and bulimic behaviors in 3232 European American (EA; 55.38% monozygotic) and 549 AA (42.81% monozygotic) young adult female twins from the Missouri Adolescent Female Twin Study (age range=18-29 years). A structured clinical interview assessed lifetime DSM-5 AUD (minus craving) and bulimic behaviors. Biometrical twin modeling was conducted to generate age-adjusted estimates of genetic and environmental influences on AUD, bulimic behaviors, and their comorbidity. Estimates of genetic and environmental contributions on AUD and bulimic behaviors could be equated across EA and AA women. Additive genetic effects accounted for 59% (95% CI: 50%, 66%) and 43% (33%, 52%) of the variance in AUD and bulimic behaviors, respectively, with the remainder due to non-shared environmental effects. Shared genetic factors (rg=.33 (.18, .49)) were solely responsible for the correlation between phenotypes; the non-shared environmental correlation was not significant (re=.10 (-.05, .25)).Findings indicate similar magnitudes of genetic and environmental effects on AUD and bulimic behaviors for EA and AA women and implicate common genetic mechanisms underlying liability to these problem behaviors.

Theoretical Foundations Of Research Focused On HIV Prevention Among Substance-Involved Women: A Review Of Observational and Intervention Studies Auerbach JD, Smith LR. J Acquir Immune Defic Syndr. 2015; 69 Suppl 2: S146-154.

Although substance use continues to be a significant component of HIV risk among women worldwide, to date, relatively little attention has been paid in research, services, or policy to substance-involved women (SIW). HIV acquisition for SIW stems from transmission risks directly related to substance use and risks associated with sexual activity in which power to negotiate risk and safety are influenced by dynamics of male partnerships, sex work, and criminalization (of both drug use and sex work), among other factors. As such, HIV risk for SIW resides as much in the environment-physical, social, cultural, economic, and political- in which drug use occurs as it does from transmission- related behaviors of individual women. To reduce HIV infections among SIW, it

is important to specify the interaction of individual- and environmental-level factors, including, but not limited to those related to women own substance use that can and ought to be changed. This involves theorizing about the interplay of gender, substance use, and HIV risk, and incorporating that theoretical understanding into intervention design and evaluation. A review of the published literature focused on HIV prevention among SIW revealed a general lack of theoretical and conceptual foundation specific to the gender-related and environmental drivers of HIV in this population. Greater theoretical linkages to intersectionality and syndemic approaches are recommended to better identify and target relevant mechanisms by which the interplay of gender dynamics and substance use potentiate the likelihood of HIV acquisition and transmission among SIW.

Aggregate and Event-level Associations Between Substance Use and Sexual Behavior Among Gay and Bisexual Men: Comparing Retrospective and Prospective Data Rendina HJ, Moody RL, Ventuneac A, Grov C, Parsons JT. Drug Alcohol Depend. 2015; 154: 199-207.
Despite limited research, some evidence suggests that examining substance use at multiple levels may be of greater utility in predicting sexual behavior than utilizing one level of measurement, particularly when investigating different substances simultaneously. The authors aimed to examine aggregate and event-level associations between three forms of substance use - alcohol, marijuana, and club drugs - and two sexual behavior outcomes - sexual engagement and condomless, anal sex (CAS).Analyses focused on both 6-week timeline follow-back (TLFB; retrospective) and 30-day daily diary (prospective) data among a demographically diverse sample of 371 highly sexually active HIV-positive and HIV-negative gay and bisexual men. Models from both TLFB and diary showed that event-level use of alcohol, marijuana, and club drugs was associated with increased sexual engagement, while higher aggregated frequency marijuana and any frequency club drug use were associated with decreased sexual engagement. Event-level use of club drugs was consistently associated with increased odds of CAS across both TLFB and diary models while higher frequency marijuana use was most consistently associated with a lower odds of CAS. Findings indicated that results are largely consistent between retrospective and prospective data, but that retrospective results for substance use and sexual engagement were generally greater in magnitude. These results suggest that substance use primarily acts to increase sexual risk at the event-level and less so through individual-level frequency of use; moreover, it primarily does so by increasing the likelihood of sex on a given day with fewer significant associations with the odds of CAS on sex days.

Adolescents' Use Of Medical Marijuana: A Secondary Analysis Of Monitoring the Future Data Boyd CJ, Veliz PT, McCabe SE. J Adolesc Health. 2015; 57(2): 241-244.
The aims of this study were to examine adolescents' annual use of medical marijuana and determine if legal medical marijuana users are at lower risk for frequent marijuana use and other substance use when compared to adolescents who use diverted medical marijuana or from an illicit source. Public access Monitoring the Future data were used for this secondary analysis. The total weighted sample size was 4394 12th graders. Users of medical marijuana and diverted medical marijuana had notable odds of using daily, using prescription drugs, and using illicit drugs among other substance use behaviors. Medical marijuana users had much higher odds of using medical marijuana because of being "hooked" when compared to diverted medical users and illicit users. This study is the first to provide nationally representative data on three groups of adolescent marijuana users. Although most adolescents use illicit sources, more adolescents appear to be using diverted medical marijuana, than using medical marijuana legally.

Individual and Neighborhood Predictors Of Mortality Among HIV-positive Latinos With History Of Injection Drug Use, Florida, 2000-2011 Sheehan DM, Trepka MJ, Fennie KP, Prado G, Madhivanan P, Dillon FR, Maddox LM. Drug Alcohol Depend. 2015; 154: 243-250.
The objectives are to examine disparities in all-cause mortality risk among HIV-positive Latinos with injection drug use (IDU) history, and to identify individual- and neighborhood-level predictors. Florida surveillance data for persons diagnosed with HIV 2000-2008 were merged with 2007-2011 administrative data from the American Community Survey. Hazard ratios (HR) were calculated using multi-level weighted Cox regression adjusting for individual and neighborhood (ZCTA-level) factors. Of 10,989 HIV-positive Latinos, 10.3% had IDU history. Latinos with IDU history were at increased mortality risk compared with Latinos without IDU history after controlling for individual and neighborhood factors (adjusted HR [aHR] 1.61, 95% confidence interval [CI] 1.43-1.80). Factors associated with mortality for those with IDU history included: being 40-59 (aHR 6.48, 95% CI 1.41-121.05) and ≥ 60 years (aHR 18.75, 95% CI 3.83-356.45) compared with 13-19 years of age; being diagnosed with AIDS within 3 months of HIV (aHR 2.31, 95% CI 1.87-2.86); residing in an area with â ≥ 50% Latinos compared with <25% Latinos (aHR 1.56, 95% CI 1.19-2.04); and residing in a rural compared with an urban area at the time of diagnosis (aHR 1.73, 95% CI 1.06-2.70). Race and neighborhood poverty were not predictors among those with IDU, but were among those without. HIV-positive Latinos with IDU history are at increased mortality risk and have unique contributing factors. Tertiary prevention strategies should target those who are older, diagnosed at later stages, and those who live in predominantly Latino and rural areas.

Sexual Violence and HIV Infection Associated With Adolescent Vs Adult Entry Into The Sex Trade In Mexico Silverman JG, Servin A, Goldenberg SM, Magis-Rodriguez C, Ritter J, Raj A, Brouwer KC. JAMA. 2015; 314(5): 516-518.
Adolescents migrating from Central America and Mexico to the United States are at risk for being trafficked into the sex industry in Mexico's northern border cities. Research from other regions indicates that those entering the sex trade as adolescents (vs as adults) are more likely to experience sexual violence and human immunodeficiency virus (HIV) risk during initiation to the sex trade and to become infected with HIV.

The Moderating Role Of Cognitive Capacities In the Association Between Social Norms and Drinking Behaviors Meisel SN, Colder CR, Hawk LW. Alcohol Clin Exp Res. 2015; 39(6): 1049-1056.
The literature documents related yet distinct social normative influences on adolescent drinking. Descriptive norms refer to perceptions of how much others engage in a particular behavior, whereas injunctive norms refer to the extent to which others approve of a particular behavior. Theoretical formulations suggest that whether descriptive or injunctive norms guide drinking behavior depends on cognitive factors related to executive functioning. Cognitive capacities, specifically inhibitory control (IC) and preplanning, were tested as moderators of the association between social norms and alcohol use using a longitudinal design and community sample of adolescents. This longitudinal study included 387 adolescents and 3 annual waves of data. Behavioral tasks assessed IC (Stop Signal Task) and preplanning (Tower of London) and social norms and drinking were assessed using self-report measures. Significant interactions were found for descriptive and injunctive norms with preplanning and descriptive norms with IC. As hypothesized, descriptive norms were stronger prospective predictors of alcohol use at low levels of cognitive preplanning, whereas injunctive norms were stronger prospective predictors at high levels of cognitive preplanning. Descriptive norms prospectively predicted alcohol use at high, but not at low levels of IC. These findings

highlight the complexity of normative influences and suggest that descriptive and injunctive norms have differential effects on future drinking for individuals with different cognitive capacities.

Cannabis Smoking and Diabetes Mellitus: Results From Meta-analysis With Eight Independent Replication Samples Alshaarawy O, Anthony JC. Epidemiology. 2015; 26(4): 597-600.
In preclinical animal studies, evidence links cannabis with hyperphagia, obesity, and insulin resistance. Epidemiologic data, however, suggest an inverse cannabis smoking-diabetes mellitus association. Here, the authors offer epidemiologic estimates from eight independent replications from (1) the National Health and Nutrition Examination Surveys, and (2) the National Surveys on Drug Use and Health (2005-2012). For each national survey participant, computer-assisted self-interviews assess cannabis smoking and physician-diagnosed diabetes mellitus; the National Health and Nutrition Examination Surveys provide additional biomarker values and a composite diabetes diagnosis. Regression analyses produce estimates of cannabis smoking-diabetes associations. Meta-analyses summarize the replication estimates. Recently active cannabis smoking and diabetes mellitus are inversely associated. The meta-analytic summary odds ratio is 0.7 (95% confidence interval = 0.6, 0.8). Current evidence is too weak for causal inference, but there now is a more stable evidence base for new lines of clinical translational research on a possibly protective (or spurious) cannabis smoking-diabetes mellitus association suggested in prior research.

The Academic Consequences Of Marijuana Use During College Arria AM, Caldeira KM, Bugbee BA, Vincent KB, O'Grady KE. Psychol Addict Behav. 2015; 29(3): 564-575.
Although several studies have shown that marijuana use can adversely affect academic achievement among adolescents, less research has focused on its impact on postsecondary educational outcomes. This study utilized data from a large longitudinal cohort study of college students to test the direct and indirect effects of marijuana use on college grade point average (GPA) and time to graduation, with skipping class as a mediator of these outcomes. A structural equation model was evaluated taking into account a variety of baseline risk and protective factors (i.e., demographics, college engagement, psychological functioning, alcohol and other drug use) thought to contribute to college academic outcomes. The results showed a significant path from baseline marijuana use frequency to skipping more classes at baseline to lower first-semester GPA to longer time to graduation. Baseline measures of other drug use and alcohol quantity exhibited similar indirect effects on GPA and graduation time. Over time, the rate of change in marijuana use was negatively associated with rate of change in GPA, but did not account for any additional variance in graduation time. Percentage of classes skipped was negatively associated with GPA at baseline and over time. Thus, even accounting for demographics and other factors, marijuana use adversely affected college academic outcomes, both directly and indirectly through poorer class attendance. Results extend prior research by showing that marijuana use during college can be a barrier to academic achievement. Prevention and early intervention might be important components of a comprehensive strategy for promoting postsecondary academic achievement.

The Hepatitis C Virus Epidemics In Key Populations (including People Who Inject Drugs, Prisoners and MSM): The Use Of Direct-acting Antivirals As Treatment For Prevention Martin NK, Vickerman P, Dore GJ, Hickman M. Curr Opin HIV AIDS. 2015; 10(5): 374-380.
The burden of hepatitis C virus (HCV) is high among people who inject drugs (PWID) and prisoners, and increasing among HIV-infected MSM, who are key populations for HCV transmission in high-income countries and may also play a role in many in low- and middle-income

countries. There is an increasing interest in the use of HCV antiviral treatment for prevention in these populations. Numerous theoretical modelling studies have explored the potential impact of HCV treatment for prevention among PWID in a range of global settings, generally finding that modest and achievable levels of HCV treatment, especially with interferon-free direct-acting antiviral therapy (IFN-free DAAs), could substantially reduce HCV chronic prevalence among PWID within the next 10-20 years. In addition, modelling studies have shown HCV testing and treatment in prison (including prevention benefits) could be cost-effective if continuity of care is ensured, or HCV treatments are shortened with DAAs. Modelling work among HIV-infected MSM has shown that further HCV treatment scale-up is likely required despite high treatment rates in this population. However, no empirical studies have explored whether HCV treatment can reduce HCV prevalence and prevent onwards transmission among those at risk of transmission. HCV treatment for key populations such as PWID, prisoners and MSM could become an important HCV prevention intervention, especially in the IFN-free DAA era. However, there is an urgent need to test these hypotheses through empirical studies.

Substance Use and Physical Dating Violence: The Role Of Contextual Moderators Reyes HLM, Foshee VA, Tharp AT, Ennett ST, Bauer D J. Am J Prev Med. 2015; 49(3): 467-475.
Theoretic models suggest that associations between substance use and dating violence perpetration may vary in different social contexts, but few studies have examined this proposition. The current study examined whether social control and violence in the neighborhood, peer, and family contexts moderate the associations between substance use (heavy alcohol use, marijuana, and hard drug use) and adolescent physical dating violence perpetration. Adolescents in the eighth, ninth, and tenth grades completed questionnaires in 2004 and again four more times until 2007 when they were in the tenth, 11th, and 12th grades. Multilevel analysis was used to examine interactions between each substance and measures of neighborhood, peer, and family social control and violence as within-person (time-varying) predictors of physical dating violence perpetration across eighth through 12th grade (N=2,455). Analyses were conducted in 2014. Physical dating violence perpetration increased at time points when heavy alcohol and hard drug use were elevated; these associations were weaker when neighborhood social control was higher and stronger when family violence was higher. Also, the association between heavy alcohol use and physical dating violence perpetration was weaker when teens had more-prosocial peer networks and stronger when teens and peers reported more physical dating violence. Linkages between substance use and physical dating violence perpetration depend on substance use type and levels of contextual violence and social control. Prevention programs that address substance use-related dating violence should consider the role of social contextual variables that may condition risk by influencing adolescents and aggression propensity.

Armed Conflict, Substance Use and HIV: A Global Analysis Kerridge BT, Saha TD, Hasin DS. AIDS Behav. 2015.
Armed conflict is frequently assumed to be a contributor to the global HIV epidemic, but existing evidence is sparse. The authors examined the relationship between armed conflict between 2002 and 2008 and HIV disability life years (DALYs) in 2010 among WHO Member States. Using partial least squares analysis they also examined moderation of the armed conflict-HIV link by two susceptibility constructs (background risk, substance use) and one vulnerability mediator (numbers of refugees, people on ART, and total HIV spending). Background risk directly impacted HIV DALYs ($p< 0.05$), substance use moderated the conflict-HIV relationship ($p <0.01$). The vulnerability construct mediated the conflict-HIV association ($p<0.01$). Findings underscore the need to align HIV prevention/intervention efforts with pre-existing HIV burden and reduce the

impact of natural disasters on the populace in conflict-affected states. Integration of substance prevention/harm reduction programs within national HIV responses, attention to most-at-risk populations and increased surveillance/treatment of drug resistant HIV and TB is warranted.

Adolescent Obesity and Future Substance Use: Incorporating the Psychosocial Context Lanza HI, Grella CE, Chung PJ. J Adolesc. 2015; 45: 20-30.
A growing body of work has shown that obese adolescents are at risk of engaging in problematic substance use, but mixed findings highlight the complexity of the relationship. Incorporating the psychosocial context into this research may inform past discrepancies. The current study assessed whether obese adolescents had a higher likelihood of experiencing a psychosocial context that predicted problematic substance use in young adulthood. Latent class analysis on 10,637 adolescents from The National Longitudinal Study of Adolescent to Adult Health (Add Health) identified four psychosocial classes in adolescence: Adjusted, Deviant Peer/Victimization, Moderate Depression, and Maladjusted. Obese adolescents were more likely to belong to the Maladjusted class, characterized by higher levels of depression and deviant peer affiliation. Those in the Maladjusted class had the second highest levels of cigarette smoking and marijuana use in young adulthood. Obese adolescents and psychosocial context should be considered in future research linking obesity and substance use.

HIV Treatment and Prevention: A Simple Model To Determine Optimal Investment Juusola JL, Brandeau ML. Med Decis Making. 2015.
The aim of this study was to create a simple model to help public health decision makers determine how to best invest limited resources in HIV treatment scale-up and prevention. A linear model was developed for determining the optimal mix of investment in HIV treatment and prevention, given a fixed budget. The model incorporates estimates of secondary health benefits accruing from HIV treatment and prevention and allows for diseconomies of scale in program costs and subadditive benefits from concurrent program implementation. Data sources were published literature. The target population was individuals infected with HIV or at risk of acquiring it. Illustrative examples of interventions include preexposure prophylaxis (PrEP), community-based education (CBE), and antiretroviral therapy (ART) for men who have sex with men (MSM) in the US. Outcome measures were incremental cost, quality-adjusted life-years gained, and HIV infections averted. Base case analysis indicated that it is optimal to invest in ART before PrEP and to invest in CBE before scaling up ART. Diseconomies of scale reduced the optimal investment level. Subadditivity of benefits did not affect the optimal allocation for relatively low implementation levels. The sensitivity analysis indicated that investment in ART before PrEP was optimal in all scenarios tested. Investment in ART before CBE became optimal when CBE reduced risky behavior by 4% or less. Limitations of the study are that dynamic effects are approximated with a static model. The authors' model provides a simple yet accurate means of determining optimal investment in HIV prevention and treatment. For MSM in the US, HIV control funds should be prioritized on inexpensive, effective programs like CBE, then on ART scale-up, with only minimal investment in PrEP.

Opioid Overdose Deaths In the City and County Of San Francisco: Prevalence, Distribution, and Disparities Visconti AJ, Santos G-M, Lemos NP, Burke C, Coffin PO. J Urban Health. 2015; 92(4): 758-772.
Drug overdose is now the leading cause of unintentional death nationwide, driven by increased prescription opioid overdoses. To better understand urban opioid overdose deaths, this paper

examines geographic, demographic, and clinical differences between heroin-related decedents and prescription opioid decedents in San Francisco from 2010 to 2012. During this time period, 331 individuals died from accidental overdose caused by opioids (310 involving prescription opioids and 31 involving heroin). Deaths most commonly involved methadone (45.9%), morphine (26.9%), and oxycodone (21.8%). Most deaths also involved other substances (74.9%), most commonly cocaine (35.3%), benzodiazepines (27.5%), antidepressants (22.7%), and alcohol (19.6%). Deaths were concentrated in a small, high-poverty, central area of San Francisco and disproportionately affected African-American individuals. Decedents in high-poverty areas were significantly more likely to die from methadone and cocaine, whereas individuals from more affluent areas were more likely die from oxycodone and benzodiazepines. Heroin decedents were more likely to be within a younger age demographic, die in public spaces, and have illicit substances rather than other prescription opioids. Overall, heroin overdose death, previously common in San Francisco, is now rare. Prescription opioid overdose has emerged as a significant concern, particularly among individuals in high-poverty areas. Deaths in poor and affluent regions involve different causative opioids and co-occurring substances.

Police Encounters Among Needle Exchange Clients In Baltimore: Drug Law Enforcement As A Structural Determinant Of Health Beletsky L, Cochrane J, Sawyer AL, Serio-Chapman C, Smelyanskaya M, Han J, Robinowitz N, Sherman SG. Am J Public Health. 2015; 105(9): 1872-1879.

The authors piloted a monitoring mechanism to document police encounters around programs targeting people who inject drugs (PWID), and assessed their demographic predictors at 2 Baltimore, Maryland, needle exchange program (NEP) sites. In a brief survey, 308 clients quantified, characterized, and sited recent police encounters. Multivariate linear regression determined encounter predictors, and we used geocoordinate maps to illustrate clusters. Within the past 6 months, clients reported a median of 3 stops near NEP sites (interquartile range [IQR] = 0-7.5) and a median of 1 arrest in any location (IQR = 0-2). Three respondents reported police referral to the NEP. Being younger (P = .009), being male (P = .033), and making frequent NEP visits (P = .02) were associated with reported police stops. Among clients reporting arrest or citation for syringe possession, Whites were significantly less likely than non-Whites to report being en-route to or from an NEP (P < .001). Reported encounters were clustered around NEPs. Systematic surveillance of structural determinants of health for PWID proved feasible when integrated into service activities. Improved monitoring is critical to informing interventions to align policing with public health, especially among groups subject to disproportionate levels of drug law enforcement.

Optimizing Patient Treatment Decisions In An Era Of Rapid Technological Advances: The Case Of Hepatitis C Treatment Liu S, Brandeau ML, Goldhaber-Fiebert JD. Health Care Manag Sci. 2015.

How long should a patient with a treatable chronic disease wait for more effective treatments before accepting the best available treatment? The authors develop a framework to guide optimal treatment decisions for a deteriorating chronic disease when treatment technologies are improving over time. They formulate an optimal stopping problem using a discrete-time, finite-horizon Markov decision process. The goal is to maximize a patient and quality-adjusted life expectancy. The authors derive structural properties of the model and analytically solve a three-period treatment decision problem. They illustrate the model with the example of treatment for chronic hepatitis C virus (HCV). Chronic HCV affects 3-4 million Americans and has been historically difficult to treat, but increasingly effective treatments have been commercialized in the past few years. He authors show

that the optimal treatment decision is more likely to be to accept currently available treatment-despite expectations for future treatment improvement-for patients who have high-risk history, who are older, or who have more comorbidities. Insights from this study can guide HCV treatment decisions for individual patients. More broadly, the authors' model can guide treatment decisions for curable chronic diseases by finding the optimal treatment policy for individual patients in a heterogeneous population.

Plain Packaging: An Opportunity For Improved International Policy Coherence? Lencucha R, Drope J. Health Promot Int. 2015; 30(2): 281-290.
This paper highlights two salient challenges at the intersection of tobacco control and macroeconomic policy-making: (i) the use of trade and investment disputes to undermine and/or stall tobacco control legislation and (ii) the inconsistency, and thus unpredictability, of country positions across the two spheres. In the interest of improving international policy coherence, the authors suggest possible solutions to these two challenges at the national and intergovernmental levels.

Acceptability Of HIV Pre-exposure Prophylaxis (PREP) Among People Who Inject Drugs (PWID) In A Canadian Setting Escudero DJ, Kerr T, Wood E, Nguyen P, Lurie MN, Sued O, Marshall BDL. AIDS Behav. 2015; 19(5): 752-757.
A recent clinical trial provided evidence that pre-exposure prophylaxis (PrEP) has the potential to prevent HIV infection among people who inject drugs (PWID). The authors examined willingness to use PrEP among HIV-negative PWID in Vancouver, Canada (n=543) to inform PrEP implementation efforts. One third (35.4%) expressed willingness to use PrEP, with adjusted models indicating that younger age, no regular employment, requiring help injecting, engaging in sex work, and reporting multiple recent sexual partners were positively associated with willingness to use PrEP. Although willingness to use PrEP was low, PrEP was acceptable to some PWID at heightened risk for HIV infection.

The Role Of Visual Markers In Police Victimization Among Structurally Vulnerable Persons In Tijuana, Mexico Pinedo M, Burgos JL, Ojeda AV, FitzGerald D, Ojeda VD. Int J Drug Policy. 2015; 26(5): 501-508.
Law enforcement can shape HIV risk behaviours, and undermine strategies aimed at curbing HIV infection. Little is known about factors that increase vulnerability to police victimization in Mexico. This study identifies correlates of police or army victimization (i.e., harassment or assault) in the past 6 months among patients seeking care at a free clinic in Tijuana, Mexico. From January to May 2013, 601 patients attending a binational student-run free clinic completed an interviewer-administered questionnaire. Eligible participants were: (1) ≥18 years old; (2) seeking care at the clinic; and (3) spoke Spanish or English. Multivariate logistic regression analyses identified factors associated with police/army victimization in the past 6 months. More than one-third (38%) of participants reported victimization by police/army officials in the past 6 months in Tijuana. In multivariate logistic regression analyses, males (adjusted odds ratio (AOR): 3.68; 95% CI: 2.19-6.19), tattooed persons (AOR: 1.56; 95% CI: 1.04-2.33) and those who injected drugs in the past 6 months (AOR: 2.11; 95% CI: 1.29-3.43) were significantly more likely to report past 6-month police/army victimization. Recent feelings of rejection (AOR: 3.80; 95% CI: 2.47-5.85) and being denied employment (AOR: 2.23; 95% CI: 1.50-3.32) were also independently associated with police/army victimization. Structural interventions aimed at reducing stigma against vulnerable populations and increasing social incorporation may aid in reducing victimization events by

police/army in Tijuana. Police education and training to reduce abusive policing practices may be warranted.

Factors Associated With Hepatitis C Virus RNA Levels In Early Chronic Infection: The InC(3) Study Hajarizadeh B, Grady B, Page K, Kim AY, McGovern BH, Cox AL, Rice TM, Sacks-Davis R, Bruneau J, Morris M, Amin J, Schinkel J, Applegate T, Maher L, Hellard M, Lloyd AR, Prins M, Geskus RB, Dore GJ, Grebely J, InC3 Study Group. J Viral Hepat. 2015; 22(9): 708-717.

Improved understanding of natural history of hepatitis C virus (HCV) RNA levels in chronic infection provides enhanced insights into immunopathogenesis of HCV and has implications for the clinical management of chronic HCV infection. This study assessed factors associated with HCV RNA levels during early chronic infection in a population with well-defined early chronic HCV infection. Data were from an international collaboration of nine prospective cohorts studying acute HCV infection (InC(3) study). Individuals with persistent HCV and detectable HCV RNA during early chronic infection (one year [±4 months] postinfection) were included. Distribution of HCV RNA levels during early chronic infection was compared by selected host and virological factors. A total of 308 individuals were included. Median HCV RNA levels were significantly higher among males (vs females; 5.15 vs 4.74 log IU/mL; P< 0.01) and among individuals with HIV co-infection (vs no HIV; 5.89 vs 4.86; P = 0.02). In adjusted logistic regression, male sex (vs female, adjusted odds ratio [AOR]: 1.93; 95%CI: 1.01, 3.69), interferon lambda 4 (IFNL4) rs12979860 CC genotype (vs TT/CT; AOR: 2.48; 95%CI: 1.42, 4.35), HIV co-infection (vs no HIV; AOR: 3.27; 95% CI: 1.35, 7.93) and HCV genotype G2 (vs G3; AOR: 5.40; 95%CI: 1.63, 17.84) were independently associated with high HCV RNA levels (>5.6 log IU/mL = 400 000IU/mL). In conclusion, this study demonstrated that IFNL4 rs12979860 CC genotype, male sex, HIV co-infection and HCV genotype G2 are associated with high HCV RNA levels in early chronic infection. These factors exert their role as early as one year following infection.

STI/HIV Test Result Disclosure Between Female Sex Workers and Their Primary, Non-commercial Male Partners In Two Mexico-US Border Cities: A Prospective Study Pines HA, Patterson TL, Rangel G, Martinez G, Bazzi AR, Ulibarri MD, Syvertsen JL, Martin NK, Strathdee SA. Sex Transm Infect. 2015; 91(3): 207-213.

Disclosure of sexually transmitted infections (STI)/HIV diagnoses to sexual partners is not mandated by public health guidelines in Mexico. To assess the feasibility of couples-based STI/HIV testing with facilitated disclosure as a risk-reduction strategy within female sex workers & (FSW) primary partnerships, the authors examined STI/HIV test result disclosure patterns between FSWs and their primary, non-commercial male partners in two Mexico-US border cities. From 2010 to 2013, 335 participants (181 FSWs and 154 primary male partners) were followed for 24 months. At semiannual visits, participants were tested for STIs/HIV and reported on their disclosure of test results from the previous visit. Multilevel logistic regression was used to identify individual-level and partnership-level predictors of cumulative (1) non-disclosure of ≥ 1 STI test result and (2) non-disclosure of ≥1 HIV test result within couples during follow-up. Eighty-seven percent of participants reported disclosing all STI/HIV test results to their primary partners. Non-disclosure of ≥1 STI test result was more common among participants who reported an STI diagnosis as part of the study (adjusted OR=3.05, 95% CI 1.13 to 8.25), while non-disclosure of ≥1 HIV test result was more common among participants in longer-duration partnerships (AOR=1.15 per year, 95% CI 1.03 to 1.28). Drug use before/during sex within partnerships was associated with non-disclosure of both STI (AOR=5.06, 95% CI 1.64 to 15.62) and HIV (AOR=4.51, 95% CI: 1.32 to 15.39) test

results. STI/HIV test result disclosure was highly prevalent within FSWs & primary partnerships, suggesting couples-based STI/HIV testing with facilitated disclosure may be feasible for these and potentially other high-risk, socially marginalized couples.

Short-term Cessation Of Sex Work and Injection Drug Use: Evidence From A Recurrent Event Survival Analysis Gaines TL, Urada LA, Martinez G, Goldenberg SM, Rangel G, Reed E, Patterson TL, Strathdee SA. Addict Behav. 2015; 45: 63-69.
This study quantitatively examined the prevalence and correlates of short-term sex work cessation among female sex workers who inject drugs (FSW-IDUs) and determined whether injection drug use was independently associated with cessation. The authors used data from FSW-IDUs (n=467) enrolled into an intervention designed to increase condom use and decrease sharing of injection equipment but was not designed to promote sex work cessation. They applied a survival analysis that accounted for quit-re-entry patterns of sex work over 1-year stratified by city, Tijuana and Ciudad Juarez, Mexico. Overall, 55% of participants stopped sex work at least once during follow-up. Controlling for other characteristics and intervention assignment, injection drug use was inversely associated with short-term sex work cessation in both cities. In Ciudad Juarez, women receiving drug treatment during follow-up had a 2-fold increase in the hazard of stopping sex work. In both cities, income from sources other than sex work, police interactions and healthcare access were independently and significantly associated with shorter-term cessation. Short-term sex work cessation was significantly affected by injection drug use. Expanded drug treatment and counseling coupled with supportive services such as relapse prevention, job training, and provision of alternate employment opportunities may promote longer-term cessation among women motivated to leave the sex industry.

Prevalence and Predictors Of Hookah Use In US Air Force Military Recruits Linde BD, Ebbert JO, Pasker CK, Wayne Talcott G, Schroeder DR, Hanson AC, Klesges RC. Addict Behav. 2015; 47: 5-10.
Hookah use has gained recent popularity among U.S. youth. The current study describes the characteristics and correlates associated with hookah use in late adolescent and young adult US Air Force (USAF) recruits. Data were obtained from a cross-sectional questionnaire of USAF personnel in Technical Training School at Joint Base San Antonio (N=10,997). Response rate was 78%. Logistic regression was used to analyze the associations between hookah use, demographic variables, other tobacco and nicotine containing product (TNCP) use, and the social environment. The prevalence of ever hookah use was 28%; at least monthly hookah use was 10%. Increased hookah use was positively associated with Hispanic ethnicity (OR [odds ratio] 1.52; 95% CI: 1.25, 1.85), cigarette smoking (OR 4.05; CI: 3.41, 4.82) and smokeless tobacco use (OR 1.35; 95% CI: 1.07, 1.71). Hookah use was negatively associated with age (OR 0.84; 95% 0.71 to 1.00), living as married (OR 0.54; 95% CI: 0.40-0.72), African American (OR 0.53; 95% CI: 0.40, 0.69) and a 4-year degree (OR 0.54; 95% CI: 0.35, 0.82). Hookah use was highest among recruits who "many or almost all" of their friends smoked cigarettes (OR 2.43; 95% CI: 1.80, 3.30) and for those who reported willingness to try a tobacco product that claims to be safer than cigarettes (OR 3.16; 95% CI: 2.64, 3.77). Hookah use among military recruits is similar to the civilian population. A willingness to try TNCPs claiming to be safer than cigarettes may influence hookah use. Public health campaigns disseminating accurate information about hookah health risks may be needed to reduce hookah use among youth.

A Socio-cultural View Of Trends In Drug Use Indicators Golub A, Elliott L, Bennett AS. Addiction. 2015; 110(5): 740-741.
The authors have found that drug epidemics pass typically through four distinct phases: incubation, expansion, plateau and decline. The in-cubation phase starts typically with use among a highly limited subpopulation participating in a specific social con- text such as after-hours clubs, the hip-hop movement or raves. During the expansion phase, the pioneering drug users introduce the practice to the broader population, where it spreads exponentially. The plateau phase of steady widespread use appears when everyone most at risk of the new drug practice either has initiated use or at least had the opportunity to do so. During this period, youths first coming of age typically initiate use of the currently popular drug(s), if any. Eventually, an illicit drug can go out of favor heralding a gradual decline phase, during which many existing users persist in their habits but decreasing percentages of youths become users.

How Popular Is Waterpipe Tobacco Smoking? Findings From Internet Search Queries Salloum RG, Osman A, Maziak W, Thrasher JF. Tob Control. 2015; 24(5): 509-513.
Waterpipe tobacco smoking (WTS), a traditional tobacco consumption practice in the Middle East, is gaining popularity worldwide. Estimates of population-level interest in WTS over time are not documented. The authors assessed the popularity of WTS using World Wide Web search query results across four English-speaking countries. They analyzed trends in Google search queries related to WTS, comparing these trends with those for electronic cigarettes between 2004 and 2013 in Australia, Canada, the UK and the USA. Weekly search volumes were reported as percentages relative to the week with the highest volume of searches. Web-based searches for WTS have increased steadily since 2004 in all four countries. Search volume for WTS was higher than for e-cigarettes in three of the four nations, with the highest volume in the USA. Online searches were primarily targeted at WTS products for home use, followed by searches for WTS cafés/lounges. Online demand for information on WTS-related products and venues is large and increasing. Given the rise in WTS popularity, increasing evidence of exposure-related harms, and relatively lax government regulation, WTS is a serious public health concern and could reach epidemic levels in Western societies.

Place Of Residence Moderates the Relationship Between Emotional Closeness and Syringe Sharing Among Injection Drug Using Clients Of Sex Workers In the US-Mexico Border Region Wagner KD, Pitpitan EV, Valente TW, Strathdee SA, Rusch M, Magis-Rodriguez C, Chavarin CV, Patterson TL. AIDS Behav. 2015; 19(6): 987-995.
Injection drug-using men from the US and Mexico who purchase sex in Tijuana, Mexico are at risk for transmitting HIV to their contacts in both countries via syringe sharing. The authors used social network methods to understand whether place of residence (US vs. Mexico) moderated the effect of emotional closeness on syringe sharing. They interviewed 199 drug-using men who reported paying/trading for sex in Tijuana, Mexico using an epidemiological and social network survey and collected samples for HIV/STI testing. Seventy-two men reported using injection drugs with 272 network contacts. Emotional closeness was strongly associated with syringe sharing in relationship where the partner lives in the US, while the relationship between emotional closeness and syringe sharing was considerably less strong in dyads where the partner lives in Mexico. Efforts to reduce HIV risk behaviors in emotionally close relationships are needed, and could benefit from tailoring to the environmental context of the relationship.

Incidence and Prevalence Of Hepatitis C Virus Infection Among Persons Who Inject Drugs In New York City: 2006-2013 Jordan AE, Des Jarlais DC, Arasteh K, McKnight C, Nash D, Perlman DC. Drug Alcohol Depend. 2015; 152: 194-200.
Hepatitis C virus infection is a source of significant preventable morbidity and mortality among persons who inject drugs (PWID). The authors sought to assess trends in hepatitis C virus (HCV) infection among PWID from 2006 to 2013 in New York City (NYC).Annual cross-sectional surveys of PWID entering a large drug abuse treatment program were performed. Risk behavior questionnaires were administered, and HIV and HCV testing were conducted. Comparisons were made with prior prevalence and incidence estimates in 1990-1991 and 2000-2001 reflecting different periods of combined prevention and treatment efforts. HCV prevalence among PWID (N: 1535) was 67% (95% CI: 66-70%) during the study period, and was not significantly different from that observed in 2000-2001. The estimated HCV incidence among new injectors (persons injecting for ≤6 years) during 2006-2013 was 19.5/100 PYO (95% CI: 17-23) and did not differ from that observed in 2000-2001 (18/100 PYO, 95% CI: 14-23/100). Despite the expansion of combined prevention programming between 2000-2001 and 2006-2013, HCV prevalence remained high. Estimated HCV incidence among new injectors also remained high, and not significantly lower than in 2000-2001, indicating that expanded combined prevention efforts are needed to control the HCV epidemic among PWID in NYC.

Antiretroviral Drug Diversion Links Social Vulnerability To Poor Medication Adherence In Substance Abusing Populations Tsuyuki K, Surratt HL. AIDS Behav. 2015; 19(5): 869-881.
Antiretroviral (ARV) medication diversion to the illicit market has been documented in South Florida, and linked to sub-optimal adherence in people living with HIV. ARV diversion reflects an unmet need for care in vulnerable populations that have difficulty engaging in consistent HIV care due to competing needs and co-morbidities. This study applies the Gelberg-Andersen behavioral model of health care utilization for vulnerable populations to understand how social vulnerability is linked to ARV diversion and adherence. Cross-sectional data were collected from a targeted sample of vulnerable people living with HIV in South Florida between 2010 and 2012 (n = 503). Structured interviews collected quantitative data on ARV diversion, access and utilization of care, and ARV adherence. Logistic regression was used to estimate the goodness-of-fit of additive models that test domain fit. Linear regression was used to estimate the effects of social vulnerability and ARV diversion on ARV adherence. The best fitting model to predict ARV diversion identifies having a low monthly income and unstable HIV care as salient enabling factors that promote ARV diversion. Importantly, health care need factors did not protect against ARV diversion, evidence that immediate competing needs are prioritized even in the face of poor health for this sample. The authors also find that ARV diversion provides a link between social vulnerability and sub-optimal ARV adherence, with ARV diversion and domains from the Behavioral Model explaining 25 % of the variation in ARV adherence. These analyses reveal great need to improve engagement in HIV care for vulnerable populations by strengthening enabling factors (e.g. patient-provider relationship) to improve retention in HIV care and ARV adherence for vulnerable populations.

Determinants Of Cigarette Smoking Initiation In Jordanian Schoolchildren: Longitudinal Analysis McKelvey K, Attonito J, Madhivanan P, Yi Q, Mzayek F, Maziak W. Nicotine Tob Res. 2015; 17(5): 552-558.
The objective of this study was to identify determinants of cigarette smoking initiation, by gender, among schoolchildren in Irbid, Jordan. Between 2008 and 2011, data were collected annually using self-reported questionnaires over 4-years in a prospective cohort of 1,781 students recruited from all

7th grade classes in 19 secondary schools, selected out of a total 60, using probability-proportionate to-size method. Independent predictors of smoking initiation were identified among the cigarette naive participants (N = 1,454) with mixed-effect multivariable logistic regression. Participants were 12.6 years of age on average at baseline. 29.8% of the 1,454 students (37.2% of boys and 23.7% of girls) initiated cigarette smoking by 10th grade. Of those who initiated (n = 498), 47.2% of boys and 37.2% of girls initiated smoking in the 8th grade. Determinants of cigarette smoking initiation included ever smoking a waterpipe, low cigarette refusal self-efficacy, intention to start smoking cigarettes, and having friends who smoked. For girls, familial smoking was also predictive of cigarette initiation. This study shows that many Jordanian youth have an intention to initiate cigarette smoking and are susceptible to cigarette smoking modeled by peers and that girls are influenced as well by familial cigarette smoking. Prevention efforts should be tailored to address culturally relevant gender norms, help strengthen adolescents and self-efficacy to refuse cigarettes, and foster strong non-smoking social norms.

Structural Determinants Of Inconsistent Condom Use With Clients Among Migrant Sex Workers: Findings Of Longitudinal Research In An Urban Canadian Setting Sou J, Shannon K, Li J, Nguyen P, Strathdee SA, Shoveller J, Goldenberg SM. Sex Transm Dis. 2015; 42(6): 312-316.

Migrant women in sex work experience unique risks and protective factors related to their sexual health. Given the dearth of knowledge in high-income countries, the authors explored factors associated with inconsistent condom use by clients among migrant female sex workers over time in Vancouver, BC. Questionnaire and HIV/sexually transmitted infection testing data from a longitudinal cohort, An Evaluation of Sex Workers Health Access, were collected from 2010 to 2013. Logistic regression using generalized estimating equations was used to model correlates of inconsistent condom use by clients among international migrant sex workers over a 3-year study period. Of 685 participants, analyses were restricted to 182 (27%) international migrants who primarily originated from China. In multivariate generalized estimating equations analyses, difficulty accessing condoms (adjusted odds ratio [AOR], 3.76; 95% confidence interval [CI], 1.13-12.47) independently correlated with increased odds of inconsistent condom use by clients. Servicing clients in indoor sex work establishments (e.g., massage parlors) (AOR, 0.34; 95% CI, 0.15-0.77), and high school attainment (AOR, 0.22; 95% CI, 0.09-0.50) had independent protective effects on the odds of inconsistent condom use by clients. Findings of this longitudinal study highlight the persistent challenges faced by migrant sex workers in terms of accessing and using condoms. Migrant sex workers who experienced difficulty in accessing condoms were more than 3 times as likely to report inconsistent condom use by clients. Laws, policies, and programs promoting access to safer, decriminalized indoor work environments remain urgently needed to promote health, safety, and human rights for migrant workers in the sex industry.

Perceived Stigma Among People With Chronic Health Conditions: The Influence Of Age, Stressor Exposure, and Psychosocial Resources Brown RL. Res Aging. 2015; 37(4): 335-360.

This study addresses whether age, functional limitation and other stressor exposure, and psychosocial coping resources influence variation in perceived stigma and the form this influence takes (i.e., independent and/or interdependent). Using data from two waves of a large community study of adults (age 20-93) with chronic health conditions (n = 417), a residual change regression analysis considers direct and moderating factors influencing perceived stigma over a 3-year period. Age, functional limitation, the experience of discrimination, and self-esteem independently account for variation in perceived stigma. Moderation tests reveal that age is associated with a greater

increase in stigma in the context of greater functional limitation and increases in limitation. Functional limitation and stressor exposure are also associated with declines in stigma in the context of greater mastery and self-esteem. Multiple processes bear on perceived stigma among people with chronic health conditions. Implications for stigma and stress research are discussed.

The Racial Disparities In STI In The U.S.: Concurrency, STI Prevalence, and Heterogeneity In Partner Selection Hamilton DT, Morris M. Epidemics. 2015; 11: 56-61.
There is a large and persistent racial disparity in STI in the U.S. which has placed non-Hispanic-Blacks at disproportionately high risk. The authors tested a hypothesis that both individual-level risk factors (partner number, anal sex, condom use) and local-network features (concurrency and assortative mixing by race) combine to account for the association between race and chlamydia status. Data from the Longitudinal Survey of Adolescent Health Wave III were used. Chlamydia status was determined using biomarkers. Individual-level risk behaviors were self-reported. Network location variables for concurrency and assortative mixing were imputed using egocentrically sample data on sexual partnerships. After controlling for demographic attributes including age, sex, marital status, education and health care access there remained a strong association between race and chlamydia status (OR = 5.23, 95% CI [3.83-7.15], $p < .001$ for Non-Hispanic Blacks with Non-Hispanic Whites as the reference category). The inclusion of individual-level risk factors did not alter the association between race and chlamydia (OR = 5.23 for Non-Hispanic Blacks). The inclusion of concurrency and assortative mixing by race substantially reduced the association between race and chlamydia status (OR = 1.87, 95% CI [0.89-3.91] $p > .05$ for Non-Hispanic Blacks).

HIV, HCV, and Health-Related Harms Among Women Who Inject Drugs: Implications For Prevention and Treatment Iversen J, Page K, Madden A, Maher L. J Acquir Immune Defic Syndr. 2015; 69 Suppl 2: S176-181.
Although an estimated 3.5 million women inject drugs globally, women are outnumbered 4 to one by men who inject drugs and are often ignored or overlooked in the development and delivery of prevention and treatment services for this population. This study aimed to identify key comorbidities prevalent among women who inject drugs (WWID), consider factors that contribute to vulnerability of this population, and examine implications for prevention and treatment. The literature was reviewed to examine the specific challenges and needs of WWID. We searched health-related bibliographic databases and grey literature to identify studies conducted among WWID and studies conducted among people who inject drugs (PWID), where results were disaggregated by gender and policies/guidelines/reports relevant to WWID.WWID face a range of unique, gender-specific, and often additional challenges and barriers. The lack of a targeted focus on WWID by prevention and treatment services and harm-reduction programs increases women and vulnerability to a range of health-related harms, including blood-borne viral and sexually transmitted infections, injection-related injuries, mental health issues, physical and sexual violence, poor sexual and reproductive health, issues in relation to childbearing and child care, and pervasive stigma and discrimination. There is a need to improve the collection and reporting of gender-disaggregated data on prevalence of key infections and prevention and treatment service access and program coverage. Women-focused services and integrating gender equity and human rights into the harm-reduction programming will be a prerequisite if improvements in the health, safety, and well-being of this often invisible and highly vulnerable population are to be achieved.

Women Who Use Or Inject Drugs: An Action Agenda For Women-Specific, Multilevel, and Combination HIV Prevention and Research El-Bassel N, Strathdee SA. J Acquir Immune Defic Syndr. 2015; 69 Suppl 2: S182-190.
Women account for more than half of all individuals living with HIV globally. Despite increasing drug and HIV epidemics among women, women who use drugs are rarely found in research, harm reduction programs, or drug and HIV treatment and care. Women who use drugs continue to face challenges that increase their vulnerability to HIV and other comorbidities because of high rates of gender-based violence, human rights violations, incarceration, and institutional and societal stigmatization. This special issue emphasizes how the burdens of HIV, drug use, and their co-occurring epidemics affect women in a global context. Articles included focus on the epidemiologies of HIV and hepatitis C virus and other comorbidities; HIV treatment, prevention, and care; and policies affecting the lives of women who use drugs. This issue also highlights the state of the science of biomedical and behavioral research related to women who use drugs. The final article highlights the major findings of articles covered and presents a call to action regarding needed research, treatment, and preventive services for women who use drugs. To address these needs, we advocate for women-specific thinking and approaches that consider the social, micro, and macro contexts of women and lives. The authors present a women-specific risk environment framework that reflects the unique lives and contexts of women who use drugs and provides a call to action for intervention, prevention, and policies.

Predictors Of Waterpipe Smoking Progression Among Youth In Irbid, Jordan: A Longitudinal Study (2008-2011) Jaber R, Madhivanan P, Khader Y, Mzayek F, Ward KD, Maziak W. Drug Alcohol Depend. 2015; 153: 265-270.
The predictors of waterpipe smoking progression are yet to be examined using a longitudinal study that is guided by a theoretical model of behavioral change. This study identifies the gender-specific predictors of waterpipe smoking progression among adolescents in Irbid, Jordan. This study uses data from a school longitudinal study of smoking behavior in Irbid, Jordan. A random sample of 19 schools was selected by probability proportionate to size. A total of 1781 seventh graders were enrolled at baseline, and completed a questionnaire annually from 2008 through 2011. Students who reported ever smoking waterpipe (N=864) at any time point were assessed for progression (escalation in the frequency of waterpipe smoking) in the subsequent follow-up. Grouped-time survival analysis was used to identify the risk of progression. During the three years of follow-up, 29.6% of students progressed in waterpipe smoking. Predictors of waterpipe smoking progression were higher mother education, enrollment in public school, frequent physical activity, and low refusal self-efficacy among boys, having ever smoked cigarettes, and having friends and siblings who smoke waterpipe among girls. Awareness of harms of waterpipe was protective among boys and seeing warning labels on the tobacco packs was protective among girls. Even at this early stage, about a third of waterpipe smokers progressed in their habit during the 3 year follow up. Factors predicting progression of use differed by gender, which calls for gender-specific approaches to waterpipe interventions among Jordanian youth.

Addiction and Treatment Experiences Among Active Methamphetamine Users Recruited From A Township Community In Cape Town, South Africa: A Mixed-methods Study Meade CS, Towe SL, Watt MH, Lion RR, Myers B, Skinner D, Kimani S, Pieterse D. Drug Alcohol Depend. 2015; 152: 79-86.
Since 2000, there has been a dramatic increase in methamphetamine use in South Africa, but little is known about the experiences of out-of-treatment users. This mixed-methods study describes the

substance use histories, addiction symptoms, and treatment experiences of a community-recruited sample of methamphetamine users in Cape Town. Using respondent driven sampling, 360 methamphetamine users (44% female) completed structured clinical interviews to assess substance abuse and treatment history and computerized surveys to assess drug-related risks. A sub-sample of 30 participants completed in-depth interviews to qualitatively explore experiences with methamphetamine use and drug treatment. Participants had used methamphetamine for an average of 7.06 years (SD=3.64). They reported using methamphetamine on an average of 23.49 of the past 30 days (SD=8.90); 60% used daily. The majority (90%) met ICD-10 criteria for dependence, and many reported severe social, financial, and legal consequences. While only 10% had ever received drug treatment, 90% reported that they wanted treatment. In the qualitative interviews, participants reported multiple barriers to treatment, including beliefs that treatment is ineffective and relapse is inevitable in their social context. They also identified important motivators, including desires to be drug free and improve family functioning. This study yields valuable information to more effectively respond to emerging methamphetamine epidemics in South Africa and other low- and middle-income countries. Interventions to increase uptake of evidence-based services must actively seek out drug users and build motivation for treatment, and offer continuing care services to prevent relapse. Community education campaigns are also needed.

Substance Use and HIV Among Female Sex Workers and Female Prisoners: Risk Environments and Implications For Prevention, Treatment, and Policies Strathdee SA, West BS, Reed E, Moazen B, Azim T, Dolan K. J Acquir Immune Defic Syndr. 2015; 69 Suppl 2: S110-117.

Female sex workers (FSWs) and female prisoners experience elevated HIV prevalence relative to the general population because of unprotected sex and unsafe drug use practices, but the antecedents of these behaviors are often structural in nature. The authors review the literature on HIV risk environments for FSWs and female prisoners, highlighting similarities and differences in the physical, social, economic, and policy/legal environments that need to be understood to optimize HIV prevention, treatment, and policy responses. Sex work venues, mobility, gender norms, stigma, debt, and the laws and policies governing sex work are important influences in the HIV risk environment among FSWs, affecting their exposure to violence and ability to practice safer sex and safer drug use behaviors. Female prisoners are much more likely to have a drug problem than do male prisoners and have higher HIV prevalence, yet are much less likely to have access to HIV prevention and treatment and access to drug treatment in prison. Women who trade sex or are imprisoned and engage in substance use should not be considered in separate silos because sex workers have high rates of incarceration and many female prisoners have a history of sex work. Repeated cycles of arrest, incarceration, and release can be socially and economically destabilizing for women, exacerbating their HIV risk. This dynamic interplay requires a multisectoral approach to HIV prevention and treatment that appreciates and respects that not all women are willing, able, or want to stop sex work or drug use. Women who engage in sex work, use drugs, or are imprisoned come from all communities and deserve sustained access to HIV prevention and treatment for substance use and HIV, helping them and their families to lead healthy and satisfying lives.

Incidence and Predictors Of HIV and Sexually Transmitted Infections Among Female Sex Workers and Their Intimate Male Partners In Northern Mexico: A Longitudinal, Multilevel Study Bazzi AR, Rangel G, Martinez G, Ulibarri MD, Syvertsen JL, Bazzi SA, Roesch S, Pines HA, Strathdee SA. Am J Epidemiol. 2015; 181(9): 723-731.
Preventing human immunodeficiency virus (HIV) infection and other sexually transmitted infections (STIs) requires an understanding of sexual relationship factors beyond the individual level. The authors estimated HIV/STI incidence and identified time-varying predictors of STI acquisition in a prospective cohort study of female sex workers and their intimate (noncommercial) male partners in northern Mexico. From 2010 to 2013, couples underwent behavioral and biological assessments biannually for 24 months. Among 413 initially HIV-uninfected participants, 8 seroconverted during follow-up. Incidence of HIV (1.12 cases/100 person-years (PY)), chlamydia (9.47 cases/100 PY), active syphilis (4.01 cases/100 PY), and gonorrhea (1.78 cases/100 PY) was higher among women than among men (HIV: $P = 0.069$; all STIs combined: $P < 0.001$). In multivariable conditional logistic regression with individual fixed effects and correlated error terms within couples, risk of STI acquisition was significantly higher among women who had recently used cocaine, crack, or methamphetamine (adjusted odds ratio (OR) = 2.13, 95% confidence interval (CI): 1.07, 4.28). STI risk was lower among women who reported physically assaulting their male partners (adjusted OR = 0.44, 95% CI: 0.22, 0.86) and among men whose female partners had regular sex-work clients (adjusted OR = 0.38, 95% CI: 0.14, 1.03). Improving vulnerable couples & sexual health will require addressing the contexts in which drug use, interpersonal conflict, and economic vulnerability converge.

How To Define E-cigarette Prevalence? Finding Clues In The Use Frequency Distribution Amato MS, Boyle RG, Levy D. Tob Control. 2015.
E-cigarette use has rapidly increased. Recent studies define prevalence using a variety of measures; competing definitions challenge cross-study comparison. The authors sought to understand patterns of use by investigating the number of days out of the past 30 days when adults had used e-cigarettes. They used the 2014 Minnesota Adult Tobacco Survey, a random digit dial population survey (n=9304 adults). Questions included ever using e-cigarettes, number of days used in the past 30 days and reasons for use. Smoking status was determined by combustible cigarette use. Histograms of e-cigarette use were visually inspected for current, former and never smokers with any 30-day e-cigarette use. Different definitions of current use were compared. Use ≤5 days in the past 30 days demarcated a cluster of infrequent users at the low end of the distribution. Among those with use in the past 30 days, infrequent users were the majorities of current (59%) and never smokers (89.5%), but fewer than half of former smokers (43.2%). Infrequent users were more likely to cite curiosity and less likely to cite quitting/cutting down other tobacco use as reasons for use. Defining adult prevalence as any use in the past 30 days may include experimenters unlikely to continue use, and is of questionable utility for population surveillance of public health trends over time. Defining prevalence as >5 days excludes those infrequent users.

Association Between Non-fatal Opioid Overdose and Encounters With Healthcare and Criminal Justice Systems: Identifying Opportunities For Intervention Wagner KD, Liu L, Davidson PJ, Cuevas-Mota J, Armenta RF, Garfein RS. Drug Alcohol Depend. 2015; 153: 215-220.
Accidental overdose, driven largely by opioids, is a leading cause of death among people who inject drugs (PWIDs). The authors conducted secondary analysis of data from a cohort of PWIDs to identify venues where high-risk PWID could be targeted by overdose education/naloxone distribution (OEND) programs. 573 PWIDs completed a quantitative survey between June, 2012

and January, 2014, which was analyzed using multivariable logistic regression. The dependent variable was a dichotomous indicator of experiencing a heroin/opioid-related overdose in the past six months. Independent variables included: demographics, drug use behavior, and encounters with two venues - the health care and criminal justice systems - that could serve as potential venues for OEND programs. Almost half (41.5%) reported ever experiencing a heroin/opioid overdose, and 45 (7.9%) reported experiencing at least one heroin/opioid overdose in the past six months. In the final multivariable model, receiving care in a hospital in the past six months (Adjusted Odds Ratio [AdjOR] 4.08, 95% Confidence Interval [C.I.] 2.07, 8.04, $p<0.001$) and being arrested for drug possession in the past six months (AdjOR 5.17, 95% C.I. 2.37, 11.24, $p<0.001$) were associated with experiencing an opioid overdose in the past six months. Identifying venues outside of those that traditionally target services to PWIDs (i.e., syringe exchange programs) will be critical to implementing OEND interventions at a scale sufficient to address the growing epidemic of heroin/opioid related deaths. Clinical settings, such as hospitals, and drug-related encounters with law enforcement officers are promising venues for the expansion of OEND programs.

Long-term Effectiveness Of Accelerated Hepatitis B Vaccination Schedule In Drug Users Shah DP, Grimes CZ, Nguyen AT, Lai D, Hwang L-Y. Am J Public Health. 2015; 105(6): e36-43.
The authors demonstrated the effectiveness of an accelerated hepatitis B vaccination schedule in drug users. They compared the long-term effectiveness of accelerated (0-1-2 months) and standard (0-1-6 months) hepatitis B vaccination schedules in preventing hepatitis B virus (HBV) infections and anti-hepatitis B (anti-HBs) antibody loss during 2-year follow-up in 707 drug users (HIV and HBV negative at enrollment and completed 3 vaccine doses) from February 2004 to October 2009. Drug users in the accelerated schedule group had significantly lower HBV infection rates, but had a similar rate of anti-HBs antibody loss compared with the standard schedule group over 2 years of follow-up. No chronic HBV infections were observed. Hepatitis C positivity at enrollment and age younger than 40 years were independent risk factors for HBV infection and antibody loss, respectively. An accelerated vaccination schedule was more preferable than a standard vaccination schedule in preventing HBV infections in drug users. To overcome the disadvantages of a standard vaccination schedule, an accelerated vaccination schedule should be considered in drug users with low adherence. This study should be repeated in different cohorts to validate the authors' findings and establish the role of an accelerated schedule in hepatitis B vaccination guidelines for drug users.

Accounting For Dropout Reason In Longitudinal Studies With Nonignorable Dropout Moore CM, MaWhinney S, Forster JE, Carlson NE, Allshouse A, Wang X, Routy J-P, Conway B, Connick E. Stat Methods Med Res. 2015.
Dropout is a common problem in longitudinal cohort studies and clinical trials, often raising concerns of nonignorable dropout. Selection, frailty, and mixture models have been proposed to account for potentially nonignorable missingness by relating the longitudinal outcome to time of dropout. In addition, many longitudinal studies encounter multiple types of missing data or reasons for dropout, such as loss to follow-up, disease progression, treatment modifications and death. When clinically distinct dropout reasons are present, it may be preferable to control for both dropout reason and time to gain additional clinical insights. This may be especially interesting when the dropout reason and dropout times differ by the primary exposure variable. The authors extend a semi-parametric varying-coefficient method for nonignorable dropout to accommodate dropout reason. They apply their method to untreated HIV-infected subjects recruited to the Acute Infection and Early Disease Research Program HIV cohort and compare longitudinal CD4(+) T cell count in

injection drug users to nonusers with two dropout reasons: anti-retroviral treatment initiation and loss to follow-up.

Sex-Related Disparities In Criminal Justice and HIV Treatment Outcomes: A Retrospective Cohort Study Of HIV-Infected Inmates Meyer JP, Cepeda J, Taxman FS, Altice FL. Am J Public Health. 2015; 105(9): 1901-1910.
The authors evaluated sex-related differences in HIV and criminal justice (CJ) outcomes. They quantified sex-related differences in criminal offenses, incarcerations, and HIV outcomes among all HIV-infected inmates on antiretroviral therapy (ART) in Connecticut (2005-2012). Computed criminogenic risk scores estimated future CJ involvement. Stacked logistic regression models with random effects identified significant correlates of HIV viral suppression on CJ entry, reflecting preceding community-based treatment. Compared with 866 HIV-infected men on ART (1619 incarcerations), 223 women (461 incarcerations) were more likely to be younger, White, and medically insured, with shorter incarceration periods (mean = 196.8 vs 368.1 days), mostly for public disorder offenses. One third of both women and men had viral suppression on CJ entry, correlating positively with older age and having treated comorbidities. Entry viral suppression inversely correlated with incarceration duration for women and with criminogenic risk score for men. In the largest contemporary cohort of HIV-infected inmates on ART, women & higher prevalence of nonviolent offenses and treatable comorbidities supports alternatives to incarceration strategies. Sex-specific interventions for CJ populations with HIV effectively align public health and safety goals.

Structural Determinants Of Client Perpetrated Violence Among Female Sex Workers In Two Mexico-U.S. Border Cities Conners EE, Silverman JG, Ulibarri M, Magis-Rodriguez C, Strathdee SA, Staines-Orozco H, Patterson TL, Brouwer KC. AIDS Behav. 2015.
Female sex workers (FSWs) are disproportionately affected by both HIV and gender-based violence, such as that perpetrated by clients (CPV). The authors used a structural determinants framework to assess correlates of physical or sexual CPV in the past 6 months among FSWs in the Mexico/U.S. border cities of Ciudad Juárez and Tijuana. Bivariate and multivariate logistic regression analysis identified individual, client, interpersonal, work environment and macrostructural factors associated with recent CPV. Among 496 FSWs, 5% experienced recent CPV. Witnessing violence towards other FSWs in one & neighborhood (aOR 5.6, 95% CI 1.8-17.2), having a majority of foreign (aOR 3.5, 95% CI 1.4-8.4) or substance using (aOR 4.0, 95% CI 1.5-10.4) clients, and being a street worker (aOR 3.0, 95Â % CI 1.1-7.7) were independently associated with recent CPV. Our findings underscore the vulnerability of FSWs and the need to design policies and interventions addressing macro-level influences on CPV rather than exclusively targeting individual behaviors.

Factors Associated With Smoking Frequency Among Current Waterpipe Smokers In The United States: Findings From The National College Health Assessment II Haider MR, Salloum RG, Islam F, Ortiz KS, Kates FR, Maziak W. Drug Alcohol Depend. 2015; 153: 359-363.
Some waterpipe smokers exhibit nicotine dependent behaviors such as increased use over time and inability to quit, placing them at high risk of adverse health outcomes. This study examines the determinants of dependence by measuring frequency of use among current waterpipe smokers using a large national U.S. Data were drawn from four waves (Spring/Fall 2009 and Spring/Fall 2010) of the American College Health Association-National College Health Assessment datasets. The sample was restricted to students who smoked a waterpipe at least once in the past 30 days

(N=19,323). Ordered logistic regression modeled the factors associated with higher frequency of waterpipe smoking. Among current waterpipe smokers, 6% used a waterpipe daily or almost daily (20-29 days). Daily cigarette smokers were at higher odds of smoking a waterpipe at higher frequencies compared with non-smokers of cigarettes (OR=1.81; 95% CI=1.61-2.04). There was a strong association between daily cigar smoking and higher frequency of waterpipe smoking (OR=7.77; 95% CI=5.49-11.02). Similarly, students who used marijuana had higher odds of smoking a waterpipe at higher frequencies (OR=1.57; 95% CI=1.37-1.81). Daily consumers of other addictive substances are at a higher risk of intensive waterpipe smoking and thus higher risk of waterpipe dependence. Intervention programs must incorporate methods to reduce waterpipe dependence and subsequently prevent its deleterious health effects.

Marijuana Use and Its Association With Participation, Navigation, and Enrollment In Health Research Among African Americans Webb FJ, Striley CW, Cottler LB. J Ethn Subst Abuse. 2015; 1-15.
This analysis examined the association between marijuana (Mj) use, willingness to participate, navigation and enrollment in health research among African Americans. Data from HealthStreet, a community-engagement model implemented in North Central Florida that reduces health disparities by engaging and linking community members to medical and social services and health research opportunities, were analyzed to determine willingness of African American Mj users to participate, be navigated to and enroll in health research studies. Among 1,496 African American community members, 8.0% were current Mj users, 30.3% were past Mj users and 61.7% reported never using Mj. Current and past Mj users were more willing to volunteer for a research study that only involved the use of medical records, required an overnight stay in a hospital or clinic, or might require use of medical equipment compared to those who never used Mj. Current Mj users were significantly less likely to be navigated (95% CI: 0.21-0.58) to health research studies while past Mj users (95% CI: 1.05-2.64) were significantly more likely to be enrolled in health research studies. Navigating and enrolling Mj users into health research studies could help decrease health disparities and increase health equity for the entire community since study findings would undoubtedly be more representative of the entire community rather than a select few.

Live To Tell: Narratives Of Methamphetamine-using Women Taken Hostage By Their Intimate Partners In San Diego, CA Ludwig-Barron N, Syvertsen JL, Lagare T, Palinkas LA, Stockman JK. Int J Drug Policy. 2015; 26(9): 843-850.
Hostage-taking, an overlooked phenomenon in public health, constitutes a severe form of intimate partner violence and may be a precursor to female homicide within relationships characterized by substance use. Criminal justice studies indicate that most hostage incidents are male-driven events with more than half of all cases associated with a prior history of violence and substance use. Methamphetamine use increases a woman' risk of partner violence, with methamphetamine-using individuals being up to nine times more likely to commit homicide. As homicide is the most lethal outcome of partner violence and methamphetamine use, this study aims to characterize the potential role of hostage-taking within these intersecting epidemics. Methamphetamine-using women enrolled in an HIV behavioural intervention trial (FASTLANE-II) who reported experiences of partner violence were purposively selected to participate in qualitative sub-studies (Women Study I & II). Twenty-nine women, ages 26-57, participated in semi-structured interviews that discussed relationship dynamics, partner violence, drug use and sexual practices. Findings indicated four cases of women being held hostage by a partner, with two women describing two separate hostage experiences. Women discussed partner jealousy, drug withdrawal symptoms, heightened emotional

states from methamphetamine use, and escalating violent incidents as factors leading up to hostage-taking. Factors influencing lack of reporting incidents to law enforcement included having a criminal record, fear of partner retaliation, and intentions to terminate the relationship when the partner is incarcerated. Educating women on the warning signs of hostage-taking within the context of methamphetamine use and promoting behaviour change among male perpetrators can contribute to reducing the risk of homicide. Furthermore, bridging the gap between health services and law enforcement agencies and providing comprehensive services that address the needs of methamphetamine-using women in violent relationships can prevent or minimize potential harm to vulnerable women.

Correlates To Seroprevalent Herpes Simplex Virus Type 2 Among Rural Appalachian Drug Users Stephens DB, Young AM, Mullins UL, Havens JR. J Med Virol. 2015:
Herpes simplex virus type 2 (HSV-2) is the most common cause of genital ulcer disease and, along with substance abuse, an important HIV risk factor. Therefore, the purpose of this study was to examine HSV-2 seroprevalence in a sample of drug users in rural Appalachia. Rural Appalachian individuals age 18 or older reporting non-medical use of prescription opioids, heroin, crack/cocaine, or methamphetamine in the past 6 months (n =499) were included. Behavioral, demographic, and sexual network data were collected using interviewer-administered questionnaires. Participants' serum was tested for HSV-2 antibodies using the Biokit rapid test (Lexington, MA). The estimated population seroprevalence of HSV-2 was 14.4% (95%CI: 9.6-19.4%). Only 8.8% were aware of being HSV-2+, and unprotected sex was reported in 80% of serodiscordant sexual relationships. In a multivariate model, female gender, age, older age at first oral sex, and frequency of unprotected sex in the sexual network were independently associated with HSV-2 seropositivity. Despite lower seroprevalence than that reported in similar studies of substance abusers, targeted interventions to reduce sexual risk behavior are warranted in this underserved population. Network-informed approaches with particular focus on women, older individuals, and those engaging in frequent unprotected sex are recommended. J. Med. Virol. 2015.

Impact Of Conflict and Displacement On Risk Behaviours Amongst People Who Inject Drugs In Kabul, Afghanistan Todd CS, Nasir A, Stanekzai MR, Fiekert K, Sipsma HL, Strathdee SA, Vlahov D. Int J Drug Policy. 2015.
Theoretical work posits that drug-related risk behaviour increases during armed conflict; however, few studies have been conducted in conflict settings. The objective of this analysis is to determine whether conflict or local displacement impact risk behaviours among people who inject drugs (PWID) in Kabul, Afghanistan. Consenting PWID aged ≥18 years completed interviews at 3, 6, 9, 12, 18, and 24 months of follow-up. Quarters with peak conflict or local displacement exposure were defined and associations with injecting drug use and sexual risk behaviours analyzed with generalized estimating equations. Of 483 PWID enrolled, 385 completed ≥1 follow-up visit (483.8 person-years) between 2007 and 2009. All participants were male, with 35% initiating injecting as a refugee. Sharing syringes (Odds Ratio (OR)) =8.53, 95% Confidence Interval (CI): 2.58-28.2) and sexually transmitted infection (STI) symptoms (OR=1.72, 95% CI: 1.00-2.96) increased significantly during peak conflict quarters, while odds of STI symptoms (OR=0.06, 95% CI: 0.02-0.20) and arrest (OR=0.61, 95% CI: 0.40-0.93) were significantly lower during periods of displacement. Syringe sharing significantly increased during peak conflict periods amongst PWID in Kabul. Programming should include instruction for coping with conflict and prepare clients for harm reduction needs during conflict.

Global, Regional, and National Incidence, Prevalence, and Years Lived With Disability For 301 Acute and Chronic Diseases and Injuries In 188 Countries, 1990-2013: A Systematic Analysis For The Global Burden Of Disease Study 2013 Global Burden of Disease Study 2013 Collaborators. Lancet. 2015; 386(9995): 743-800.

Up-to-date evidence about levels and trends in disease and injury incidence, prevalence, and years lived with disability (YLDs) is an essential input into global, regional, and national health policies. In the Global Burden of Disease Study 2013 (GBD 2013), the authors estimated these quantities for acute and chronic diseases and injuries for 188 countries between 1990 and 2013.Estimates were calculated for disease and injury incidence, prevalence, and YLDs using GBD 2010 methods with some important refinements. Results for incidence of acute disorders and prevalence of chronic disorders are new additions to the analysis. Key improvements include expansion to the cause and sequelae list, updated systematic reviews, use of detailed injury codes, improvements to the Bayesian meta-regression method (DisMod-MR), and use of severity splits for various causes. An index of data representativeness, showing data availability, was calculated for each cause and impairment during three periods globally and at the country level for 2013. In total, 35 620 distinct sources of data were used and documented to calculated estimates for 301 diseases and injuries and 2337 sequelae. The comorbidity simulation provides estimates for the number of sequelae, concurrently, by individuals by country, year, age, and sex. Disability weights were updated with the addition of new population-based survey data from four countries. Disease and injury were highly prevalent; only a small fraction of individuals had no sequelae. Comorbidity rose substantially with age and in absolute terms from 1990 to 2013. Incidence of acute sequelae were predominantly infectious diseases and short-term injuries, with over 2 billion cases of upper respiratory infections and diarrhoeal disease episodes in 2013, with the notable exception of tooth pain due to permanent caries with more than 200 million incident cases in 2013. Conversely, leading chronic sequelae were largely attributable to non-communicable diseases, with prevalence estimates for asymptomatic permanent caries and tension-type headache of 2·4 billion and 1·6 billion, respectively. The distribution of the number of sequelae in populations varied widely across regions, with an expected relation between age and disease prevalence. YLDs for both sexes increased from 537·6 million in 1990 to 764·8 million in 2013 due to population growth and ageing, whereas the age-standardized rate decreased little from 114·87 per 1000 people to 110·31 per 1000 people between 1990 and 2013. Leading causes of YLDs included low back pain and major depressive disorder among the top ten causes of YLDs in every country. YLD rates per person, by major cause groups, indicated the main drivers of increases were due to musculoskeletal, mental, and substance use disorders, neurological disorders, and chronic respiratory diseases; however HIV/AIDS was a notable driver of increasing YLDs in sub-Saharan Africa. Also, the proportion of disability-adjusted life years due to YLDs increased globally from 21·1% in 1990 to 31·2% in 2013. Ageing of the world & population is leading to a substantial increase in the numbers of individuals with sequelae of diseases and injuries. Rates of YLDs are declining much more slowly than mortality rates. The non-fatal dimensions of disease and injury will require more and more attention from health systems. The transition to non-fatal outcomes as the dominant source of burden of disease is occurring rapidly outside of sub-Saharan Africa. Our results can guide future health initiatives through examination of epidemiological trends and a better understanding of variation across countries. Bill & Melinda Gates Foundation.

Love, Trust, and HIV Risk Among Female Sex Workers and Their Intimate Male Partners Syvertsen JL, Bazzi AR, Martinez G, Rangel MG, Ulibarri MD, Fergus KB, Amaro H, Strathdee SA. Am J Public Health. 2015; 105(8): 1667-1674.
The authors examined correlates of love and trust among female sex workers and their noncommercial male partners along the Mexico-US border. From 2011 to 2012, 322 partners in Tijuana and Ciudad, Juárez Mexico, completed assessments of love and trust. Cross-sectional dyadic regression analyses identified associations of relationship characteristics and HIV risk behaviors with love and trust. Within 161 couples, love and trust scores were moderately high (median 70/95 and 29/40 points, respectively) and correlated with relationship satisfaction. In regression analyses of HIV risk factors, men and women who used methamphetamine reported lower love scores, whereas women who used heroin reported slightly higher love. In an alternate model, men with concurrent sexual partners had lower love scores. For both partners, relationship conflict was associated with lower trust. Love and trust are associated with relationship quality, sexual risk, and drug use patterns that shape intimate partners & HIV risk. HIV interventions should consider the emotional quality of sex workers & intimate relationships.

Recent HIV Testing Prevalence, Determinants, and Disparities Among U.S. Older Adult Respondents To The Behavioral Risk Factor Surveillance System Ford CL, Godette DC, Mulatu MS, Gaines TL. Sex Transm Dis. 2015; 42(8): 405-410.
Although routine human immune deficiency virus (HIV) testing during health care visits is recommended for most adults, many older adults (i.e., ages 50-64 years) do not receive it. This study identified factors associated with HIV testing in the past 12 months (i.e., recent HIV testing) among US adults in the 3 categories of older adulthood (50-54, 55-59, and 60-64 years) for which routine HIV testing is recommended. This was a cross-sectional analysis of data from US older adult respondents to the 2010 Behavioral Risk Factor Surveillance System. The authors calculated prevalence (proportions) of HIV testing by age category and race/ethnicity. Using multiple logistic regression, they identified predisposing, enabling, and need factors associated with recent HIV testing within and across age categories, by race/ethnicity and controlling for covariates. HIV testing prevalence was low (<5%), varied by race/ethnicity, and decreased with age. Within and across age categories, the odds of testing were highest among blacks (odds ratio [OR], 3.47; 95% confidence interval [CI], 2.82-4.25) and higher among Latinos (OR, 2.06; 95% CI, 1.50-2.84) and the oldest and youngest categories of American Indians/Alaska Natives (OR, 2.48; 95% CI, 1.11-5.55; OR, 2.98; 95% CI, 1.49-5.95) than among whites. Those reporting a recent doctor visit (OR, 2.32; 95% CI, 1.92-2.74) or HIV risk behaviors (OR, 3.50; 95% CI, 2.67-4.59) had higher odds of HIV testing. Regardless of risk, the oldest older adults, whites, and older women may forego HIV testing. Doctor visits may facilitate HIV testing. Additional research is needed to understand why eligible older adults seen by providers may not be screened for HIV infection.

Socio-structural and Behavioral Risk Factors Associated With Trafficked History Of Female Bar/spa Entertainers In The Sex Trade In The Philippines Urada LA, Halterman S, Raj A, Tsuyuki K, Pimentel-Simbulan N, Silverman JG. Int J Gynaecol Obstet. 2015.
The aim of this study was to explore factors associated with trafficking (deceptive/coercive entry to sex trade) among female bar/spa entertainers who traded sex in the Philippines. Female bar/spa entertainers who traded sex in the past 6months were recruited from 25bar/spa venues in Metro Manila (April 2009-January 2010) and assessed via cross-sectional survey data collection for HIV-risk-related socio-structural factors associated with deceptive/coercive entry into the sex trade. The study employed hierarchical linear modeling. Of 166bar/spa entertainers assessed, 19 (11.4%)

reported being deceived/coerced (i.e. trafficked) into their first jobs. Trafficking history was independently associated with current drug use (adjusted odds ratio [AOR] 2.05; 95% confidence interval [CI] 1.00-3.97) decreased availability of condoms at venues for entertainers (AOR 0.18; 95% CI 0.05-0.71) and, conversely, increased peer support for practicing safer sex behaviors (AOR 3.08; 95% CI 1.63-5.09). Those deceived/coerced into their positions were more likely than non-trafficked women to have been recruited by an agency who came to their rural province (AOR 12.07; 95% CI 1.77-82.25) as opposed to getting the job from advertisement (AOR 0.10; 95% CI 0.02-0.65) or a friend/acquaintance (AOR 0.02; 95% CI 0.00-0.48).The findings have implications for designing interventions to prevent and target trafficked women in the Philippines who may be more vulnerable to substance use and, potentially, HIV infection.

Tobacco Research In The Military: Reflections On 20 Years Of Research In The United States Air Force Talcott GW, Ebbert JO, Klesges RC, Linde BD, Seals RW, Krukowski RA, Grieser EA, Oh JY, Martin-Zona DM. Mil Med. 2015; 180(8): 848-850.
The U.S. military is one of the world's largest employers. Approximately 30% of active duty military personnel smoke cigarettes and more than 14% use smokeless tobacco. The military has historically supported tobacco use and more recently is attempting to combat its use. Through 20 years of collaborative research with the United States Air Force, we have learned that smoking bans are effective, recruits who have never previously smoked cigarettes initiate tobacco use, smokeless tobacco serves as a gateway for smoking initiation, smoking is associated with discharge, smoking adds significant proximal training costs, tobacco use increases during deployment, and tobacco quitline counseling with a provision of medication is effective. These findings may provide groundwork for future tobacco control efforts in the U.S. military.

Cost-effectiveness Of Improvements In Diagnosis and Treatment Accessibility For Tuberculosis Control In India Suen S-C, Bendavid E, Goldhaber-Fiebert JD. Int J Tuberc Lung Dis. 2015; 19(9): 1115-24, i-xv.
Inaccurate diagnosis and inaccessibility of care undercut the effectiveness of high-quality anti-tuberculosis treatment and select for resistance. Rapid diagnostic systems, such as Xpert(®) MTB/RIF for tuberculosis (TB) diagnosis and drug susceptibility testing (DST), and programs that provide high-quality DOTS anti-tuberculosis treatment to patients in the unregulated private sector (public-private mix [PPM]), may help address these challenges, albeit at increased cost. The authors extended a microsimulation model of TB in India calibrated to demographic, epidemiologic, and care trends to evaluate 1) replacing DST with Xpert; 2) replacing microscopy and culture with Xpert to diagnose multidrug-resistant TB (MDR-TB) and non-MDR-TB; 3) implementing nationwide PPM; and combinations of (3) with (1) or (2).PPM (assuming costs of $38/person) and Xpert improved health and increase costs relative to the status quo. PPM alone or with Xpert cost <1 gross domestic product/capita per quality-adjusted life-year gained relative to the next best intervention, and dominated Xpert interventions excluding PPM. While both PPM and Xpert are promising tools for combatting TB in India, PPM should be prioritized over Xpert, as private sector engagement is more cost-effective than Xpert alone and, if sufficient resources are available, would substantially increase the value of Xpert if both interventions are implemented together.

Feasibility Of Tuberculosis Treatment Monitoring By Video Directly Observed Therapy: A Binational Pilot Study Garfein RS, Collins K, Muoz, F, Moser K, Cerecer-Callu P, Raab F, Rios P, Flick A, Ziga ML, Cuevas-Mota J, Liang K, Rangel G, Burgos JL, Rodwell TC, Patrick K. Int J Tuberc Lung Dis. 2015; 19(9): 1057-1064.

Although directly observed therapy (DOT) is recommended worldwide for monitoring anti-tuberculosis treatment, transportation and personnel requirements limit its use. The aim of this study was to evaluate the feasibility and acceptability of video DOT (VDOT), which allows patients to record and transmit medication ingestion via videos watched remotely by health care providers to document adherence. The authors conducted a single-arm trial among tuberculosis (TB) patients in San Diego, California, USA, (n = 43) and Tijuana, Mexico (n = 9) to represent high- and low-resource settings. Pre-/post-treatment interviews assessed participant characteristics and experiences. Adherence was defined as the proportion of observed doses to expected doses. The mean age was 37 years (range 18-86), 50% were male, and 88% were non-Caucasian. The mean duration of VDOT use was 5.5 months (range 1-11). Adherence was similar in San Diego (93%) and Tijuana (96%). Compared to time on in-person DOT, 92% preferred VDOT, 81% thought VDOT was more confidential, 89% never/rarely had problems recording videos, and 100% would recommend VDOT to others. Seven (13%) participants were returned to in-person DOT and six (12%) additional participants had their phones lost, broken or stolen. VDOT was feasible and acceptable, with high adherence in both high- and low-resource settings. Efficacy and cost-effectiveness studies are needed.

Creating Impact With Operations Research In Health: Making Room For Practice In Academia Brandeau ML. Health Care Manag Sci. 2015.
Operations research (OR)-based analyses have the potential to improve decision making for many important, real-world health care problems. However, junior scholars often avoid working on practical applications in health because promotion and tenure processes tend to value theoretical studies more highly than applied studies. This paper discusses the author experiences in using OR to inform and influence decisions in health and provides a blueprint for junior researchers who wish to find success by taking a similar path. This involves selecting good problems to study, forming productive collaborations with domain experts, developing appropriate models, identifying the most salient results from an analysis, and effectively disseminating findings to decision makers. The paper then suggests how journals, funding agencies, and senior academics can encourage such work by taking a broader and more informed view of the potential role and contributions of OR to solving health care problems. Making room in academia for the application of OR in health follows in the tradition begun by the founders of operations research: to work on important real-world problems where operations research can contribute to better decision making.

Transition To Injecting Drug Use In Iran: A Systematic Review Of Qualitative and Quantitative Evidence Rahimi-Movaghar A, Amin-Esmaeili M, Shadloo B, Noroozi A, Malekinejad M. Int J Drug Policy. 2015; 26(9): 808-819.
Injection drug use, a behavior associated with significant adverse health effects, has been increasing over the past decade in Iran. This study aims to systematically review the epidemiological and qualitative evidence on factors that facilitate or protect the transition to injection drug use in Iran. The authors conducted electronic searches in five international (Medline, Web of Science, EMBASE, CINAHL, PsycINFO), one regional (IMEMR) and three Iranian (Iranmedex, Iranpsych, IranDoc) databases, as well as contacting experts in the field. Two trained researchers screened documents to identify relevant studies and independently dual-extracted data following pre-specified protocol. The authors applied principles of thematic analysis for qualitative data and applied a random effect meta-analysis model for age of first injection. A total of 38 documents from 31 studies met eligibility criteria, from which more than 50% were implemented from 2006 to 2008. The weighted mean age of first injection was 25.8 (95% Confidence Interval: 25.3-26.2). Between

1998 and 2011, the age of first injection was relatively stable. Overall, drug users had used drugs for 6-7 years before they started injection use. Heroin was the first drug of injection in the majority of the cases. The authors identified factors influencing the initiation of or transition to injection use at various levels, including: (1) individual (pleasure-seeking behavior, curiosity and development of drug dependency commonly reported), (2) social and environmental (role of peer drug users in the first injection use, the economic efficiency associated with injections and the wide availability of injectable form of drugs in the market).Harm reduction policies in Iran have almost exclusively focused on drug injectors in Iran. However, given the extent of the non-injection drug use epidemic, evidence from this study can provide insight on points of interventions for the prevention of the transition to injection use.

Underascertainment Of Acute Hepatitis C Virus Infections In The U.S. Surveillance System: A Case Series and Chart Review Onofrey S, Aneja J, Haney GA, Nagami EH, DeMaria Jr, A, Lauer GM;,Hills-Evans K, Barton K, Kulaga S, Bowen MJ, Cocoros N, McGovern BH, Church DR, Kim AY. Ann Intern Med. 2015; 163(4): 254-261.
In 2010, the incidence of hepatitis C virus (HCV) infection in the United States was estimated to be 17,000 cases annually, based on 850 acute HCV cases reported to the Centers for Disease Control and Prevention by local public health authorities. Absence of symptomatic disease and lack of a specific laboratory test for acute infection complicates diagnosis and surveillance. To validate estimates of the incidence of acute HCV infection by determining the reporting rate of clinical diagnoses of acute infection to the Massachusetts Department of Public Health (MDPH) and Centers for Disease Control and Prevention. Case series and chart review. Two hospitals and the state correctional health care system in Massachusetts.183 patients clinically diagnosed with acute HCV infection from 2001 to 2011 and participating in a research study. Rate of electronic case reporting of acute HCV infection to the MDPH and rate of subsequent confirmation according to national case definitions.149 of 183 (81.4%) clinical cases of acute HCV infection were reported to the MDPH for surveillance classification. The MDPH investigated 43 of these reports as potential acute cases of HCV infection based on their surveillance requirements; ultimately, only 1 met the national case definition and was counted in nationwide statistics published by the Centers for Disease Control and Prevention. Discordance in clinical and surveillance classification was often related to missing clinical or laboratory data at the MDPH as well as restrictive definitions, including requirements for negative hepatitis A and B laboratory results. Findings may not apply to other jurisdictions because of differences in resources for surveillance. Clinical diagnoses of acute HCV infection were grossly underascertained by formal surveillance reporting. Incomplete clinician reporting, problematic case definitions, limitations of diagnostic testing, and imperfect data capture remain major limitations to accurate case ascertainment despite automated electronic laboratory reporting. These findings may have implications for national estimates of the incidence of HCV infection.

Social and Structural Challenges To Drug Cessation Among Couples In Northern Mexico: Implications For Drug Treatment In Underserved Communities Bazzi AR, Syvertsen JL, Roln ML, Martinez G, Rangel G, Vera A, Amaro H, Ulibarri MD, Hernandez DO. Strathdee SA. J Subst Abuse Treat. 2015.
Available drug treatment modalities may inadequately address social and structural contexts surrounding recovery efforts. This mixed methods analysis drew on (1) surveys with female sex workers and their intimate male partners and (2) semi-structured interviews with a subsample of 41 couples (n=82 individuals, 123 total interviews) in Northern Mexico. Descriptive and content

analyses examined drug cessation and treatment experiences. Perceived need for drug treatment was high, yet only 35% had ever accessed services. Financial and institutional barriers (childcare needs, sex-segregated facilities) prevented partners from enrolling in residential programs together or simultaneously, leading to self-treatment attempts. Outpatient methadone was experienced more positively, yet financial constraints limited access and treatment duration. Relapse was common, particularly when one partner enrolled alone while the other continued using drugs. Affordable, accessible, evidence-based drug treatment and recovery services that acknowledge social and structural contexts surrounding recovery are urgently needed for drug-involved couples.

Acute Hepatitis C Virus Infection Induces Consistent Changes In Circulating MicroRNAs That Are Associated With Nonlytic Hepatocyte Release El-Diwany R, Wasilewski LN, Witwer KW, Bailey JR, Page K, Ray SC, Cox AL, Thomas DL, Balagopal A. J Virol. 2015; 89(18): 9454-9464.

Plasma microRNAs (miRNAs) change in abundance in response to disease and have been associated with liver fibrosis severity in chronic hepatitis C virus (HCV) infection. However, the early dynamics of miRNA release during acute HCV infection are poorly understood. In addition, circulating miRNA signatures have been difficult to reproduce among separate populations. The authors studied plasma miRNA abundance during acute HCV infection to identify an miRNA signature of early infection. They measured 754 plasma miRNAs by quantitative PCR array in a discovery cohort of 22 individuals before and during acute HCV infection and after spontaneous resolution (n = 11) or persistence (n = 11) to identify a plasma miRNA signature. The discovery cohort derived from the Baltimore Before and After Acute Study of Hepatitis. During acute HCV infection, increases in miR-122 ($P < 0.01$) and miR-885-5p ($P_{corrected} < 0.05$) and a decrease in miR-494 ($P_{corrected} < 0.05$) were observed at the earliest time points after virus detection. Changes in miR-122 and miR-885-5p were sustained in persistent ($P < 0.001$) but not resolved HCV infection. The circulating miRNA signature of acute HCV infection was confirmed in a separate validation cohort that was derived from the San Francisco-based You Find Out (UFO) Study (n = 28). As further confirmation, cellular changes of signature miRNAs were examined in a tissue culture model of HCV in hepatoma cells: HCV infection induced extracellular release of miR-122 and miR-885-5p despite unperturbed intracellular levels. In contrast, miR-494 accumulated intracellularly ($P < 0.05$). Collectively, these data are inconsistent with necrolytic release of hepatocyte miRNAs into the plasma during acute HCV infection of humans. MicroRNAs are small noncoding RNA molecules that emerging research shows can transmit regulatory signals between cells in health and disease. HCV infects 2% of humans worldwide, and chronic HCV infection is a major cause of severe liver disease. The authors profiled plasma miRNAs in injection drug users before, during, and (in the people with resolution) after HCV infection. They discovered miRNA signatures of acute and persistent viremia and confirmed these findings two ways: (i) in a separate cohort of people with newly acquired HCV infection and (ii) in an HCV cell culture system. These results demonstrate that acute HCV infection induces early changes in the abundance of specific plasma miRNAs that may affect the host response to HCV infection.

PREVENTION RESEARCH

Diffusion of Intervention Effects: The Impact Of A Family-Based Substance Use Prevention Program On Friends of Participants Rulison KL, Feinberg M, Gest SD, Osgood DW. Journal of Adolescent Health 2015.
The authors tested whether effects of the Strengthening Families Program for Youth 10e14 (SFP10-14) diffused from intervention participants to their friends. They also tested which program effects on participants accounted for diffusion. Data are from 5,449 students (51% female; mean initial age ¼ 12.3 years) in the PROmoting School-community-university Partnerships to Enhance Resilience community intervention trial (2001e2006) who did not participate in SFP10-14 (i.e., nonparticipants). At each of five waves, students identified up to seven friends and self-reported past month drunkenness and cigarette use, substance use attitudes, parenting practices, and unsupervised time spent with friends. The authors computed two measures of indirect exposure to SFP10-14: total number of SFP-attending friends at each wave and cumulative proportion of SFP-attending friends averaged across the current and all previous post-intervention waves. Three years post-intervention, the odds of getting drunk (odds ratio ¼ 1.4) and using cigarettes (odds ratio ¼ 2.7) were higher among nonparticipants with zero SFP-attending friends compared with nonparticipants with three or more SFP-attending friends. Multilevel analyses also provided evidence of diffusion: nonparticipants with a higher cumulative proportion of SFP attending friends at a given wave were less likely than their peers to use drugs at that wave. Effects from SFP10-14 primarily diffused through friendship networks by reducing the amount of unstructured socializing (unsupervised time that nonparticipants spent with friends), changing friends' substance use attitudes, and then changing nonparticipants' own substance use attitudes. Program developers should consider and test how interventions may facilitate diffusion to extend program reach and promote program sustainability.

Within-person Coupling Of Changes In Cortisol, Testosterone, and DHEA Across The Day In Adolescents Marceau K, Ruttle PL, Shirtcliff EA, Hastings PD, Klimes-Dougan B, Zahn-Waxler C. Dev Psychobiol. 2015; 57(6): 654-669.
The authora comprehensively examined within-person and between-person associations between cortisol and DHEA and cortisol and testosterone across the day. Data are from a sample of 213 adolescents aged 11-16 (M=13.7, SD=1.5 years) from the Northeastern US who were oversampled for psychopathology symptoms. Six repeated measures of hormone levels across 3 days were used to test three specific questions of cortisol-DHEA and cortisol-testosterone associations within individuals (coupling) across the day, and one question of cortisol-DHEA and cortisol-testosterone diurnal slopes were associated between adolescents. Results consistently revealed positive cortisol-DHEA and cortisol-testosterone coupling across the day, often more pronounced in girls relative to boys. Cortisol and DHEA slopes were positively associated, whereas cortisol and testosterone were negatively associated between-adolescents. Findings suggest multiple mechanisms and highlight the multifaceted nature of associations of hormone changes during adolescence and importance of considering both axes for between- and within-person aspects of neuroendocrine development. Dev Psychobiol 57: 654-669, 2015.

Blending Qualitative and Computational Linguistics Methods For Fidelity Assessment: Experience With The Familias Unidas Preventive Intervention Gallo C, Pantin H, Villamar J, Prado G, Tapia M, Ogihara M, Cruden G, Brown CH. Adm Policy Ment Health. 2015; 42(5): 574-585.
Careful fidelity monitoring and feedback are critical to implementing effective interventions. A wide range of procedures exist to assess fidelity; most are derived from observational assessments (Schoenwald and Garland, Psycholog Assess 25:146-156, 2013). However, these fidelity measures are resource intensive for research teams in efficacy/effectiveness trials, and are often unattainable or unmanageable for the host organization to rate when the program is implemented on a large scale. The authors present a first step towards automated processing of linguistic patterns in fidelity monitoring of a behavioral intervention using an innovative mixed methods approach to fidelity assessment that uses rule-based, computational linguistics to overcome major resource burdens. Data come from an effectiveness trial of the Familias Unidas intervention, an evidence-based, family-centered preventive intervention found to be efficacious in reducing conduct problems, substance use and HIV sexual risk behaviors among Hispanic youth. This computational approach focuses on "joining," which measures the quality of the working alliance of the facilitator with the family. Quantitative assessments of reliability are provided. Kappa scores between a human rater and a machine rater for the new method for measuring joining reached 0.83. Early findings suggest that this approach can reduce the high cost of fidelity measurement and the time delay between fidelity assessment and feedback to facilitators; it also has the potential for improving the quality of intervention fidelity ratings.

Monitoring Of Non-cigarette Tobacco Use Using Google Trends Cavazos-Rehg PA, Krauss MJ, Spitznagel EL, Lowery A, Grucza RA, Chaloupka FJ, Bierut LJ. Tob Control. 2015;24(3): 249-255.
Google Trends is an innovative monitoring system with unique potential to monitor and predict important phenomena that may be occurring at a population level. The authors sought to validate whether Google Trends can additionally detect regional trends in youth and adult tobacco use. They compared 2011 Google Trends relative search volume data for cigars, cigarillos, little cigars and smokeless tobacco with state prevalence of youth (grades 9-12) and adult (age 18 and older) use of these products using data from the 2011 United States state-level Youth Risk Behaviors Surveillance System and the 2010-2011 United States National Survey on Drug Use and Health (NSDUH), respectively. The authors used the Pearson correlation coefficient to measure the associations. They found significant positive correlations between state Google Trends cigar relative search volume and prevalence of cigar use among youth (r=0.39, R(2).154, p=0.018) and adults (r=0.49, R(2)0.243, p<0.001). Similarly, they found that the correlations between state Google Trends smokeless tobacco relative search volume and prevalence of smokeless tobacco use among youth and adults were both positive and significant (r=0.46, R(2)=0.209, p=0.003 and r=0.48, R(2)=0.226, p0.001, respectively). The results of this study validate that Google Trends has the potential to be a valuable monitoring tool for tobacco use. The near real-time monitoring features of Google Trends may complement traditional surveillance methods and lead to faster and more convenient monitoring of emerging trends in tobacco use.

When The Test Of Mediation Is More Powerful Than The Test Of The Total Effect O'Rourke HP, MacKinnon DP. Behav Res Methods. 2015; 47(2): 424-442.
Although previous research has studied power in mediation models, the extent to which the inclusion of a mediator will increase power has not been investigated. To address this deficit, in a first study the authors compared the analytical power values of the mediated effect and the total

effect in a single-mediator model, to identify the situations in which the inclusion of one mediator increased statistical power. The results from this first study indicated that including a mediator increased statistical power in small samples with large coefficients and in large samples with small coefficients, and when coefficients were nonzero and equal across models. Next, the authors identified conditions under which power was greater for the test of the total mediated effect than for the test of the total effect in the parallel two-mediator model. These results indicated that including two mediators increased power in small samples with large coefficients and in large samples with small coefficients, the same pattern of results that had been found in the first study. Finally, the authors assessed the analytical power for a sequential (three-path) two-mediator model and compared the power to detect the three-path mediated effect to the power to detect both the test of the total effect and the test of the mediated effect for the single-mediator model. The results indicated that the three-path mediated effect had more power than the mediated effect from the single-mediator model and the test of the total effect. Practical implications of these results for researchers are then discussed.

Experiencing Aggression In Clubs: Social Group and Individual Level Predictors Miller BA, Bourdeau B, Johnson M, Voas R. Prev Sci. 2015; 16(4): 527-537.
To examine the social drinking group influence on the individual experiences of physical or sexual aggression at clubs, data were collected from 368 groups (N=986 individuals). Both group and individual level indicators were examined for impact on self-reports of physical and sexual aggression experiences while at the club. Recent aggressive experiences and perpetration, concerns for group safety, one own plans and assessment of other group member's plans to drink to the point of intoxication, and personal characteristics were examined, using both individual and group indicators. At exit, participants reported experiencing physical aggression (12.3 %) and sexual aggression (12.6 %) at the club. Using generalized linear mixed modeling to account for nested data (club, event, and group), group level indicators predicted both the individual' physical and sexual aggression experiences. Especially for experiences of physical aggression, group effects are notable. Being in a group whose members' recently experienced physical aggression increased the risk for the individual. Interestingly, groups that had higher levels of planned intoxication decreased risks of experiencing aggression, while a discrepancy in these intentions among group members increased the risks. Group effects were also noted for experiencing sexual aggression. High levels of prior experiences for sexual aggression in the group increased the risks for the individual during the event. Also, being in a group that is identified as having at least one member who is frequently drunk increases the risk for experiencing sexual aggression. These findings inform prevention strategies for young adults engaged in high-risk behaviors by targeting social drinking groups who frequent clubs.

Local Support For Alcohol Control Policies and Perceptions Of Neighborhood Issues In Two College Communities Fairlie AM, DeJong W, Wood MD. Subst Abus. 2015; 36(3): 289-296.
Although valuable, national opinion surveys on alcohol policy may be less informative for policy development at the local level. Using samples of adult residents in 2 college communities, the present study: (1) measured public support for local alcohol control policies to stem underage drinking and alcohol overservice in on-premise outlets, (2) assessed residents' opinions regarding neighborhood problems, and (3) identified factors associated with strong policy support. The authors administered random-sample telephone surveys to residents aged 21 years and older in college communities located in Community 1 (N = 501; mean age = 57.4 years, SD = 14.7) and Community 2 (N = 505; mean age = 56.0 years, SD = 15.2). The response rates were typical of

telephone surveys (Community 1: 33.5%; Community 2: 29.9%). The authors assessed support for 16 alcohol control policies and the occurrence of specific types of neighborhood incidents (e.g., witnessing intoxicated people). They used multiple regression analyses to determine factors associated with policy support. Residents in Community 1 reported significantly higher weekly alcohol use, a greater number of witnessed neighborhood incidents, and a higher level of perceived neighborhood problems than did residents in Community 2. Residents in Community 1 perceived local alcohol control policies and their enforcement to be significantly stricter. Overall, policy support was high and did not differ between the communities. In both communities, higher policy support was significantly associated with being female, being older, less weekly alcohol use, and lower perceived strictness of alcohol control policies and enforcement. It is important for campus officials and community leaders to be aware of and publicize favorable public opinion when advocating for policy change, especially at the local level. Information on residents' perceptions of the neighborhood issues they face can also inform local policy and enforcement efforts.

Maladaptive Social Information Processing In Childhood Predicts Young Men's Atypical Amygdala Reactivity To Threat Choe DE, Shaw DS, Forbes EE. J Child Psychol Psychiatry. 2015; 56(5): 549-557.
Maladaptive social information processing, such as hostile attributional bias and aggressive response generation, is associated with childhood maladjustment. Although social information processing problems are correlated with heightened physiological responses to social threat, few studies have examined their associations with neural threat circuitry, specifically amygdala activation to social threat. A cohort of 310 boys participated in an ongoing longitudinal study and completed questionnaires and laboratory tasks assessing their social and cognitive characteristics the boys were between 10 and 12 years of age. At age 20, 178 of these young men underwent functional magnetic resonance imaging and a social threat task. At age 22, adult criminal arrest records and self-reports of impulsiveness were obtained. Path models indicated that maladaptive social information-processing at ages 10 and 11 predicted increased left amygdala reactivity to fear faces, an ambiguous threat, at age 20 while accounting for childhood antisocial behavior, empathy, IQ, and socioeconomic status. Exploratory analyses indicated that aggressive response generation - the tendency to respond to threat with reactive aggression - predicted left amygdala reactivity to fear faces and was concurrently associated with empathy, antisocial behavior, and hostile attributional bias, whereas hostile attributional bias correlated with IQ. Although unrelated to social information-processing problems, bilateral amygdala reactivity to anger faces at age 20 was unexpectedly predicted by low IQ at age 11. Amygdala activation did not mediate associations between social information processing and number of criminal arrests, but both impulsiveness at age 22 and arrests were correlated with right amygdala reactivity to anger facial expressions at age 20. Childhood social information processing and IQ predicted young men's amygdala response to threat a decade later, which suggests that childhood social-cognitive characteristics are associated with the development of neural threat processing and adult adjustment.

Describing and Predicting Developmental Profiles Of Externalizing Problems From Childhood To Adulthood Petersen IT, Bates JE, Dodge KA, Lansford JE, Pettit GS. Dev Psychopathol. 2015; 27(3): 791-818.
This longitudinal study considers externalizing behavior problems from ages 5 to 27 (N = 585). Externalizing problem ratings by mothers, fathers, teachers, peers, and self-report were modeled with growth curves. Risk and protective factors across many different domains and time frames were included as predictors of the trajectories. A major contribution of the study is in demonstrating

how heterotypic continuity and changing measures can be handled in modeling changes in externalizing behavior over long developmental periods. On average, externalizing problems decreased from early childhood to preadolescence, increased during adolescence, and decreased from late adolescence to adulthood. There was strong nonlinear continuity in externalizing problems over time. Family process, peer process, stress, and individual characteristics predicted externalizing problems beyond the strong continuity of externalizing problems. The model accounted for 70% of the variability in the development of externalizing problems. The model predicted values showed moderate sensitivity and specificity in prediction of arrests, illegal drug use, and drunk driving. Overall, the study showed that by using changing, developmentally relevant measures and simultaneously taking into account numerous characteristics of children and their living situations, research can model lengthy spans of development and improve predictions of the development of later, severe externalizing problems.

Improving Our Ability To Evaluate Underlying Mechanisms Of Behavioral Onset And Other Event Occurrence Outcomes: A Discrete-Time Survival Mediation Model Fairchild AJ, Abara WE, Gottschall AC, Tein J-Y, Prinz RJ. Eval Health Prof. 2015; 38(3): 315-342.
The purpose of this article is to introduce and describe a statistical model that researchers can use to evaluate underlying mechanisms of behavioral onset and other event occurrence outcomes. Specifically, the article develops a framework for estimating mediation effects with outcomes measured in discrete-time epochs by integrating the statistical mediation model with discrete-time survival analysis. The methodology has the potential to help strengthen health research by targeting prevention and intervention work more effectively as well as by improving our understanding of discretized periods of risk. The model is applied to an existing longitudinal data set to demonstrate its use, and programming code is provided to facilitate its implementation.

Increasing Statistical Power In Mediation Models Without Increasing Sample Size Fritz MS, Cox MG, MacKinnon DP. Eval Health Prof. 2015; 38(3): 343-366.
Inadequate statistical power to detect treatment effects in health research is a problem that is compounded when testing for mediation. In general, the preferred strategy for increasing power is to increase the sample size, but there are many situations where additional participants cannot be recruited, necessitating the use of other methods to increase statistical power. Many of these other strategies, commonly applied to analysis of variance and multiple regression models, can be applied to mediation models with similar results. Additional predictors or blocking variables will increase or decrease statistical power, however, depending on whether these variables are related to the mediator, the outcome, or both. The effect of these two methods on the power for tests of mediation is illustrated through the use of simulations. Implications for health researchers using these methods are discussed.

Implications Of Ongoing Neural Development For The Measurement Of The Error-related Negativity In Childhood DuPuis D, Ram N, Willner CJ, Karalunas S, Segalowitz SJ, Gatzke-Kopp LM. Dev Sci. 2015; 18(3): 452-468.
Event-related potentials (ERPs) have been proposed as biomarkers capable of reflecting individual differences in neural processing not necessarily detectable at the behavioral level. However, the role of ERPs in developmental research could be hampered by current methodological approaches to quantification. ERPs are extracted as an average waveform over many trials; however, actual amplitudes would be misrepresented by an average if there was high trial-to-trial variability in signal latency. Low signal temporal consistency is thought to be a characteristic of immature neural

systems, although consistency is not routinely measured in ERP research. The present study examined the differential contributions of signal strength and temporal consistency across trials in the error-related negativity (ERN) in 6-year-old children, as well as the developmental changes that occur in these measures. The 234 children were assessed annually in kindergarten, 1st, and 2nd grade. At all assessments signal strength and temporal consistency were highly correlated with the average ERN amplitude, and were not correlated with each other. Consistent with previous findings, ERN deflections in the averaged waveform increased with age. This was found to be a function of developmental increases in signal temporal consistency, whereas signal strength showed a significant decline across this time period. In addition, average ERN amplitudes showed low-to-moderate stability across the three assessments whereas signal strength was highly stable. In contrast, signal temporal consistency did not evidence rank-order stability across these ages. Signal strength appears to reflect a stable individual trait whereas developmental changes in temporal consistency may be experientially influenced.

Negative Relational Schemas Predict the Trajectory Of Coercive Dynamics During Early Childhood Smith JD, Dishion TJ, Shaw DS, Wilson MN. J Abnorm Child Psychol. 2015; 43(4): 693-703.
Coercive family processes are germane to the development of problem behaviors in early childhood, yet the cognitive and affective underpinnings are not well understood. The authors hypothesized that one antecedent of early coercive interactions is the caregiver's implicit affective attitudes toward the child, which in this article are termed relational schemas. Relational schemas have previously been linked to coercion and problem behaviors, but there has yet to be an examination of the association between relational schemas and trajectories of coercion during early childhood. The authors examined 731 indigent caregiver-child dyads (49% female children) from a randomized intervention trial of the Family Check-Up. Predominantly biological mothers participated. A speech sample was used to assess relational schemas at age 2. Coercive interactions were assessed observationally each year between ages 2 and 4. Caregiver and teacher reports of children's oppositional and aggressive behaviors were collected at age 7.5 and 8.5. Path analysis revealed that negative relational schemas were associated with less steep declines in coercion during this period, which in turn were predictive of ratings of oppositional and aggressive behaviors at age 7.5/8.5 after controlling for baseline levels, positive relational schemas, child gender, ethnicity, and cumulative risk. Intervention condition assignment did not moderate this relationship, suggesting the results represent a naturally occurring process. Given the link between persistent early coercion and later deleterious outcomes, relational schemas that maintain and amplify coercive dynamics represent a potential target for early intervention programs designed to improve parent-child relationships.

Sexual Esteem In Emerging Adulthood: Associations With Sexual Behavior, Contraception Use, And Romantic Relationships Maas MK, Lefkowitz ES. J Sex Res. 2015; 52(7): 795-806.
Sexual esteem is an integral psychological aspect of sexual health (Snell & Papini, 1989), yet it is unclear whether sexual esteem is associated with sexual health behavior among heterosexual men and women. The current analysis used a normative framework for sexual development (Lefkowitz & Gillen, 2006; Tolman & McClelland, 2011) by examining the association of sexual esteem with sexual behavior, contraception use, and romantic relationship characteristics. Participants (N = 518; 56.0% female; mean age = 20.43 years; 26.8% identified as Hispanic/Latino; among non-Hispanic/Latinos, 27.2% of the full sample identified as European American, 22.4% Asian American, 14.9% African American, and 8.7% multiracial) completed Web-based surveys at a large

Northeastern university. Participants who had oral sex more frequently, recently had more oral and penetrative sex partners (particularly for male participants), and spent more college semesters in romantic relationships tended to have higher sexual esteem than those who had sex less frequently, with fewer partners, or spent more semesters without romantic partners. Sexually active male emerging adults who never used contraception during recent penetrative sex tended to have higher sexual esteem than those who did use it, whereas female emerging adults who never used contraception tended to have lower sexual esteem than those who did use it. Implications of these results for the development of a healthy sexual self-concept in emerging adulthood are discussed.

Combined Influences Of Genes, Prenatal Environment, Cortisol, and Parenting On The Development Of Children's Internalizing Versus Externalizing Problems Marceau K, Laurent HK, Neiderhiser JM, Reiss D, Shaw DS, Natsuaki MN, Fisher PA, Leve LD. Behav Genet. 2015; 45(3): 268-282.
Research suggests that genetic, prenatal, endocrine, and parenting influences across development individually contribute to internalizing and externalizing problems in children. The present study tests the combined contributions of genetic risk for psychopathology, prenatal environments (maternal drug use and internalizing symptoms), child cortisol at age 4.5 years, and overreactive parenting influences across childhood on 6-year-old children internalizing and externalizing problems. The authors used data from an adoption design that included 361 domestically adopted children and their biological and adopted parents prospectively followed from birth. Only parenting influences contributed (independently) to externalizing problems. However, genetic influences were indirectly associated with internalizing problems (through increased prenatal risk and subsequent morning cortisol), and parenting factors were both directly and indirectly associated with internalizing problems (through morning cortisol). Results suggest that prenatal maternal drug use/symptoms and children morning cortisol levels are mechanisms of genetic and environmental influences on internalizing problems, but not externalizing problems, in childhood.

Suicidal Behavior Outcomes Of Childhood Sexual Abuse: Longitudinal Study Of Adjudicated Girls Rabinovitch SM, Kerr DCR, Leve LD, Chamberlain P. Suicide Life Threat Behav. 2015; 45(4): 431-447.
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 (7-12Â years later). Early forced CSA was related to lifetime suicide attempt and NSSI history and (marginally) to postbaseline 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.

Feasibility, Acceptability, and Preliminary Efficacy Of A Live-Chat Social Media Intervention To Reduce HIV Risk Among Young Men Who Have Sex With Men Lelutiu-Weinberger C, Pachankis JE, Gamarel KE, Surace A, Golub SA, Parsons JT. AIDS Behav. 2015; 19(7): 1214-1227.
Given the popularity of social media among young men who have sex with men (YMSM), and in light of YMSM elevated and increasing HIV rates, the authors tested the feasibility, acceptability and preliminary efficacy of a live chat intervention delivered on Facebook in reducing condomless anal sex and substance use within a group of high risk YMSM in a pre-post design with no control

group. Participants (N=41; 18-29 years old) completed up to eight one-hour motivational interviewing and cognitive behavioral skills-based online live chat intervention sessions, and reported on demographic, psychosocial, and behavioral characteristics at baseline and immediately post-intervention. Analyses indicated that participation in the intervention (n=31) was associated with reductions of days of drug and alcohol use in the past month and instances of anal sex without a condom (including under the influence of substances), as well as increases in knowledge of HIV-related risks at 3-month follow-up. This pilot study argues for the potential of this social media-delivered intervention to reduce HIV risk among a most vulnerable group in the United States, in a manner that was highly acceptable to receive and feasible to execute. A future randomized controlled trial could generate an intervention blueprint for providers to support YMSM wellbeing by reaching them regardless of their geographical location, at a low cost.

Sleep and Circadian Contributions To Adolescent Alcohol Use Disorder Hasler BP, Soehner AM, Clark DB. Alcohol. 2015; 49(4): 377-387.
Adolescence is a time of marked changes across sleep, circadian rhythms, brain function, and alcohol use. Starting at puberty, adolescents' endogenous circadian rhythms and preferred sleep times shift later, often leading to a mismatch with the schedules imposed by secondary education. This mismatch induces circadian misalignment and sleep loss, which have been associated with affect dysregulation, increased drug and alcohol use, and other risk-taking behaviors in adolescents and adults. In parallel to developmental changes in sleep, adolescent brains are undergoing structural and functional changes in the circuits subserving the pursuit and processing of rewards. These developmental changes in reward processing likely contribute to the initiation of alcohol use during adolescence. Abundant evidence indicates that sleep and circadian rhythms modulate reward function, suggesting that adolescent sleep and circadian disturbance may contribute to altered reward function, and in turn, alcohol involvement. In this review, the authors summarize the relevant evidence and propose that these parallel developmental changes in sleep, circadian rhythms, and neural processing of reward interact to increase risk for alcohol use disorder (AUD).

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. 2015; 16(4): 538-549.
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, White168) 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.

Toward Scientific Equity For The Prevention Of Depression and Depressive Symptoms In Vulnerable Youth Perrino T, Beardslee W, Bernal G, Brincks A, Cruden G, Howe G, Murry V, Pantin H, Prado G, Sandler I, Brown CH. Prev Sci. 2015; 16(5): 642-651.
Certain subgroups of youth are at high risk for depression and elevated depressive symptoms, and experience limited access to quality mental health care. Examples are socioeconomically disadvantaged, racial/ ethnic minority, and sexual minority youth. Research shows that there are efficacious interventions to prevent youth depression and depressive symptoms. These preventive interventions have the potential to play a key role in addressing these mental health disparities by reducing youth risk factors and enhancing protective factors. However, there are comparatively few preventive interventions directed specifically to these vulnerable subgroups, and sample sizes of diverse subgroups in general prevention trials are often too low to assess whether preventive interventions work equally well for vulnerable youth compared to other youth. In this paper, the authors describe the importance and need for "scientific equity," or equality and fairness in the amount of scientific knowledge produced to understand the potential solutions to such health disparities. The authors highlight possible strategies for promoting scientific equity, including the following: increasing the number of prevention research participants from vulnerable subgroups, conducting more data synthesis analyses and implementation science research, disseminating preventive interventions that are efficacious for vulnerable youth, and increasing the diversity of the prevention science research workforce. These strategies can increase the availability of research evidence to determine the degree to which preventive interventions can help address mental health disparities. Although this paper utilizes the prevention of youth depression as an illustrative case example, the concepts are applicable to other health outcomes for which there are disparities, such as substance use and obesity.

Correlates Of Individual Versus Joint Participation In Online Survey Research With Same-Sex Male Couples Starks TJ, Millar BM, Parsons JT. AIDS Behav. 2015; 19(6): 963-969.
Internet-based surveys are commonly utilized as a cost-effective mechanism for data collection in social and health psychology research. Little is known about the differences between partnered gay men who participate alone compared to those with partners who also agree to participate. A sample of 260 partnered gay/bisexual men from New York City completed an online survey covering demographic characteristics, sexual behavior, substance use, and relationship satisfaction. Upon completion, they had the option to send the study link to their partner. In total, 104 (40%) participants successfully recruited their partners, 90 (34.6%) were unsuccessful, and 66 (25.4%) declined the option to refer their partners. Men who did not refer their partners were significantly older, in relationships longer, and reported higher personal income. Participants who successfully recruited partners reported significantly higher relationship satisfaction. While generalizability is limited given the diversity of methodological factors that influence research participation, these data provide an initial insight into the effects on sample composition imposed by the implementation of dyadic (vs. unpaired) designs in online studies.

Understanding Early Contextual and Parental Risk Factors For The Development Of Limited Prosocial Emotions Waller R, Shaw DS, Forbes EE, Hyde LW. J Abnorm Child Psychol. 2015; 43(6): 1025-1039.
A growing body of evidence suggests that parenting influences the development of youth callous unemotional (CU) behavior. However, less is known about the effects of parenting or contextual risk factors' limited prosocial emotions' (LPE), a recent conceptualization of CU behavior added to the DSM-5. The authors focused on LPE at ages 10-12 and age 20 among low income, urban males (N=310), and examined potential developmental precursors, including contextual risk factors assessed during infancy and observed maternal warmth during the toddler period. They found unique direct associations between maternal warmth, maternal aggression, and low empathetic awareness on LPE at ages 10-12, controlling for concurrent self-reported antisocial behavior. Further, there were indirect effects of maternal aggression, low empathetic awareness, and difficult infant temperament assessed in infancy on LPE at ages 10-12 via their influence on maternal warmth at age 2. Finally, there were lasting indirect effects of parental warmth on LPE at age 20, via LPE at ages 10-12. The authors discuss the implications of these findings for ecological models of antisocial behavior and LPE development, and preventative interventions that target the broader early parenting environment.

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. 2015; 52(5): 704-713.
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.

Race-based Differentials In the Impact Of Mental Health and Stigma On HIV Risk Among Young Men Who Have Sex With Men Lelutiu-Weinberger C, Gamarel KE, Golub SA, Parsons JT. Health Psychol. 2015; 34(8): 847-856.
In the U.S., young men who have sex with men (YMSM) are disproportionately affected by HIV, with YMSM of color being the most impacted by the epidemic. To advance prevention research, the authors examined race-based differences in gay-related stress in conjunction with the moderating role of mental health on substance use and sexual risk among 206 high-risk YMSM, recruited September, 2007-2010. Negative binomial regressions and 3-way interaction graphs indicated that psychological distress and acute gay-related stigma placed all participants at most risk for HIV acquisition. Low psychological distress appeared to "buffer" all YMSM against HIV risk, whereas the reverse was evidenced for those reporting low gay-related stigma and psychological distress. YMSM of color reported more risk behavior, and less decreases in risk with attenuated psychological distress, compared with White YMSM. The authors hypothesize these trends to be associated with experiencing multiple stigmatized identities, indicating points of intervention for YMSM of color to achieve positive identity integration. There were sharper increases in HIV risk

behavior for White YMSM with increasing gay-related stigma than for YMSM of color, which could be attributed to the latter prolonged exposure to discrimination necessitating building coping skills to manage the influx of adversity. Emphases on: (a) identity-based interventions for YMSM of color; and (b) skills-based interventions for White YMSM should supplement existing successful HIV risk-reduction programs. Lastly, mental health needs to be a target of intervention, as it constitutes a protective factor against HIV risk for all YMSM.

Tobacco May Mask Poorer Episodic Memory Among Young Adult Cannabis Users Schuster RM, Crane NA, Mermelstein R, Gonzalez R. Neuropsychology. 2015; 29(5): 759-766.
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 individual effects on episodic memory and related brain structures, few studies have examined the effects 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.

Early Starting, Aggressive, and/or Callous-unemotional? Examining The Overlap and Predictive Utility Of Antisocial Behavior Subtypes Hyde LW, Burt SA, Shaw DS, Donnellan MB, Forbes EE. J Abnorm Psychol. 2015; 124(2): 329-342.
Antisocial behavior (AB) in adolescence predicts problematic outcomes in adulthood. However, researchers have noted marked heterogeneity within the broad group of youth engaging in these destructive behaviors and have attempted to identify those with distinct etiologies and different trajectories of symptoms. In the present study, the authors evaluate 3 prominent AB subtyping approaches: age of onset, presence of callous-unemotional (CU) traits, and aggressive versus rule-breaking symptoms. They examined the overlap of these subtypes and their predictive validity in a diverse sample of 268 low-income young men followed prospectively from adolescence into emerging adulthood. They found that those with early starting AB were uniquely high on aggressive symptoms but not on CU traits. Early starting AB and both aggression and rule breaking measured during adolescence predicted most subsequent psychiatric and AB outcomes in early adulthood in univariate models, whereas CU traits were only predictive of adolescent arrests, later substance dependence diagnosis, and later CU traits. Finally, after accounting for shared variance among predictor variables, we found that aggressive symptoms explained the most unique variance in predicting several later outcomes (e.g., antisocial personality disorder) over and above other subtyping approaches. Results are discussed in relation to of the use of existing subtyping approaches to AB, noting that aggression and age of onset but not CU traits appear to be the best at predicting later negative outcome.

HIV Risk, Health, and Social Characteristics Of Sexual Minority Female Injection Drug Users In Baltimore German D, Latkin CA. AIDS Behav. 2015; 19(7): 1361-1365.
Female injection drug users (IDU) who report sex with women are at increased risk for HIV and social instability, but it is important to assess whether these disparities also exist according to sexual minority identity rather than behaviorally defined categories. Within a sample of current IDU in Baltimore, about 17% of female study participants (n=307) identified as gay/lesbian/bisexual. In controlled models, sexual minorities were three times as likely to report sex exchange behavior and four times as likely to report a recent STI. Injection risk did not differ significantly, but sexual minority women reported higher prevalence of socio-economic instability, negative health indicators, and fewer network financial, material, and health support resources. There is a need to identify and address socio-economic marginalization, social support, and health issues among female IDUs who identify as lesbian or bisexual.

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; 232(13): 2217-2226.
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-naive 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 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.

Penalized Regression Procedures For Variable Selection In the Potential Outcomes Framework Ghosh D, Zhu Y, Coffman DL. Stat Med. 2015; 34(10): 1645-1658.
A recent topic of much interest in causal inference is model selection. In this article, the authors describe a framework in which to consider penalized regression approaches to variable selection for causal effects. The framework leads to a simple 'impute, then select' class of procedures that is agnostic to the type of imputation algorithm as well as penalized regression used. It also clarifies how model selection involves a multivariate regression model for causal inference problems and that these methods can be applied for identifying subgroups in which treatment effects are homogeneous. Analogies and links with the literature on machine learning methods, missing data, and imputation are drawn. A difference least absolute shrinkage and selection operator algorithm is defined, along with its multiple imputation analogs. The procedures are illustrated using a well-known right-heart catheterization dataset.

Factor Structure and Initial Validation Of A Multidimensional Measure Of Difficulties In The Regulation Of Positive Emotions: The DERS-Positive Weiss NH, Gratz KL, Lavender JM. Behav Modif. 2015; 39(3): 431-453.
Emotion regulation difficulties are a transdiagnostic construct relevant to numerous clinical difficulties. Although the Difficulties in Emotion Regulation Scale (DERS) is a multidimensional measure of maladaptive ways of responding to emotions, it focuses on difficulties with the regulation of negative emotions and does not assess emotion dysregulation in the form of problematic responding to positive emotions. The aim of this study was to develop and validate a measure of clinically relevant difficulties in the regulation of positive emotions (DERS-Positive). Findings revealed a three-factor structure and supported the internal consistency and construct validity of the total and subscale scores.

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; 45(): 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 35 week 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 30 weeks, 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 30 weeks through delivery (19.9±2.9 versus 21.2±2.2; p=.002). Controlling for age, income, unemployment, gravida, and father 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.

Substance Use Among Male Sex Workers In Vietnam: Prevalence, Onset, and Interactions With Sexual Risk Yu G, Clatts MC, Goldsamt LA, Giang LM. Int J Drug Policy. 2015; 26(5): 516-521.
HIV research in Vietnam has focused primarily on its large heroin injector population. Data on men who have sex with men [MSM], particularly the large and growing population of men who exchange sex for money or other material rewards, male sex workers [MSWs], is very limited. Data derive from a cross-sectional study of MSW, age 16-35, recruited using community sampling methods in three cities in 2010-2011, including Hanoi, Ho Chi Minh City [HCMC], and Nha Trang City (n=710). Assessments included demographic characteristics, substance use, sexual risk, and use of health services. A series of "event" questions were used to assess the influence of alcohol and drugs on sexual risk. Both tobacco and alcohol are initiated at a young age and most participants currently use both substances overall across all three cities. While alcohol and tobacco use precede the initiation of sex work, stimulant and opiate use are initiated following the initiation of sex work.

There was substantial overlap between substance use and sexual risk, and this overlap was strongest in sexual events involving male and female elective partners rather than sex work clients. Although rates of HIV infection in this group are low, this may be an artifact of the young age of the sample. High rates of drug use, including alcohol, tobacco and illicit drugs, coupled with high rates of ulcerative STIs such as HPV, suggest the potential for rapid amplification of STI/HIV risk among MSW and their complex sex partnering networks.

Taking Care Of Themselves: How Long-term Injection Drug Users Remain HIV and Hepatitis C Free Meylakhs P, Friedman SR, Mateu-Gelabert P, Sandoval M, Meylakhs N. Sociol Health Illn. 2015; 37(4): 626-641.
Though prevalence of HIV and especially Hepatitis C is high among people who inject drugs (PWID) in New York, about a third of those who have injected for 8-15 years have avoided infection by either virus despite their long-term drug use. Based on life history interviews with 35 long-term PWID in New York, this article seeks to show how successful integration and performance of various drug using and non-drug using roles may have contributed to some of these PWID staying uninfected with either virus. The authors argue that analysis of non-risk related aspects of the lives of the risk-takers (PWID) is very important in understanding their risk-taking behaviour and its outcomes (infection statuses). Drawing on work-related, social and institutional resources, our double-negative informants underwent both periods of stability and turmoil without getting infected.

Impulsivity and Cigarette Craving Among Adolescent Daily and Occasional Smokers Mathew AR, Burris JL, Froeliger B, Saladin ME, Carpenter MJ. Addict Behav. 2015; 45: 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. The authors 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.106 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.

STI/HIV Test Result Disclosure Between Female Sex Workers and Their Primary, Non-commercial Male Partners In Two Mexico-US Border Cities: A Prospective Study Pines HA, Patterson TL, Rangel G, Martinez G, Bazzi AR, Ulibarri MD, Syvertsen JL, Martin NK, Strathdee SA. Sex Transm Infect. 2015; 91(3): 207-213.
Disclosure of sexually transmitted infections (STI)/HIV diagnoses to sexual partners is not mandated by public health guidelines in Mexico. To assess the feasibility of couples-based STI/HIV testing with facilitated disclosure as a risk-reduction strategy within female sex workers' (FSW)

primary partnerships, the authors examined STI/HIV test result disclosure patterns between FSWs and their primary, non-commercial male partners in two Mexico-US border cities. From 2010 to 2013, 335 participants (181 FSWs and 154 primary male partners) were followed for 24 months. At semiannual visits, participants were tested for STIs/HIV and reported on their disclosure of test results from the previous visit. Multilevel logistic regression was used to identify individual-level and partnership-level predictors of cumulative (1) non-disclosure of ≥1 STI test result and (2) non-disclosure of ≥1 HIV test result within couples during follow-up. Eighty-seven percent of participants reported disclosing all STI/HIV test results to their primary partners. Non-disclosure of ≥1 STI test result was more common among participants who reported an STI diagnosis as part of the study (adjusted OR=3.05, 95% CI 1.13 to 8.25), while non-disclosure of ≥1 HIV test result was more common among participants in longer-duration partnerships (AOR=1.15 per year, 95% CI 1.03 to 1.28). Drug use before/during sex within partnerships was associated with non-disclosure of both STI (AOR=5.06, 95% CI 1.64 to 15.62) and HIV (AOR=4.51, 95% CI: 1.32 to 15.39) test results. STI/HIV test result disclosure was highly prevalent within FSWs primary partnerships, suggesting couples-based STI/HIV testing with facilitated disclosure may be feasible for these and potentially other high-risk, socially marginalized couples.

How Does Intimate Partner Violence Affect Condom and Oral Contraceptive Use In The United States?: A Systematic Review Of The Literature. Bergmann JN, Stockman JK. Contraception. 2015; 91(6): 438-455.

Intimate partner violence (IPV) is estimated to affect 25% of adult women in the United States alone. IPV directly impacts women's ability to use contraception, resulting in many of unintended pregnancies and STIs. This review examines the relationship between IPV and condom and oral contraceptive use within the United States at two levels: the female victim perspective on barriers to condom and oral contraceptive use, in conjunction with experiencing IPV (Aim 1) and the male perpetrator perspective regarding condom and oral contraceptive use (Aim 2). The authors systematically reviewed and synthesized all publications meeting the study criteria published since 1997. They aimed to categorize the results by emerging themes related to each study aim. They identified 42 studies that met their inclusion criteria. They found 37 studies that addressed Aim 1. Within this they identified three themes: violence resulting in reduced condom or oral contraceptive use (n=15); condom or oral contraceptive use negotiation (n=15); which they further categorized as IPV due to condom or oral contraceptive request, perceived violence (or fear) of IPV resulting in decreased condom or oral contraceptive use, and sexual relationship power imbalances decreasing the ability to use condoms or oral contraceptives; and reproductive coercion (n=7). The authors found 5 studies that addressed Aim 2. Most studies were cross-sectional, limiting the ability to determine causality between IPV and condom or oral contraceptive use; however, most studies did find a positive relationship between IPV and decreased condom or oral contraceptive use. Quantitative, qualitative, and mixed methods research has demonstrated the linkages between female IPV victimization/male IPV perpetration and condom or oral contraceptive use. However, additional qualitative and longitudinal research is needed to improve the understanding of dynamics in relationships with IPV and determine causality between IPV, intermediate variables (e.g., contraceptive use negotiation, sexual relationship power dynamics, reproductive coercion), and condom and oral contraceptive use. Assessing the relationship between IPV and reproductive coercion may elucidate barriers to contraceptive use as well as opportunities for interventions to increase contraceptive use (such as forms of contraception with less partner influence) and reduce IPV and reproductive coercion.

Genome-Wide Association Study Of Behavio ral 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; 45(4): 375-381.
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.

Divergent Responses Of the Amygdala and Ventral Striatum Predict Stress-related Problem Drinking In Young Adults: Possible Differential Markers Of Affective and Impulsive Pathways Of Risk For Alcohol Use Disorder Nikolova YS, Knodt AR, Radtke SR, Hariri AR. Mol Psychiatry. 2015.
Prior work suggests that there may be two distinct pathways of alcohol use disorder (AUD) risk: one associated with positive emotion enhancement and behavioral impulsivity, and another associated with negative emotion relief and coping. The authors sought to map these two pathways onto individual differences in neural reward and threat processing assessed using blood-oxygen-level-dependent functional magnetic resonance imaging in a sample of 759 undergraduate students (426 women, mean age 19.65 ±1.24 years) participating in the Duke Neurogenetics Study. The authors demonstrate that problem drinking is highest in the context of stress and in those with one of two distinct neural phenotypes: (1) a combination of relatively low reward-related activity of the ventral striatum (VS) and high threat-related reactivity of the amygdala; or (2) a combination of relatively high VS activity and low amygdala reactivity. In addition, the authors demonstrate that the relationship between stress and problem alcohol use is mediated by impulsivity, as reflected in monetary delay discounting rates, for those with high VS-low amygdala reactivity, and by anxious/depressive symptomatology for those with the opposite neural risk phenotype. Across both neural phenotypes, we found that greater divergence between VS and amygdala reactivity predicted greater risk for problem drinking. Finally, for those individuals with the low VS-high amygdala risk phenotype we found that stress not only predicted the presence of AUD diagnosis at the time of neuroimaging but also subsequent problem drinking reported 3 months following study completion. These results offer new insight into the neural basis of AUD risk and suggest novel biological targets for early individualized treatment or prevention. Molecular Psychiatry advance online publication, 30 June 2015; doi:10.1038/mp.2015.85.

Aberrant Orbitofrontal Connectivity In Marijuana Smoking Adolescents Lopez-Larson MP, Rogowska J, Yurgelun-Todd D. Dev Cogn Neurosci. 2015.
Orbitofrontal (OFC) circuits have been implicated in the pathophysiology of substance use disorders. The current study examined OFC functional connectivity differences in marijuana-using adolescents (MJ) and non-using healthy controls (HC).Functional magnetic resonance imaging (fMRI) resting-state data were obtained on a 3T MRI scanner on 31 HC and 43 heavy MJ smokers. Image analyses were performed between groups (MJ, HC) for the left and right OFC separately. Regression analyses between OFC functional connectivity and lifetime MJ use, age of first MJ use and impulsivity also were performed. Increased OFC functional connectivity to frontal and motor regions was observed in heavy MJ users compared to HC. Earlier age of first MJ use was associated with increased functional connectivity of the right OFC to motor regions. High lifetime MJ use was associated with increased OFC functional connectivity to posterior brain regions in MJ youth. Findings indicate atypical OFC functional connectivity patterns in attentional/executive, motor and reward networks in adolescents with heavy MJ use. These anomalies may be related to suboptimal decision making capacities and increased impulsivity. Results also suggest different OFC connectivity patterns may be present in adolescents with early onset of MJ use and high lifetime exposure to MJ.

The Underlying Role Of Posttraumatic Stress Disorder Symptoms In the Association Between Intimate Partner Violence and Deliberate Self-harm Among African American Women Weiss NH, Dixon-Gordon KL, Duke AA, Sullivan TP. Compr Psychiatry. 2015; 59: 8-16.
African American women are at heightened risk for intimate partner violence (IPV) and its negative consequences, including health-compromising behaviors. Deliberate self-harm (DSH) is one clinically-relevant behavior that has been understudied among African American women generally and those with exposure to IPV in particular. To date, no studies have examined factors that may account for the relationship between IPV and DSH. Therefore, the goal of the present study was to examine the intercorrelations among IPV (physical, psychological, and sexual), PTSD, and DSH history and versatility, and the potentially mediating role of PTSD symptoms in the IPV-DSH relation. Participants were 197 African American community women currently experiencing IPV. Sixty participants (31%) reported a history of DSH. Among participants who reported DSH, there was an average endorsement of 2.3 unique forms of deliberate self-harm (i.e., DSH versatility). Significant positive associations were detected among physical IPV severity, psychological IPV severity, PTSD symptom severity, and DSH history and versatility. PTSD symptom severity mediated the relationships between physical and psychological IPV severity and DSH history and versatility. Results highlight the relevance of PTSD symptoms to DSH and suggest that treatments targeting PTSD symptoms may be useful in reducing DSH among IPV-exposed African American women.

The Depression Distress Amplification Model In Adolescents: A Longitudinal Examination Of Anxiety Sensitivity Cognitive Concerns, Depression and Suicidal Ideation Capron DW, Allan NP, Ialongo NS, Leen-Feldner E, Schmidt NB. J Adolesc. 2015; 41: 17-24.
Adolescents with comorbid anxiety and depression are at significantly increased risk of suicide. The recently proposed depression distress amplification model appears to have promise for explaining the relations between anxiety, depression, and suicidality, but it has not been tested in adolescents. Participants were 524 adolescents followed over two years. Baseline data for the current report were collected by trained interviewers while the adolescents were in eighth grade. Data were obtained in the same manner when the adolescents were in tenth grade. Baseline anxiety sensitivity cognitive

concerns significantly predicted suicidal ideation two years later, above and beyond baseline suicidal ideation and depression. Further, consistent with the depression distress amplification model, anxiety sensitivity cognitive concerns interacted with depressive symptoms to predict suicidal ideation. This report extends the empirical and theoretical support for a relationship between anxiety sensitivity cognitive concerns and suicidality.

Transactional Sex Among Men Who Have Sex With Men In Latin America: Economic, Sociodemographic, and Psychosocial Factors Oldenburg CE, Perez-Brumer AG, Biello KB, Landers SJ, Rosenberger JG, Novak DS, Mayer KH, Mimiaga MJ. Am J Public Health. 2015; 105(5): e95-e102.
The authors assessed factors associated with engagement in transactional sex among men who have sex with men recruited from one of the largest Internet sites for men seeking social or sexual interactions with other men in Latin America. They constructed multilevel logistic regression models to analyze factors associated with engagement in transactional sex in 17 Latin American countries in 2012. Of 24,051 respondents, 1,732 (7.2%) reported being paid for sexual intercourse in the past 12 months. In a multivariable model, higher country-level unemployment was associated with increased odds of transactional sex (adjusted odds ratio [AOR] =1.07 per 1% increase in unemployment; 95% confidence interval [CI] =1.00, 1.13). Individual or interpersonal factors associated with increased odds of engagement in transactional sex included self-reported HIV (AOR=1.33; 95% CI=1.04, 1.69) or sexually transmitted infection (AOR=1.33; 95% CI=1.11, 1.59), childhood sexual abuse history (AOR=1.75; 95% CI=1.48, 2.06), intimate partner violence (past 5 years, AOR=1.68; 95% CI=1.45, 1.95), and sexual compulsivity (AOR=1.77; 95% CI=1.49, 2.11). Structural-level economic interventions and those that address individual and interpersonal factors may improve HIV prevention efforts among men who have sex with men who engage in transactional sex.

Short-term Cessation Of Sex Work and Injection Drug Use: Evidence From A Recurrent Event Survival Analysis Gaines TL, Urada LA, Martinez G, Goldenberg SM, Rangel G, Reed E, Patterson TL, Strathdee SA. Addict Behav. 2015; 45: 63-69.
This study quantitatively examined the prevalence and correlates of short-term sex work cessation among female sex workers who inject drugs (FSW-IDUs) and determined whether injection drug use was independently associated with cessation. The authors used data from FSW-IDUs (n=467) enrolled into an intervention designed to increase condom use and decrease sharing of injection equipment but was not designed to promote sex work cessation. They applied a survival analysis that accounted for quit-re-entry patterns of sex work over 1-year stratified by city, Tijuana and Ciudad Juarez, Mexico. Overall, 55% of participants stopped sex work at least once during follow-up. Controlling for other characteristics and intervention assignment, injection drug use was inversely associated with short-term sex work cessation in both cities. In Ciudad Juarez, women receiving drug treatment during follow-up had a 2-fold increase in the hazard of stopping sex work. In both cities, income from sources other than sex work, police interactions and healthcare access were independently and significantly associated with shorter-term cessation. Short-term sex work cessation was significantly affected by injection drug use. Expanded drug treatment and counseling coupled with supportive services such as relapse prevention, job training, and provision of alternate employment opportunities may promote longer-term cessation among women motivated to leave the sex industry.

Adolescent Heavy Drinkers' Amplified Brain Responses To Alcohol Cues Decrease Over One Month Of Abstinence Brumback T, Squeglia LM, Jacobus J, Pulido C, Tapert SF, Brown SA. Addict Behav. 2015; 46: 45-52.
Heavy drinking during adolescence is associated with increased reactivity to alcohol related stimuli and to differential neural development. Alcohol cue reactivity has been widely studied among adults with alcohol use disorders, but little is known about the neural substrates of cue reactivity in adolescent drinkers. The current study aimed to identify changes in blood-oxygen level dependent (BOLD) signal during a cue reactivity task pre- and post-monitored abstinence from alcohol. Demographically matched adolescents (16.0-18.9 years, 54% female) with histories of heavy episodic drinking (HD; n=22) and light or non-drinking control teens (CON; n=16) were recruited to participate in a month-long study. All participants completed a functional Magnetic Resonance Imaging (fMRI) scan with an alcohol cue reactivity task and substance use assessments at baseline and after 28 days of monitored abstinence from alcohol and drugs (i.e., urine toxicology testing every 48-72 h). Repeated-measure analysis of variance (ANOVA) examined main effects of group, time, and group—time interactions on BOLD signal response in regions of interest defined by functional differences at baseline. The HD group exhibited greater ($p<.01$) BOLD activation than CON to alcohol cues relative to neutral cues in all regions of interest (ROIs; bilateral striatum/globus pallidus, left anterior cingulate, bilateral cerebellum, and parahippocampal gyrus extending to the thalamus/substantia nigra) across time points. Group —time effects showed that HD exhibited greater BOLD activation to alcohol cues than CON at baseline in left anterior cingulate cortex and in the right cerebellar region, but these decreased to non-significance after one month of monitored abstinence. In all ROIs examined, HD exhibited greater BOLD response than CON to alcohol relative to neutral beverage picture cues at baseline, indicating heightened cue reactivity to alcohol cues in heavy drinking adolescents prior to the onset of any alcohol use diagnosis. Across the majority of these brain regions, differences in BOLD response were no longer apparent following a month of abstinence, suggesting a decrease in alcohol cue reactivity among adolescent non-dependent heavy drinkers as a consequence of abstaining from alcohol. These results highlight the malleability of adolescent brain function despite no formal intervention targeting cue reactivity. Increased understanding of the neural underpinnings of cue reactivity could have implications for prevention and intervention strategies in adolescent heavy alcohol users.

Longitudinal Trajectories Of Marijuana Use From Adolescence To Young Adulthood Passarotti AM, Crane NA, Hedeker D, Mermelstein RJ. Addict Behav. 2015; 45: 301-308.
Marijuana use is increasingly widespread among adolescents and young adults; however, few studies have examined longitudinal trajectories of marijuana use during this important developmental period. As such, the authors examined adolescent trajectories of marijuana use and the psychosocial factors that may differentiate individuals who escalate their marijuana use over adolescence and young adulthood from those who do not. Participants were 1,204 9th and 10th graders at baseline who were over-sampled for cigarette use and were followed over 6-years, as part of an extensive longitudinal study, the Social and Emotional Contexts of Adolescent Smoking Patterns (SECASP) study. Growth Mixture Modeling (GMM) was used to model trajectories of marijuana use and Mixed Effects Regression analyses were used to examine psychosocial correlates of marijuana use escalation over time. Results revealed three trajectories of non-escalating users (low users, medium users, and high users) and one escalating user trajectory. The authors found that relative to Non-escalators the Escalators had higher cigarette smoking ($p<.0001$), novelty-seeking ($p=.02$), aggressive and anti-social behavior ($p<.007$), and problem behavior related to peer context ($p=.04$). Moreover, there were important time and Group by Time interactions in some of these

relationships. On the other hand, parental control and depression did not differ between escalators and low and medium non-escalating users. Cigarette smoking, novelty-seeking, aggressive and anti-social behavior, and peer influence are related to 'escalating' marijuana use throughout adolescence and young adulthood.

Risky Sexual Behavior and Substance Use Among Adolescents: A Meta-analysis Ritchwood TD, Ford H, DeCoster J, Sutton M, Lochman JE. Child Youth Serv Rev. 2015; 52: 74-88.
This study presents the results of a meta-analysis of the association between substance use and risky sexual behavior among adolescents. 87 studies fit the inclusion criteria, containing a total of 104 independent effect sizes that incorporated more than 120,000 participants. The overall effect size for the relationship between substance use and risky sexual behavior was in the small to moderate range (r = .22, CI = .18, .26). Further analyses indicated that the effect sizes did not substantially vary across the type of substance use, but did substantially vary across the type of risky sexual behavior being assessed. Specifically, mean effect sizes were smallest for studies examining unprotected sex (r = .15, CI = .10, .20), followed by studies examining number of sexual partners (r = .25, CI = .21, .30), those examining composite measures of risky sexual behavior (r = .38, CI = .27, .48), and those examining sex with an intravenous drug user (r = .53, CI = .45, .60). Furthermore, these results revealed that the relationship between drug use and risky sexual behavior is moderated by several variables, including sex, ethnicity, sexuality, age, sample type, and level of measurement. Implications and future directions are discussed.

Variations In Parental Monitoring and Predictions Of Adolescent Prescription Opioid and Stimulant Misuse Donaldson CD, Nakawaki B, Crano WD. Addict Behav. 2015; 45: 14-21.
This study examined relations between adolescents' family structures, social ties, and drug-related attitudes, and their misuse of prescription opioids and stimulants. Different relationships were anticipated for the substances based on prior research highlighting varying motivations for their use. Based on an earlier model of adolescent substance misuse, two path analytic models were tested using data from 12 to 17 year olds in the 2012 U.S. National Survey on Drug Use and Health (NSDUH: N=17,399). Female respondents reported higher levels of parental warmth, as did youth from wealthier families. Greater parental monitoring was reported by adolescents from wealthier and intact families. Parental monitoring and warmth predicted adolescents' social ties and individual differences associated with drug use, and both variables predicted prescription opioid and stimulant misuse. Contrary to previous research, for adolescents aged 12 to 14, high levels of parental monitoring, while positively associated with attitudes and social ties, also predicted higher rates of prescription stimulant misuse when combined with low levels of parental warmth. Results were cross-validated with data from the 2011 NSDUH. Analyses highlighted the importance of understanding and differentiating the underlying factors associated with adolescent prescription stimulant and opioid misuse, and the role of parental behaviors in prevention.

The Role Of Neighborhoods In Shaping Perceived Norms: An Exploration Of Neighborhood Disorder and Norms Among Injection Drug Users In Baltimore, MD Davey-Rothwell MA, Siconolfi DE, Tobin KE, Latkin CA. Health Place. 2015; 33: 181-186.
A large literature suggests that social norms contribute to HIV and substance use related behaviors. Less attention has been given to neighborhood factors that may contribute to the development of norms about risky behaviors. The authors examined the cross-sectional associations between perceptions of one neighborhood and norms of perceived prevalence of, and peer support for sex exchange and risky injection behaviors. The sample consisted of 719 people who reported injecting

heroin and cocaine and did not move in the past 6 months in Baltimore, MD. Living in a neighborhood with disorder was associated with believing that others exchanged sex, practiced risky injection behaviors (descriptive norms) and approved of risky injection behavior (injunctive norms).

Detecting Initiation Or Risk For Initiation Of Substance Use Before High School During Pediatric Well-child Check-ups Ridenour TA, Willis D, Bogen DL, Novak S, Scherer J, Reynolds MD, Zhai ZW, Tarter RE. Drug Alcohol Depend. 2015; 150: 54-62.
Youth substance use (SU) is prevalent and costly, affecting mental and physical health. American Academy of Pediatrics and Affordable Care Act call for SU screening and prevention. The Youth Risk Index (©) (YRI) was tested as a screening tool for having initiated and propensity to initiate SU before high school (which forecasts SU disorder). YRI was hypothesized to have good to excellent psychometrics, feasibility and stakeholder acceptability for use during well-child check-ups. A high-risk longitudinal design with two cross-sectional replication samples, ages 9-13 was used. Analyses included receiver operating characteristics and regression analyses. A one-year longitudinal sample (N=640) was used for YRI derivation. Replication samples were a cross-sectional sample (N=345) and well-child check-up patients (N=105) for testing feasibility, validity and acceptability as a screening tool. YRI has excellent test-retest reliability and good sensitivity and specificity for concurrent and one-year-later SU (odds ratios=7.44, CI=4.3-13.0) and conduct problems (odds ratios=7.33, CI=3.9-13.7). Results were replicated in both cross-sectional samples. Well-child patients, parents and pediatric staff rated YRI screening as important, acceptable, and a needed service. Identifying at-risk youth prior to age 13 could reap years of opportunity to intervene before onset of SU disorder. Most results pertained to YRI association with concurrent or recent past risky behaviors; further replication ought to specify its predictive validity, especially adolescent-onset risky behaviors. YRI well identifies youth at risk for SU and conduct problems prior to high school, is feasible and valid for screening during well-child check-ups, and is acceptable to stakeholders.

Specific Dimensions Of Impulsivity Are Differentially Associated With Daily and Non-daily Cigarette Smoking In Young Adults Lee DC, Peters JR, Adams ZW, Milich R, Lynam DR. Addict Behav. 2015; 46: 82-85.
Young adults are at risk for initiation of tobacco use and progression to tobacco dependence. Not every person who smokes cigarettes becomes tobacco dependent, however, and non-daily smoking is becoming more prevalent among those who use tobacco. It is likely that individual differences in psychosocial and behavioral factors influence risk for engaging in non-daily and daily cigarette smoking. The objective of this study was to investigate the associations between impulsivity and smoking status in young adults who vary in frequency of cigarette smoking. Young adult first-year college students between the ages of 18-24 (512) were classified to one of three groups: non-smokers, non-daily smokers, or daily smokers, and impulsivity was assessed using the UPPS-P (negative and positive urgency, lack of premeditation, lack of perseverance, sensation seeking). When all impulsivity dimensions were used simultaneously to predict smoking status, negative urgency predicted increased risk of membership in the daily smoking group and lack of premeditation predicted increased risk of membership in the non-daily smoking group. These results suggest that dimensions of impulsivity may contribute differentially to forms of smoking behavior in young adults.

The Predictive Utility Of Early Childhood Disruptive Behaviors For School-Age Social Functioning Brennan LM, Shaw DS, Dishion TJ, Wilson MN. J Abnorm Child Psychol. 2015; 43(6): 1187-1199.
Research suggests that school-age children with disruptive behavior (DB) problems frequently demonstrate impaired social skills and experience rejection from peers, which plays a crucial role in the pathway to more serious antisocial behavior. A critical question is which DB problems in early childhood are prognostic of impaired social functioning in school-age children. This study examines the hypothesis that aggression in early childhood will be the more consistent predictor of compromised social functioning than inattentive, hyperactive-impulsive, or oppositional behavior. Participants included an ethnically diverse sample of 725 high-risk children from 3 geographically distinct areas followed from ages 2 to 8.5. Four latent growth models of DB from child ages 2 to 5, and potential interactions between dimensions, were used to predict latent parent and teacher ratings of school-age social dysfunction. Analyses were conducted in a multi-group format to examine potential differences between intervention and control group participants. Results showed that age 2 aggression was the DB problem most consistently associated with both parent- and teacher-rated social dysfunction for both groups. Early starting aggressive behavior may be particularly important for the early identification of children at risk for school-age social difficulties.

Self-Efficacy For Sexual Risk Reduction and Partner HIV Status As Correlates Of Sexual Risk Behavior Among HIV-Positive Adolescent Girls and Women Boone MR, Cherenack EM, Wilson PA; ATN 086/106 Protocol Team. AIDS Patient Care STDS. 2015; 29(6): 346-353.
Little is known about the correlates of sexual risk behavior among HIV-positive adolescent girls and women in the United States. This study investigates two potential factors related to unprotected vaginal and anal intercourse (UVAI) that have yet to be thoroughly studied in this group: self-efficacy for sexual risk reduction and partner HIV status. Data was analyzed from 331 HIV-positive adolescent girls and women between 12 and 24 years old who reported vaginal and/or anal intercourse with a male partner in the past 3 months at fifteen sites across the United States. Results show that overall self-efficacy (B=-0.15, p=0.01), self-efficacy to discuss safe sex with one partner (B=-0.14, p=0.01), and self-efficacy to refuse unsafe sex (B=-0.21, p=0.01) are related to UVAI episodes. Participants with only HIV-positive partners or with both HIV-positive and HIV-negative partners showed a trend towards higher percentages of UVAI episodes compared to participants with only HIV-negative partners (F (2, 319) =2.80, p=0.06). These findings point to the importance of including self-efficacy and partner HIV status in risk-reduction research and interventions developed for HIV-positive adolescent girls and young women.

Examining Emotion Regulation As An Outcome, Mechanism, Or Target Of Psychological Treatments Gratz KL, Weiss NH, Tull MT. Curr Opin Psychol. 2015; 3: 85-90.
This paper reviews the extant literature on emotion regulation (ER) in psychological interventions. First, the authors review current conceptualizations of ER, highlighting a model with established clinical utility (particularly with regard to the development of new interventions and modification of existing interventions). Next, they review the literature on the effects of psychological interventions on ER, from traditional cognitive-behavioral and acceptance-based behavioral interventions that do not target ER directly to treatments that directly target ER as one component of a larger or more comprehensive treatment, as well as the preliminary research examining ER as a mechanism of change in these treatments. Finally, extant data on three treatments developed specifically to address ER are reviewed, with an emphasis on the ER-specific treatment with the most empirical support to date (emotion regulation group therapy).

Gender Differences In Planning Ability and Hepatitis C Virus Among People Who Inject Drugs Scheidell JD, Khan MR, Clifford LM, Dunne EM, Keen 2nd, LD, Latimer WW, Addict Behav. 2015; 47: 33-37.
Hepatitis C virus (HCV) is primarily spread through risky injection practices, including sharing needles, cookers, cottons, rinse water, and the practice of backloading. An important aspect of harm reduction for people who inject drugs (PWID) is to identify factors that contribute to safer injection. Planning ability may influence risky injection practices and gender differences in factors that drive injection practices indicate a need to examine associations between planning and injection behaviors in men versus women. Data from the NEURO-HIV Epidemiologic Study was restricted to those who had ever injected in their lifetime (n=456). Impaired planning ability was assessed with the Tower of London and defined as a standardized total excess move score below the 10th percentile. The authors used logistic regression to estimate the gender-specific adjusted odds ratios (AOR) and 95% confidence intervals (CI) for associations between impaired planning, each injection practice, and biologically-confirmed HCV. Impaired planning ability was associated with sharing needles (AOR=2.93, 95% CI: 1.33, 6.47), cookers (AOR=3.13, 95% CI: 1.22, 8.02), cottons (AOR=2.89, 95% CI: 1.23, 6.78), rinse water (AOR=2.43, 95% CI: 1.15, 5.14), and backloading (AOR=2.68, 95% CI: 1.26, 5.70) and HCV (AOR=3.42, 95% CI: 1.03, 11.38) among men. Planning ability was not significantly associated with the injection behaviors or HCV among women, suggesting that other factors likely contribute to risky injection practices. Interventions to promote harm reduction among PWID should ascertain and strengthen planning ability. Women may have additional barriers to practicing safe injection beyond impaired planning abilities, which should also be addressed.

Fathers Matter: Involving and Engaging Fathers In the Child Welfare System Process Campbell CA, Howard D, Rayford BS, Gordon DM. Child Youth Serv Rev. 2015; 53: 84-91.
Research suggests that children with involved and engaged fathers tend to have more positive outcomes relative to physical, cognitive, and social emotional health. Of children who become involved in the child welfare system, involving multiple parents in the case (e.g. mother and father) often results in a greater chance of a child returning home, fewer placement episodes, and reduced trauma that may be caused by separation anxiety. With the rise of single parenting homes (which are mostly maternal) in the United States, child welfare agencies are examining the efficacy of engaging multiple caregivers (esp. fathers) in the child welfare process. Research suggests that in order to involve fathers in child welfare processes, practices and policies must be intentional in implementing systems and protocols that encourage involvement of all parents regardless of relationship status of the parents. However, few child welfare agencies are required to inquire about fathers or involve fathers in the child case. The purpose of this paper is to highlight efforts of the Connecticut Comprehensive Outcome Review (CCOR) process and discuss challenges and lessons learned from interviews and listening forums/focus groups that included social workers and fathers who are involved in the child welfare system in the state of Connecticut. Recommendations and considerations on engaging and involving fathers are discussed.

Determining Ethyl Glucuronide Cutoffs When Detecting Self-reported Alcohol Use In Addiction Treatment Patients Lowe JM, McDonell MG, Leickly E, Angelo FA, Vilardaga R, McPherson S, Srebnik D, Roll J, Ries RK. Alcohol Clin Exp Res. 2015; 39(5): 905-910.
Ethyl glucuronide (EtG) is an alcohol biomarker with potential utility as a clinical research and alcohol treatment outcome. Debate exists regarding the appropriate cutoff level for determining alcohol use, particularly with the EtG immunoassay. This study determined the EtG immunoassay

cutoff levels that most closely correspond to self-reported drinking in alcohol-dependent outpatients. Eighty adults with alcohol dependence and mental illness, taking part in an alcohol treatment study, provided urine samples 3 times per week for up to 16 weeks (1,589 samples). Self-reported drinking during 120 hours prior to each sample collection was assessed. Receiver operating characteristic analyses were conducted to assess the ability of the EtG immunoassay to detect self-reported alcohol use across 24- to 120-hour time periods. Sensitivity and specificity of EtG immunoassay cutoff levels was compared in 100 ng/ml increments (100 to 500ng/ml) across 24 to 120hours. Over half (57%) of the 1,589 samples indicated recent alcohol consumption. The EtG immunoassay closely corresponded to self-reported drinking from 24 (area under the curve [AUC] = 0.90, 95% confidence interval [CI]: 0.88, 0.92) to 120 hours (AUCÂ = 0.88, 95% CI: 0.87, 0.90). When cutoff levels were compared across 24 to 120 hours, 100 ng/ml had the highest sensitivity (0.93 to 0.78) and lowest specificity (0.67 to 0.85). Relative to 100Â ng/ml, the 200 ng/ml cutoff demonstrated a reduction in sensitivity (0.89 to 0.67), but improved specificity (0.78 to 0.94). The 300, 400, and 500 ng/ml cutoffs demonstrated the lowest sensitivity (0.86 to 0.33) and highest specificity (0.86 to 0.97) over 24 to 120 hours. For detecting alcohol use for >24 hours, the 200 ng/ml cutoff level is recommended for use as a research and clinical outcome.

Burden Of Substance Use Disorders, Mental Illness, and Correlates Of Infectious Diseases Among Soon-to-be Released Prisoners In Azerbaijan Azbel L, Wickersham JA, Wegman MP, Polonsky M, Suleymanov M, Ismayilov R, Dvoryak S, Rotberga S, Altice FL. Drug Alcohol Depend. 2015; 151: 68-75.
Despite low HIV prevalence in the South Caucasus region, transmission is volatile. Little data are available from this region about addiction and infectious diseases among prisoners who transition back to communities. A nation-wide randomly sampled biobehavioral health survey was conducted in 13 non-specialty Azerbaijani prisons among soon-to-be-released prisoners. After informed consent, participants underwent standardized health assessment surveys and testing for HIV, hepatitis B and C, and syphilis. Of the 510 participants (mean age = 38.2 years), 11.4% were female, and 31.9% reported pre-incarceration drug injection, primarily of heroin. Prevalence of HCV (38.2%), HIV (3.7%), syphilis (3.7%), and HBV (2.7%) was high. Among the 19 HIV-infected inmates, 14 (73.7%) were aware of their HIV status, 12 (63.2%) were receiving antiretroviral therapy (ART), and 5 (26.3%) had CD4 < 350 cells/mL (4 of these were on ART). While drug injection was the most significant independent correlate of HCV (AOR = 12.9; p = 0.001) and a significant correlate of HIV (AOR = 8.2; p = 0.001), both unprotected sex (AOR = 3.31; p = 0.049) and working in Russia/Ukraine (AOR = 4.58; p = 0.008) were also correlated with HIV. HIV and HCV epidemics are concentrated among people who inject drugs (PWIDs) in Azerbaijan, and magnified among prisoners. A transitioning HIV epidemic is emerging from migration from high endemic countries and heterosexual risk. The high diagnostic rate and ART coverage among Azerbaijani prisoners provides new evidence that HIV treatment as prevention in former Soviet Union (FSU) countries is attainable, and provides new insights for HCV diagnosis and treatment as new medications become available. Within prison evidence-based addiction treatments with linkage to community care are urgently needed.

Personality Profiles and Frequent Heavy Drinking In Young Adulthood Zhang J, Bray BC, Zhang M, Lanza ST. Pers Individ Dif. 2015; 80: 18-21.
Few studies examining the link between personality and alcohol use have adopted a comprehensive modeling framework to take into account individuals' profiles across multiple personality traits. In this study, latent profile analysis (LPA) was applied to a national sample of young adults in the

United States to identify subgroups defined by their profiles of mean scores on the Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness personality factors. Personality profiles were then used to predict heavy drinking. Five profiles were identified: Reserved, Rigid, Confident, Ordinary, and Resilient. Compared to individuals in the Ordinary profile, those with Reserved and Resilient profiles were at increased risk of frequent heavy drinking. These findings suggest which comprehensive personality profiles may place individuals at risk for problematic alcohol-related outcomes.

Place Of Residence Moderates the Relationship Between Emotional Closeness and Syringe Sharing Among Injection Drug Using Clients Of Sex Workers In the US-Mexico Border Region Wagner KD, Pitpitan EV, Valente TW, Strathdee SA, Rusch M, Magis-Rodriguez C, Chavarin CV, Patterson TL. AIDS Behav. 2015; 19(6): 987-95.
Injection drug-using men from the US and Mexico who purchase sex in Tijuana, Mexico are at risk for transmitting HIV to their contacts in both countries via syringe sharing. The authors used social network methods to understand whether place of residence (US vs. Mexico) moderated the effect of emotional closeness on syringe sharing. They interviewed 199 drug-using men who reported paying/trading for sex in Tijuana, Mexico using an epidemiological and social network survey and collected samples for HIV/STI testing. Seventy-two men reported using injection drugs with 272 network contacts. Emotional closeness was strongly associated with syringe sharing in relationships where the partner lives in the US, while the relationship between emotional closeness and syringe sharing was considerably less strong in dyads where the partner lives in Mexico. Efforts to reduce HIV risk behaviors in emotionally close relationships are needed, and could benefit from tailoring to the environmental context of the relationship.

Discrimination, Racial Identity, and Cytokine Levels Among African-American Adolescents Brody GH, Yu T, Miller GE, Chen E. J Adolesc Health. 2015; 56(5): 496-501.
Low-grade inflammation, measured by circulating levels of cytokines, is a pathogenic mechanism for several chronic diseases of aging. Identifying factors related to inflammation among African-American youths may yield insights into mechanisms underlying racial disparities in health. The purpose of the study was to determine whether (1) reported racial discrimination from ages 17-19 years forecasts heightened cytokine levels at the age of 22 years and (2) this association is lower for youths with positive racial identities. A longitudinal research design was used with a community sample of 160 African-Americans who were aged 17 years at the beginning of the study. Discrimination and racial identity were measured with questionnaires, and blood was drawn to measure basal cytokine levels. Ordinary least squares regression analyses were used to examine the hypotheses. After controlling for socioeconomic risk, life stress, depressive symptoms, and body mass index, racial discrimination ($\beta = .307$; $p < .01$), racial identity ($\beta = -.179$; $p < .05$), and their interaction ($\beta = -.180$; $p < .05$) forecast cytokine levels. Youths exposed to high levels of racial discrimination evinced elevated cytokine levels 3 years later. This association was not significant for young adults with positive racial identities. High levels of interpersonal racial discrimination and the development of a positive racial identity operate jointly to determine low-grade inflammation levels that have been found to forecast chronic diseases of aging, such as coronary disease and stroke.

Buffering Syndemic Effects In A Sexual Risk-Reduction Intervention For Male Clients Of Female Sex Workers: Results From A Randomized Controlled Trial Pitpitan EV, Strathdee SA, Semple SJ, Chavarin CV, Magis-Rodriguez C, Patterson TL. Am J Public Health. 2015; 105(9): 1866-1871.
The authors sought to test the efficacy of a sexual risk intervention for male clients of female sex workers (FSWs) and examine whether efficacy was moderated by syndemic risk. From 2010 to 2014, they conducted a 2-arm randomized controlled trial (60-minute, theory-based, safer sex intervention versus a didactic time-equivalent attention control) that included 400 male clients of FSWs on the US-Mexico border with follow-up at 4, 8, and 12 months. They measured 5 syndemic risk factors, including substance use and depression. Primary outcomes were sexually transmitted infections incidence and total unprotected sex with FSWs. Although participants in both groups became safer, there was no significant difference in behavior change between groups. However, baseline syndemic risk moderated intervention efficacy. At baseline, there was a positive association between syndemic risk and unprotected sex. Then at 12 months, longitudinal analyses showed the association depended on intervention participation (B =-0.71; 95% confidence interval [CI] = -1.22, -0.20; P = .007). Among control participants there still existed this modest association (B= 0.36; 95% CI =-0.49, 1.22; P = .09); among intervention participants there was a significant negative association (B = -0.35; 95% CI = -0.63, -0.06; P = .02). A brief intervention might attenuate syndemic risks among clients of FSWs. Other populations experiencing syndemic problems may also benefit from such programs.

Social Networks and the Diffusion Of Adolescent Problem Behavior: Reliable Estimates Of Selection and Influence From Sixth Through Ninth Grades Osgood DW, Feinberg ME, Ragan DT. Prev Sci. 2015; 16(6): 832-843.
Seeking to reduce problematic peer influence is a prominent theme of programs to prevent adolescent problem behavior. To support the refinement of this aspect of prevention programming, the authors examined peer influence and selection processes for three problem behaviors (delinquency, alcohol use, and smoking). They assessed not only the overall strengths of these peer processes, but also their consistency versus variability across settings. They used dynamic stochastic actor-based models to analyze five waves of friendship network data across sixth through ninth grades for a large sample of U.S. adolescents. The authors' sample included two successive grade cohorts of youth in 26 school districts participating in the PROSPER study, yielding 51 longitudinal social networks based on respondents' friendship nominations. For all three self-reported antisocial behaviors, they found evidence of both peer influence and selection processes tied to antisocial behavior. There was little reliable variance in these processes across the networks, suggesting that the statistical imprecision of the peer influence and selection estimates in previous studies likely accounts for inconsistencies in results. Adolescent friendship networks play a strong role in shaping problem behavior, but problem behaviors also inform friendship choices. In addition to preferring friends with similar levels of problem behavior, adolescents tend to choose friends who engage in problem behaviors, thus creating broader diffusion.

Prenatal Substance Exposure and Child Self-regulation: Pathways To Risk and Protection Eiden RD, Godleski S, Schuetz, P, Colder CR. J Exp Child Psychol. 2015; 137: 12-29.
A conceptual model of the association between prenatal cocaine exposure (PCE) and child self-regulation via maternal harshness and language development was examined. Specifically, the model tested whether PCE was associated with self-regulation either directly or indirectly via high maternal harshness and poor language development. The role of child sex, autonomic reactivity, and

cumulative environmental risk as potential moderators was also explored. The sample was 216 mother-child dyads recruited at birth and assessed at 2, 7, 13, 24, 36, and 48 months of child ages. Participating mothers were primarily African American (72%). Results indicated a significant indirect association between PCE and child effortful control at 36 months via higher maternal harshness. Autonomic reactivity moderated the association between maternal harshness and self-regulation such that among children with poor autonomic reactivity, high maternal harshness was associated with lower conscience at 3 years. Child sex and environmental risk did not moderate the association between PCE and self-regulation. Thus, the quality of caregiving experience played a significant role in the development of self-regulation among PCE children, especially those at higher autonomic risk. In particular, PCE children who also exhibit poor autonomic reactivity may be particularly susceptible to environmental influences such as parenting.

Assertive Communication In Condom Negotiation: Insights From Late Adolescent Couples' Subjective Ratings Of Self and Partner Schmid A, Leonard NR, Ritchie AS, Gwadz MV. J Adolesc Health. 2015; 57(1): 94-99.
Assertive communication has been associated with higher levels of condom use among youth using self-report survey methodology. The purpose of this study was to examine the subjective ratings of assertiveness among young, romantically involved couples in the context of a condom negotiation task. Using an innovative video-recall procedure, 32 couples (64 youth) engaged in a videotaped condom negotiation task and then rated self and partners' level of assertiveness. Both individual ratings of assertiveness and couple-level assertiveness were assessed using dyadic hierarchical linear modeling. Individuals' assertiveness was positively associated with condom use. Unexpectedly, the overall level of assertiveness in couples showed a curvilinear association with condom use. Very high and very low assertiveness was associated with lower condom use, whereas moderate levels of assertiveness were associated with higher condom use. Moderate levels of assertiveness during condom negotiation may facilitate condom use in young couples. Increasing condom use among romantic partners may require developing interventions that strengthen youths' ability to engage in assertive communication strategies that balance emotional intimacy with self-advocacy.

Neuropsychological Performance In Adolescent Marijuana Users With Co-Occurring Alcohol Use: A Three-Year Longitudinal Study Jacobus J, Squeglia LM, Infante MA, Castro N, Brumback T, Meruelo AD, Tapert SF. Neuropsychology. 2015.
The effect of adolescent marijuana use on brain development remains unclear despite relaxing legal restrictions, decreased perceived harm, and increasing use rates among youth. The aim of this 3-year prospective study was to evaluate the long-term neurocognitive effects of adolescent marijuana use. Adolescent marijuana users with concomitant alcohol use (MJ + ALC, n = 49) and control teens with limited substance use histories (CON, n = 59) were given neuropsychological and substance use assessments at project baseline, when they were ages 16-19. They were then reassessed 18 and 36 months later. Changes in neuropsychological measures were evaluated with repeated measures analysis of covariance (ANCOVA), controlling for lifetime alcohol use, and examined the effects of group, time, and group by time interactions on cognitive functioning. MJ + ALC users performed significantly worse than controls, across time points, in the domains of complex attention, memory, processing speed, and visuospatial functioning (ps <.05). Earlier age of marijuana use onset was associated with poorer processing speed and executive functioning by the 3-year follow-up (ps ≤. .02).Frequent marijuana use throughout adolescence and into young adulthood appeared linked to worsened cognitive performance. Earlier age of onset appears to be

associated with poorer neurocognitive outcomes that emerge by young adulthood, providing further support for the notion that the brain may be uniquely sensitive to frequent marijuana exposure during the adolescent phase of neurodevelopment. Continued follow-up of adolescent marijuana users will determine the extent of neural recovery that may occur if use abates.

Plasticity Of Risky Decision Making Among Maltreated Adolescents: Evidence From A Randomized Controlled Trial Weller JA, Leve LD, Kim HK, Bhimji J, Fisher PA. Dev Psychopathol. 2015; 27(2): 535-551.
Childhood maltreatment has lasting negative effects throughout the life span. Early intervention research has demonstrated that these effects can be remediated through skill-based, family-centered interventions. However, less is known about plasticity during adolescence, and whether interventions are effective many years after children experience maltreatment. This study investigated this question by examining adolescent girls' ability to make advantageous decisions in the face of risk using a validated decision-making task; performance on this task has been associated with key neural regions involved in affective processing and executive functioning. Maltreated foster girls (n = 92), randomly assigned at age 11 to either an intervention designed to prevent risk-taking behaviors or services as usual (SAU), and nonmaltreated age and socioeconomic status matched girls living with their biological parent(s) (n = 80) completed a decision-making task (at age 15-17) that assessed risk taking and sensitivity to expected value, an index of advantageous decision making. Girls in the SAU condition demonstrated the greatest decision-making difficulties, primarily for risks to avoid losses. In the SAU group, frequency of neglect was related to greater difficulties in this area. Girls in the intervention condition with less neglect performed similarly to nonmaltreated peers. This research suggests that early maltreatment may impact decision-making abilities into adolescence and that enriched environments during early adolescence provide a window of plasticity that may ameliorate these negative effects.

Dose-response Relationship Between Methadone Dose and Adherence To Antiretroviral Therapy Among HIV-positive People Who Use Illicit Opioids Lappalainen L, Nolan S, Dobrer S, Puscas C, Montaner J, Ahamad K, Dong H, Kerr T, Wood E, Milloy M-J. Addiction. 2015; 110(8): 1330-1339.
For HIV-positive individuals who use illicit opioids, engagement in methadone maintenance therapy (MMT) can contribute to improved HIV treatment outcomes. However, to the authors' knowledge, the role of methadone dosing in adherence to antiretroviral therapy (ART) has not yet been investigated. The authors sought to examine the relationship between methadone dose and ART adherence among a cohort of people who use illicit opioids. They used data from the AIDS Care Cohort to Evaluate Access to Survival Services (ACCESS) study, an ongoing prospective observational cohort of HIV-positive people who use illicit drugs in Vancouver, Canada, linked confidentially to comprehensive HIV treatment data in a setting of universal no-cost medical care, including medications. The authors evaluated the longitudinal relationship between methadone dose and the likelihood of 95% adherence to ART among ART-exposed participants during periods of engagement in MMT. Two hundred and ninety-seven ART-exposed individuals on MMT were recruited between December 2005 and May 2013 and followed for a median of 42.1months. The authors measured methadone dose at ≥ 100 versus < 100 mg/day and the likelihood of ≥ 95% adherence to ART. In adjusted generalized estimating equation (GEE) analyses, MMT dose ≥ 100 mg/day was associated independently with optimal adherence to ART [adjusted odds ratio (AOR) = 1.38; 95% confidence interval (CI) = 1.08-1.77). In a subanalysis, the authors observed a dose-response relationship between increasing MMT dose and ART adherence (AOR=1.06 per 20

mg/day increase, 95% CI =1.00-1.12).Among HIV-positive individuals in methadone maintenance therapy, those receiving higher doses of methadone (≥100 mg/day) are more likely to achieve ≥ 95% adherence to antiretroviral therapy than those receiving lower doses.

Depression Among People Who Inject Drugs and Their Intimate Partners In Kazakhstan
Shaw SA, El-Bassel N, Gilbert L, Terlikbayeva A, Hunt T, Primbetova S, Rozental Y, Chang M. Community Ment Health J. 2015.
This paper examines individual, social, and structural factors associated with depression among 728 people who inject drugs (PWID) and their intimate partners in Kazakhstan, with separate multivariate models by gender. Depression scores were higher on average among participants of both genders who recently experienced sexual intimate partner violence, food insecurity, and who had lower levels of self-rated health. Among females, higher depression scores were associated with experiencing childhood sexual abuse, lower levels of social support, and not having children. Findings highlight a need to incorporate gender differences and factors associated with depression in designing mental health services for PWID in Kazakhstan.

Prediction Of Daily Food Intake As A Function Of Measurement Modality and Restriction Status Giuliani NR, Tomiyama AJ, Mann T, Berkman ET. Psychosom Med. 2015; 77(5): 583-590.
Research on eating relies on various indices (e.g., stable, momentary, neural) to accurately reflect food-related reactivity (e.g., disinhibition) and regulation (e.g., restraint) outside the laboratory. The degree to which they differentially predict real-world consumption remains unclear. Further, the predictive validity of these indices might vary depending on whether an individual is actively restricting intake. The authors assessed food craving reactivity and regulation in 46 healthy participants (30 women, 18-30 years) using standard measurements in three modalities: a) self-reported (stable) traits using surveys popular in the eating literature, and b) momentary craving ratings and c) neural activation using aggregated functional magnetic resonance imaging data gathered during a food reactivity-and-regulation task. The authors then used these data to predict variance in real-world consumption of craved energy-dense "target" foods across 2 weeks among normal-weight participants randomly assigned to restrict or monitor target food intake. The predictive validity of four indices varied significantly by restriction. When participants were not restricting intake, momentary (B = 0.21, standard error [SE] = 0.05) and neural (B = 0.08, SE = 0.04) reactivity positively predicted consumption, and stable (B = -0.22, SE = 0.05) and momentary (B = -0.24, SE = 0.05) regulation negatively predicted consumption. When restricting, stable (B = 0.36, SE = 0.12) and neural (B = 0.51, SE = 0.12) regulation positively predicted consumption. Commonly-used indices of regulation and reactivity differentially relate to an ecologically-valid eating measurement, depending on the presence of restriction goals, and thus have strong implications for predicting real-world behaviors.

How Does Reactivity To Frustrative Non-reward Increase Risk For Externalizing Symptoms?
Gatzke-Kopp LM, Willner CJ, Jetha MK, Abenavoli RM, DuPuis D, Segalowitz SJ. Int J Psychophysiol. 2015.
Frustration is a normative affective response with an adaptive value in motivating behavior. However, excessive anger in response to frustration characterizes multiple forms of externalizing psychopathology. How a given trait subserves both normative and pathological behavioral profiles is not entirely clear. One hypothesis is that the magnitude of response to frustration differentiates normative versus maladaptive reactivity. Disproportionate increases in arousal in response to frustration may exceed normal regulatory capacity, thus precipitating aggressive or antisocial

responses. Alternatively, pathology may arise when reactivity to frustration interferes with other cognitive systems, impairing the individual's ability to respond to frustration adaptively. In this paper the authors examine these two hypotheses in a sample of kindergarten children. First they examine whether children with conduct problems (CP; n=105) are differentiated from comparison children (n=135) with regard to magnitude of autonomic reactivity (cardiac and electrodermal) across a task that includes a frustrative non-reward block flanked by two reward blocks. Second they examine whether cognitive processing, as reflected by magnitude of the P3b brain response, is disrupted in the context of frustrative non-reward. Results indicate no differences in skin conductance, but a greater increase in heart rate during the frustration block among children in the CP group. Additionally, the CP group was characterized by a pronounced decrement in P3b amplitude during the frustration condition compared with both reward conditions. No interaction between cardiac and P3b measures was observed, suggesting that each system independently reflects a greater sensitivity to frustration in association with externalizing symptom severity.

Brain Development In Heavy-drinking Adolescents Squeglia LM, Tapert SF, Sullivan EV, Jacobus J, Meloy MJ, Rohlfing T, Pfefferbaum A. Am J Psychiatry. 2015; 172(6): 531-542.
Heavy alcohol use during adolescence may alter the trajectory of normal brain development. The authors measured within-subject changes in regional brain morphometry over longer intervals and in larger samples of adolescents than previously reported and assessed differences between adolescents who remained nondrinkers and those who drank heavily during adolescence as well as differences between the sexes. The authors examined gray and white matter volume trajectories in 134 adolescents, of whom 75 transitioned to heavy drinking and 59 remained light drinkers or nondrinkers over roughly 3.5 years. Each underwent MRI scanning two to six times between ages 12 and 24 and was followed for up to 8 years. The volumes of the neocortex, allocortex, and white matter structures were measured using atlas-based parcellation with longitudinal registration. Linear mixed-effects models described differences in trajectories of heavy drinkers and nondrinkers over age; secondary analyses considered the contribution of other drug use to identified alcohol use effects. Heavy-drinking adolescents showed accelerated gray matter reduction in cortical lateral frontal and temporal volumes and attenuated white matter growth of the corpus callosum and pons relative to nondrinkers. These results were largely unchanged when use of marijuana and other drugs was examined. Male and female drinkers showed similar patterns of development trajectory abnormalities. Longitudinal analysis enabled detection of accelerated typical volume decline in frontal and temporal cortical volumes and attenuated growth in principal white matter structures in adolescents who started to drink heavily. These results provide a call for caution regarding heavy alcohol use during adolescence, whether heavy drinking is the sole cause or one of several in these alterations in brain development.

The Causal Effect Of Opioid Substitution Treatment On HAART Medication Refill Adherence Nosyk B, Min JE, Colley G, Lima VD, Yip B, Milloy M-J S, Wood E, Montaner JSG. AIDS. 2015; 29(8): 965-973.
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). They 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 the authors controlled for a range of fixed and time-varying covariates. Their 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.

An Effective Tool For Identifying HIV-1 Subtypes B, C, CRF01_AE, Their Recombinant Forms, and Dual Infections In Southeast Asia By The Multi-region Subtype Specific PCR (MSSP) Assay Sakkhachornphop S, Kijak GH, Beyrer C, Razak MH, Sanders-Buell E, Jittiwutikarn J, Suriyanon V, Robb ML, Kim JH, Celentano DD, McCutchan FE, Tovanabutra S. J Virol Methods. 2015; 217: 70-78.
The RV144 Thai vaccine trial has been the only vaccine study to show efficacy in preventing HIV infection. Ongoing molecular surveillance of HIV-1 in Southeast Asia is vital for vaccine development and evaluation. In this study a novel tool, the multi-region subtype specific PCR (MSSP) assay, that was able to identify subtypes B, C, CRF01_AE for Thailand, other Southeast Asian countries, India and China is described. The MSSP assay is based on a nested PCR strategy and amplifies eight short regions distributed along the HIV-1 genome using subtype-specific primers. A panel of 41 clinical DNA samples obtained primarily from opiate users in northern Thailand was used to test the assay performance. The MSSP assay provided 73-100% sensitivity and 100% specificity for the three subtypes in each genome region. The assay was then field-tested on 337 sera from HIV infected northern Thai drug users collected between 1999 and 2002. Subtype distribution was CRF01_AE 77.4% (n=261), subtype B 3.3% (n=11), CRF01_AE/B recombinant 12.2% (n=41), CRF01_AE/C recombinant 0.6% (n=2), and non-typeable 6.5% (n=22). The MSSP assay is a simple, cost-effective, and accurate genotyping tool for laboratory settings with limited resources and is sensitive enough to capture the recombinant genomes and dual infections.

Methamphetamine Injecting Is Associated With Phylogenetic Clustering Of Hepatitis C Virus Infection Among Street-involved Youth In Vancouver, Canada Cunningham EB, Jacka B, DeBeck K, Applegate TL, Harrigan PR, Krajden M, Marshall BDL, Montaner J, Lima VD, Olmstead AD, Milloy M-J, Wood E, Grebely J. Drug Alcohol Depend. 2015; 152: 272-276.
Among prospective cohorts of people who inject drugs (PWID), phylogenetic clustering of HCV infection has been observed. However, the majority of studies have included older PWID, representing distant transmission events. The aim of this study was to investigate phylogenetic clustering of HCV infection among a cohort of street-involved youth. Data were derived from a prospective cohort of street-involved youth aged 14-26 recruited between 2005 and 2012 in Vancouver, Canada (At Risk Youth Study, ARYS). HCV RNA testing and sequencing (Core-E2) were performed on HCV positive participants. Phylogenetic trees were inferred using maximum likelihood methods and clusters were identified using ClusterPicker (Core-E2 without HVR1, 90% bootstrap threshold, 0.05 genetic distance threshold). Among 945 individuals enrolled in ARYS, 16% (n=149, 100% recent injectors) were HCV antibody positive at baseline interview (n=86) or

seroconverted during follow-up (n=63). Among HCV antibody positive participants with available samples (n=131), 75% (n=98) had detectable HCV RNA and 66% (n=65, mean age 23, 58% with recent methamphetamine injection, 31% female, 3% HIV+) had available Core-E2 sequences. Of those with Core-E2 sequence, 14% (n=9) were in a cluster (one cluster of three) or pair (two pairs), with all reporting recent methamphetamine injection. Recent methamphetamine injection was associated with membership in a cluster or pair (P=0.009). In this study of street-involved youth with HCV infection and recent injecting, 14% demonstrated phylogenetic clustering. Phylogenetic clustering was associated with recent methamphetamine injection, suggesting that methamphetamine drug injection may play an important role in networks of HCV transmission.

Further Validation Of A Marijuana Purchase Task Aston ER, Metrik J, MacKillop J. Drug Alcohol Depend. 2015; 152: 32-38.
A valid measure of the relative economic value of marijuana is needed to characterize individual variation in the drugs' reinforcing value and inform evolving national marijuana policy. Relative drug value (demand) can be measured via purchase tasks, and demand for alcohol and cigarettes has been associated with craving, dependence, and treatment response. This study examined marijuana demand with a marijuana purchase task (MPT). The 22-item self-report MPT was administered to 99 frequent marijuana users (37.4% female, 71.5% marijuana use days, 15.2% cannabis dependent). Pearson correlations indicated a negative relationship between intensity (free consumption) and age of initiation of regular use ($r=-0.34$, $p<0.001$), and positive associations with use days ($r=0.26$, $p<0.05$) and subjective craving ($r=0.43$, $p<0.001$). Omax (maximum expenditure) was positively associated with use days ($r=0.29$, $p<0.01$) and subjective craving ($r=0.27$, $p<0.01$). Income was not associated with demand. An exponential demand model provided an excellent fit to the data across users ($R(2)=0.99$). Group comparisons based on presence or absence of DSM-IV cannabis dependence symptoms revealed that users with any dependence symptoms showed significantly higher intensity of demand and more inelastic demand, reflecting greater insensitivity to price increases. These results provide support for construct validity of the MPT, indicating its sensitivity to marijuana demand as a function of increasing cost, and its ability to differentiate between users with and without dependence symptoms. The MPT may denote abuse liability and is a valuable addition to the behavioral economic literature. Potential applications to marijuana pricing and tax policy are discussed.

Love On Lockdown: How Social Network Characteristics Predict Separational Concurrency Among Low Income African-American Women King KM, Latkin CA, Davey-Rothwell MA. J Urban Health. 2015; 92(3): 460-471.
One out of nine African-American men between the ages of 20 and 34 is behind bars, resulting in many African-American women losing their primary romantic partners to incarceration. Research suggests that partner incarceration may contribute to increased risk of sexually transmitted infections (STIs)/human immunodeficiency virus (HIV); however, factors associated with women decisions to begin new sexual partnerships following partner incarceration (i.e., separational concurrency) have not been well studied. This study examined the social context relevant to initiating separational concurrency, following incarceration of a primary male partner. Cross-sectional secondary data analysis of 6-month follow-up data from the CHAT Project, a social-network based HIV/sexually transmitted disease (STD) prevention study in Baltimore, MD, USA. Participants were N =196 African-American women, who reported ever having had a partner who was incarcerated for at least 6 months during the relationship. The majority (81.5%) of women were unemployed with a mean age of 41.7 years. Over half of the sample (59.5%) reported having used

crack or heroin at least once in the previous 12 months; 48.5% of the women had experienced physical abuse, with over half of the sample reporting a lifetime history of emotional abuse (54.6%). Separational concurrency, defined as answering yes to the item, "While [your] partner was incarcerated, did you have any other sexual partners?" was the primary outcome measure. After adjusting for age, drug use and unemployment the multiple logistic regression model found that women who reported a history of physical or emotional abuse were over two times as likely to report separational concurrency than women without an abuse history [adjusted odds ratio (AOR), 2.24; 95% CI, 1.24, 4.05; p =.007 and AOR, 2.44; 95% CI, 1.33, 4.46; p =.004, respectively]. Individuals who reported a higher number of drug-using sex partners (AOR, 2.49; 95% CI, 1.4, 4.5; p = .002), sex exchange partners (AOR, 4.0; 95% CI, 1.8 8.9; p =.001), and sexual partners who engaged in concurrency (AOR: 2.67; 95% CI: 1.5, 4.8; p = .001) were significantly more likely to report separational concurrency. Conversely, participants who reported more female kin in their social networks (AOR, .808; 95% CI, .67, .97; p =.025), having known network members a longer time (AOR, .997; 95% CI, .993, .999; p =.043), and higher levels of trust for network members (AOR, .761; 95% CI, .63, .92; p =.005) were significantly less likely to report separational concurrency. Results of this study demonstrate that social network characteristics may be crucial to understanding separational concurrency among African-American urban women who have lost a partner to incarceration. Social network and other resource-based interventions, which provide instrumental, social, and economic resources to women who have experienced the loss of a partner to incarceration, may be important tools in empowering women and helping to reduce the disproportionate burden of STIs/HIV among low income, African-American women.

Fearfulness Moderates the Link Between Childhood Social Withdrawal and Adolescent Reward Response Morgan JK, Shaw DS, Forbes EE. Soc Cogn Affect Neurosci. 2015; 10(6): 761-768.
Withdrawal from peers during childhood may reflect disruptions in reward functioning that heighten vulnerability to affective disorders during adolescence. The association between socially withdrawn behavior and reward functioning may depend on traits that influence this withdrawal, such as fearfulness or unsociability. In a study of 129 boys, the authors evaluated how boys' fearfulness and sociability at age 5 and social withdrawal at school at ages 6 to 10 and during a summer camp at age 9/10 were associated with their neural response to reward at age 20. Greater social withdrawal during childhood was associated with heightened striatal and mPFC activation when anticipating rewards at age 20. Fearfulness moderated this effect to indicate that social withdrawal was associated with heightened reward-related response in the striatum for boys high on fearfulness. Altered striatal response associated with social withdrawal and fearfulness predicted greater likelihood to have a lifetime history of depression and social phobia at age 20. These findings add greater specificity to previous findings that children high in traits related to fear of novelty show altered reward responses, by identifying fearfulness (but not low levels of sociability) as a potential underlying mechanism that contributes to reward alterations in withdrawn children.

Women Who Use Or Inject Drugs: An Action Agenda For Women-Specific, Multilevel, and Combination HIV Prevention and Research El-Bassel N, Strathdee SA. J Acquir Immune Defic Syndr. 2015; 69 Suppl 2: S182-190.
Women account for more than half of all individuals living with HIV globally. Despite increasing drug and HIV epidemics among women, women who use drugs are rarely found in research, harm reduction programs, or drug and HIV treatment and care. Women who use drugs continue to face challenges that increase their vulnerability to HIV and other comorbidities because of high rates of

gender-based violence, human rights violations, incarceration, and institutional and societal stigmatization. This special issue emphasizes how the burdens of HIV, drug use, and their co-occurring epidemics affect women in a global context. Articles included focus on the epidemiologies of HIV and hepatitis C virus and other comorbidities; HIV treatment, prevention, and care; and policies affecting the lives of women who use drugs. This issue also highlights the state of the science of biomedical and behavioral research related to women who use drugs. The final article highlights the major findings of articles covered and presents a call to action regarding needed research, treatment, and preventive services for women who use drugs. To address these needs, the authors advocate for women-specific thinking and approaches that consider the social, micro, and macro contexts of women's lives. They present a women-specific risk environment framework that reflects the unique lives and contexts of women who use drugs and provides a call to action for intervention, prevention, and policies.

Health In the News: An Analysis Of Magazines Coverage Of Health Issues In Veterans and Military Service Organizations Jitnarin N, Poston WSC, Haddock CK, Jahnke S. Mil Med. 2015; 180(5): 539-146.
The purpose of this study was to conduct a content analysis of Veterans and Military Service Organizations (VMSOs) magazines to determine what health-related topics VMSOs target and how they inform their constituencies about health issues. Health-related topics in 288 VMSOs magazines from 21 VMSOs published in 2011 and 2012 were coded by trained raters using a standardized manual. The top three most addressed health topics were Health Services (Health care, Insurance), Disability and Disability benefits, and post-traumatic stress disorder. Topics least frequently covered were Tobacco and Smoking cessation, Illegal drugs, Alcohol, Gulf War Syndrome, and Weight and Body composition. VMSOs are concerned about the health and well-being of their members given the considerable amount of content devoted to certain health topics such as health insurance concerns, disability, and post-traumatic stress disorder. However, other health concerns that affect a considerable number of both current military personnel and veterans and cost both the Department of Veterans Affairs and the Department of Defense millions annually, such as drug and alcohol problems, and tobacco use and smoking cessation, are infrequently covered. The results of this study improve our understanding of the health-related information that reaches the military and veteran populations through this important media outlet.

Differential Risk For Late Adolescent Conduct Problems and Mood Dysregulation Among Children With Early Externalizing Behavior Problems Okado Y, Bierman KL. J Abnorm Child Psychol. 2015; 43(4): 735-747.
To investigate the differential emergence of antisocial behaviors and mood dysregulation among children with externalizing problems, the present study prospectively followed 317 high-risk children with early externalizing problems from school entry (ages 5-7) to late adolescence (ages 17-19). Latent class analysis conducted on their conduct and mood symptoms in late adolescence revealed three distinct patterns of symptoms, characterized by: 1) criminal offenses, conduct disorder symptoms, and elevated anger ("conduct problems"), 2) elevated anger, dysphoric mood, and suicidal ideation ("mood dysregulation"), and 3) low levels of severe conduct and mood symptoms. A diathesis-stress model predicting the first two outcomes was tested. Elevated overt aggression at school entry uniquely predicted conduct problems in late adolescence, whereas elevated emotion dysregulation at school entry uniquely predicted mood dysregulation in late adolescence. Experiences of low parental warmth and peer rejection in middle childhood moderated the link between early emotion dysregulation and later mood dysregulation but did not moderate the

link between early overt aggression and later conduct problems. Thus, among children with early externalizing behavior problems, increased risk for later antisocial behavior or mood dysfunction may be identifiable in early childhood based on levels of overt aggression and emotion dysregulation. For children with early emotion dysregulation, however, increased risk for mood dysregulation characterized by anger, dysphoric mood, and suicidality--possibly indicative of disruptive mood dysregulation disorder--emerges only in the presence of low parental warmth and/or peer rejection during middle childhood.

Ecodevelopmental Predictors Of Early Initiation Of Alcohol, Tobacco, and Drug Use Among Hispanic Adolescents Bacio GA, Estrada Y, Huang S, MartÃnez M, Sardinas K, Prado G. J Sch Psychol. 2015; 53(3): 195-208.
The purpose of this cross-sectional study was to test the transactional relationships of risk and protective factors that influence initiation of alcohol, tobacco, and drug use among Hispanic youth. Ecodevelopmental theory was used to identify factors at multiple ecological levels with a focus on four school-level characteristics (i.e. school socioeconomic status, school climate, school acculturation, and school ethnic composition). A sample of 741 Hispanic adolescents (M age=13.9, SD=.67) and their caregivers were recruited from 18 participating middle schools in Miami-Dade County, FL. Structural equation modeling was used to test the hypothesized ecodevelopmental model of early substance use, accounting for school clustering effects. Results provided strong support for the model (CFI=.95; RMSEA=.03). School SES was indirectly related to the likelihood of starting substance use through perceived peer use norms (β=.03, p<.02). Similarly, school climate had an indirect effect on substance use initiation through family functioning and perceptions of peer use norms (β =-.03, p<.01). Neither school ethnic composition nor school acculturation had indirect effects on initiation of substance use. Results highlight the importance of the interplay of risk and protective factors at multiple ecological levels that impact early substance use initiation. Further, findings underscore the key role of school level characteristics on the initiation of substance use and present opportunities for intervention.

An Adolescent Substance Prevention Model Blocks The Effect Of CHRNA5 Genotype On Smoking During High School Vandenbergh DJ, Schlomer GL, Cleveland HH, Schink AE, Hair KL, Feinberg ME, Neiderhiser JM, Greenberg MT, Spoth RL, Redmond C. Nicotine Tob Res. 2015.
Prevention intervention programs reduce substance use, including smoking, but not all individuals respond. The authors tested whether response to a substance use prevention/intervention program varies based upon a set of five markers (rs16969968, rs1948, rs578776, rs588765, and rs684513) within the cluster of nicotinic acetylcholine receptor subunit genes (CHRNA5/A3/B4). Participants (N = 424) were randomly assigned to either control condition, or a family-based intervention in grade 6 and a school-based drug preventive intervention in grade 7. Smoking in the past month was assessed in grades 9-12 using a four-point scale (0 = never smoked, 1 = smoked but not in last month, 2 = one or a few times, 3 = about once a week or more). There was a main effect of both the intervention (b = -0.24, P < .05) and genotype at rs16969968 (b = 0.14, P < .05) on high school smoking. Using dummy coding to allow for nonlinear effects, individuals with the A/A genotype smoked more often than those with G/G (b = 0.33, P < .05). A genotype — intervention effect was found with reduced smoking among those with A/A and G/A genotypes to levels similar to those with the G/G genotype (G/G vs. A/A: b = -0.67, P < .05; A/G vs. A/A: b = -0.61, P < .05; G/G vs. A/G ns). Results were nonsignificant for the other four markers. Preventive interventions can reduce the genetic risk for smoking from rs16969968.

The Evidence Does Not Speak For Itself: The Role Of Research Evidence In Shaping Policy Change For the Implementation Of Publicly Funded Syringe Exchange Programs In Three US Cities Allen ST, Ruiz MS, O'Rourke A. Int J Drug Policy. 2015; 26(7): 688-695.
A breadth of literature exists that explores the utilization of research evidence in policy change processes. From this work, a number of studies suggest research evidence is applied to change processes by policy change stakeholders primarily through instrumental, conceptual, and/or symbolic applications, or is not used at all. Despite the expansiveness of research on policy change processes, a deficit exists in understanding the role of research evidence during change processes related to the implementation of structural interventions for HIV prevention among injection drug users (IDU). This study examined the role of research evidence in policy change processes for the implementation of publicly funded syringe exchange services in three US cities: Baltimore, MD, Philadelphia, PA, and Washington, DC. In-depth qualitative interviews were conducted with key stakeholders (n=29) from each of the study cities. Stakeholders were asked about the historical, social, political, and scientific contexts in their city during the policy change process. Interviews were transcribed and analyzed for common themes pertaining to applications of research evidence. In Baltimore and Philadelphia, the typological approaches (instrumental and symbolic/conceptual, respectively) to the applications of research evidence used by harm reduction proponents contributed to the momentum for securing policy change for the implementation of syringe exchange services. Applications of research evidence were less successful in DC because policymakers had differing ideas about the implications of syringe exchange program implementation and because opponents of policy change used evidence incorrectly or not at all in policy change discussions. Typological applications of research evidence are useful for understanding policy change processes, but their efficacy falls short when sociopolitical factors complicate legislative processes. Advocates for harm reduction may benefit from understanding how to effectively integrate research evidence into policy change processes in ways that confront the myriad of factors that influence policy change.

Evaluation Of Internal Validity Using Modern Test Theory: Application To Word Association Shono Y, Ames SL, Stacy AW. Psychol Assess. 2015.
Word association tests (WATs) have been widely used to examine associative/semantic memory structures and shown to be relevant to behavior and its underpinnings. Despite successful applications of WATs in diverse research areas, few studies have examined psychometric properties of these tests or other open-ended cognitive tests of common use. Modern test theory models, such as item response theory (IRT) models, are well suited to evaluate interpretations of this class of test. In this evaluation, unidimensional IRT models were fitted to the data on the WAT designed to capture associative memory relevant to an important applied issue: casual sex in a sample of 1,138 adult drug offenders. Using association instructions, participants were instructed to generate the first behavior or action that came to mind in response to cues (e.g., "hotel/motel") that might elicit casual sex-related responses. Results indicate a multitude of evidence for the internal validity of WAT score interpretations. All WAT items measured a single latent trait of casual sex-related associative memory, strongly related to the latent trait, and were invariant across gender, ethnicity, age groups, and sex partner profiles. The WAT was highly informative at average-to-high levels of the latent trait and also associated with risky sex behavior, demonstrating the usefulness of this class of test. The study illustrates the utility of the assessments in this at-risk population as well as the benefits of application of the modern test theory models in the evaluation of internal validity of open-ended cognitive test score interpretation.

Health-risk Behaviors In Teens Investigated By U.S. Child Welfare Agencies Heneghan A, Stein REK, Hurlburt MS, Zhang J, Rolls-Reutz J, Kerker BD, Landsverk J, Horwitz SM. J Adolesc Health. 2015; 56(5): 508-514.
The aim of this study was to examine prevalence and correlates of health-risk behaviors in 12- to 17.5-year-olds investigated by child welfare and compare risk-taking over time and with a national school-based sample. Data from the National Survey of Child and Adolescent Well-Being (NSCAW II) were analyzed to examine substance use, sexual activity, conduct behaviors, and suicidality. In a weighted sample of 815 adolescents' aged 12-17.5 years, prevalence and correlates for each health-risk behavior were calculated using bivariate analyses. Comparisons to data from NSCAW I and the Youth Risk Behavior Survey were made for each health-risk behavior. Overall, 65.6% of teens reported at least one health-risk behavior with significantly more teens in the 15- to 17.5-year age group reporting such behaviors (81.2% vs. 54.4%; $p \leq .001$). Almost 75% of teens with a prior out-of-home placement and 77% of teens with child behavior checklist scores ≥ 64 reported at least one health-risk behavior. The prevalence of smoking was lower than in NSCAW I (10.5% vs. 23.2%; $p \leq .05$) as was that of sexual activity (18.0% vs. 28.8%; $p \leq .05$). Prevalence of health-risk behaviors was lower among older teens in the NSCAW II sample ($n = 358$) compared with those of the 2011 Youth Risk Behavior Surveillance System high school-based sample with the exception of suicidality, which was approximately 1.5 times higher (11.3% [95% confidence interval, 6.5-19.0] vs. 7.8% [95% confidence interval, 7.1-8.5]). Health-risk behaviors in this population of vulnerable teens are highly prevalent. Early efforts for screening and interventions should be part of routine child welfare services monitoring.

Incidence and Predictors Of HIV and Sexually Transmitted Infections Among Female Sex Workers and Their Intimate Male Partners In Northern Mexico: A Longitudinal, Multilevel Study Bazzi AR, Rangel G, Martinez G, Ulibarri MD, Syvertsen JL, Bazzi SA, Roesch S, Pines HA, Strathdee SA. Am J Epidemiol. 2015; 181(9): 723-731.
Preventing human immunodeficiency virus (HIV) infection and other sexually transmitted infections (STIs) requires an understanding of sexual relationship factors beyond the individual level. The authors estimated HIV/STI incidence and identified time-varying predictors of STI acquisition in a prospective cohort study of female sex workers and their intimate (noncommercial) male partners in northern Mexico. From 2010 to 2013, couples underwent behavioral and biological assessments biannually for 24 months. Among 413 initially HIV-uninfected participants, 8 seroconverted during follow-up. Incidence of HIV (1.12 cases/100 person-years (PY)), chlamydia (9.47 cases/100 PY), active syphilis (4.01 cases/100 PY), and gonorrhea (1.78 cases/100 PY) was higher among women than among men (HIV: $P = 0.069$; all STIs combined: $P < 0.001$). In multivariable conditional logistic regression with individual fixed effects and correlated error terms within couples, risk of STI acquisition was significantly higher among women who had recently used cocaine, crack, or methamphetamine (adjusted odds ratio (OR) = 2.13, 95% confidence interval (CI): 1.07, 4.28). STI risk was lower among women who reported physically assaulting their male partners (adjusted OR = 0.44, 95% CI: 0.22, 0.86) and among men whose female partners had regular sex-work clients (adjusted OR = 0.38, 95% CI: 0.14, 1.03). Improving vulnerable couples' sexual health will require addressing the contexts in which drug use, interpersonal conflict, and economic vulnerability converge.

Mixed Picture Of Readiness For Adoption Of Evidence-based Prevention Programs In Communities: Exploratory Surveys Of State Program Delivery Systems Spoth R, Schainker LM, Redmond C, Ralston E, Yeh H-C, Perkins DF. Am J Community Psychol. 2015; 55(3-4): 253-265.
An emerging literature highlights the potential for broader dissemination of evidence-based prevention programs in communities through existing state systems, such as the land grant university Extension outreach system and departments of public education and health (DOE-DPH). This exploratory study entailed surveying representatives of the national Extension system and DOE-DPH, to evaluate dissemination readiness factors, as part of a larger project on an evidence-based program delivery model called PROSPER. In addition to assessing systems' readiness factors, differences among US regions and comparative levels of readiness between state systems were evaluated. The Extension web-based survey sample N was 958 and the DOE-DPH telephone survey N was 338, with response rates of 23 and 79 %, respectively. Extension survey results suggested only a moderate level of overall readiness nationally, with relatively higher perceived need for collaborative efforts and relatively lower perceived resource availability. There were significant regional differences on all factors, generally favoring the Northeast. Results from DOE-DPH surveys showed significantly higher levels for all readiness factors, compared with Extension systems. Overall, the findings present a mixed picture. Although there were clear challenges related to measuring readiness in complex systems, addressing currently limited dissemination resources, and devising strategies for optimizing readiness, all systems showed some readiness-related strengths.

Reducing HIV Risks In the Places Where People Drink: Prevention Interventions In Alcohol Venues Pitpitan EV, Kalichman SC. AIDS Behav. 2015.
Apart from individual alcohol drinking behavior, the context or places where people drink play a significant role in HIV transmission risk. In this paper, the authors review the research that has been conducted on alcohol venues to identify the social and structural factors (e.g., social norms, sexual behavior) that are associated with HIV risk in these places, to review HIV prevention interventions based in alcohol venues, and to discuss appropriate methodologies for alcohol venue research. Alcohol venues are defined here as places that sell or serve alcohol for onsite consumption, including bars, bottle stores, nightclubs, wine shops, and informal shebeens. Despite the many established HIV risk factors at play in alcohol venues, limited prevention strategies have been implemented in such places. A total of 11 HIV prevention interventions or programs were identified. HIV prevention interventions in alcohol venues may be conducted at the individual, social, or structural level. However, multilevel interventions that target more than one level appear to lead to the most sustainable behavior change. Strategies to incorporate alcohol venues in biomedical prevention strategies including antiretroviral therapy for alcohol users are also discussed.

Gender-Specific HIV Prevention Interventions For Women Who Use Alcohol and Other Drugs: The Evolution Of the Science and Future Directions Wechsberg WM, Deren S, Myers B, Kirtadze I, Zule WA, Howard B, El-Bassel N. J Acquir Immune Defic Syndr. 2015; 69 Suppl 2: S128-139.
The use of alcohol and other drugs (AODs) is an important driver of gender disparities in HIV prevalence. Consequently, there is a need for women-specific HIV interventions that are conceptualized to address (1) women's risk behavior, their roles in sexual relationships, and gender power dynamics and (2) other issues commonly faced by women who use AODs, such as gender-

based violence and victimization. This article presents the evolution of HIV prevention intervention research with women who use AODs. It looks at 3 generations of women-focused HIV research interventions, including first-generation projects that started in the 1990s, second-generation efforts where projects expanded in scope and included adaptions of evidence-based interventions for global relevance, and finally third-generation projects currently underway that combine biobehavioral methods and are being implemented in real-world settings. Because women who use AODs continue to report risk behaviors related to HIV, emphasis should be placed on training scientists to conduct gender-specific studies, increasing funding for new studies, and advocating to ensure that stigma-free services are available for these at-risk women.

Effects Of Prenatal Cocaine Exposure On Early Sexual Behavior: Gender Difference In Externalizing Behavior As A Mediator Min MO, Minnes S, Lang A, Yoon S, Singer LT. Drug Alcohol Depend. 2015; 153: 59-65.
Prenatal cocaine exposure (PCE) is associated with increased risk for externalizing behavior problems; childhood externalizing behavior problems are linked with subsequent early sexual behavior. The present study examined the effects of PCE on early sexual initiation (sexual intercourse prior to age 15) and whether externalizing behavior in preadolescence mediated the relationship. Three hundred fifty-four (180 PCE and 174 non-cocaine exposed; 192 girls, 142 boys), primarily African-American, low socioeconomic status, 15-year-old adolescents participated in a prospective longitudinal study. Adolescents' sexual behavior was assessed at 15 years using the Youth Risk Behavior Surveillance System. Externalizing behavior was assessed at 12 years using the Youth Self-Report. Logistic regression models indicated that adolescents with PCE (n=69, 38%) were 2.2 times more likely (95% CI=1.2-4.1, p<.01) to engage in early sexual intercourse than non-exposed peers (n=49, 28%) controlling for covariates. This relationship was fully mediated by self-reported externalizing behavior in girls but not in boys, suggesting childhood externalizing behavior as a gender moderated mediator. Blood lead level during preschool years was also related to a greater likelihood of early sexual intercourse (OR=2.6, 95% CI=1.4-4.7, p<.002). Greater parental monitoring decreased the likelihood of early sexual intercourse, while violence exposure increased the risk. PCE is related to early sexual intercourse, and externalizing behavior problems mediate PCE effects in female adolescents. Interventions targeting externalizing behavior may reduce early sexual initiation and thereby reduce HIV risk behaviors and early, unplanned pregnancy in girls with PCE.

Risks, Outcomes, and Evidence-Based Interventions For Girls In The US Juvenile Justice System Leve LD, Chamberlain P, Kim HK. Clin Child Fam Psychol Rev. 2015; 18(3): 252-279.
The proportion of the juvenile justice population that comprises females is increasing, yet few evidence-based models have been evaluated and implemented with girls in the juvenile justice system. Although much is known about the risk and protective factors for girls who participate in serious delinquency, significant gaps in the research base hamper the development and implementation of theoretically based intervention approaches. In this review, the authors first summarize the extant empirical work about the predictors and sequelae of juvenile justice involvement for girls. Identified risk and protective factors that correspond to girls' involvement in the juvenile justice system have been shown to largely parallel those of boys, although exposure rates and magnitudes of association sometimes differ by sex. Second, the authors summarize findings from empirically validated, evidence-based interventions for juvenile justice-involved youths that have been tested with girls. The interventions include Functional Family Therapy, Multisystemic Therapy, Multidimensional Family Therapy, and Treatment Foster Care Oregon

(formerly known as Multidimensional Treatment Foster Care). The authors conclude that existing evidence-based practices appear to be effective for girls. However, few studies have been sufficiently designed to permit conclusions about whether sex-specific interventions would yield any better outcomes for girls than would interventions that already exist for both sexes and that have a strong base of evidence to support them. Third, the authors propose recommendations for feasible, cost-efficient next steps to advance the research and intervention agendas for this under-researched and underserved population of highly vulnerable youths.

Suicidal Ideation and Suicide Attempts In Five Groups With Different Severities Of Gambling: Findings From The National Epidemiologic Survey On Alcohol and Related Conditions Moghaddam JF, Yoon G, Dickerson DL, Kim SW, Westermeyer J. Am J Addict. 2015; 24(4): 292-298.

Problem and pathological gamblers show high rates of suicidal behavior. However, previous research of suicide among this population has been inconsistent. Discrepancies may stem from methodological issues, including variable use of suicide nomenclature and selection bias in study samples. Furthermore, earlier research has rarely examined gambling severity aside from problem or pathological categories. This study utilized subgroups derived from a nationally representative data set, examining different characteristics of suicidal behavior and several gambling levels, including subclinical groups. Participants included 13,578 individuals who participated in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and provided information on gambling behavior, lifetime suicidal ideation, and/or lifetime suicide attempts. Five gambling groups were derived using DSM-IV criteria for pathological gambling; non-gambling, low-risk gambling, at-risk gambling, problem gambling, and pathological gambling. Problem gambling was associated with suicidal ideation [adjusted odds ratio (AOR) =1.64, 95% confidence interval (CI) = 1.19-2.26] and suicide attempts [(AOR) = 2.42, 95% (CI) = 1.60-3.67] after adjustment for sociodemographic variables. Pathological gambling was associated with suicidal ideation [(AOR) = 2.86, 95% (CI) = 1.98-4.11] and suicide attempts [(AOR) = 2.77, 95% (CI) = 1.72-4.47) after adjustment for sociodemographic variables. Results from this population sample reinforce increased rates of suicidal behavior amongst smaller, clinical samples of problem and pathological gamblers. Education for providers about gambling is recommended, including screening for gambling-related symptoms such as suicidal behavior.

Regularly Drinking Alcohol Before Sexual Activity In A Nationally Representative Sample: Prevalence, Sociodemographics, and Associations With Psychiatric and Substance Use Disorders Eaton NR, Thompson Jr, RG, Hu M-C, Goldstein RB, Saha TD, Hasin DS. Am J Public Health. 2015; 105(7): 1387-1393.

The authors addressed regular drinking before sex and its associated risk factors. From the wave 2 National Epidemiologic Survey on Alcohol and Related Conditions, a nationally representative adult US sample (fielded 2004-2005), they determined the 12-month prevalence of regularly drinking alcohol before sexual activity. Among 17,491 sexually active drinkers, the authors determined the sociodemographic, psychiatric, and substance use correlates of regularly drinking before sex. Regular presex drinking's 12-month prevalence was 1.8%. Significant bivariate sociodemographic correlates were age, gender, race/ethnicity, education, family income, marital status, and employment status. Generalized anxiety disorder and alcohol dependence were associated with significantly increased odds of being a regular presex drinker after controlling for covariates. The authors estimate that 4.3 million American adults are regular presex drinkers. Future

research should examine this public health issue at the population level, with particular focus on pathways that link it to psychopathology.

Reality and Feasibility For Pharmacy-delivered Services For PWID In Xichang, China: Comparisons Between Pharmacy Staff and PWID Yang Y, Latkin C, Luan R, Yang C. Int J Drug Policy. 2015.
In 2010, the reported overall HIV prevalence in Liangshan China (1.14%) was 19.7 times of the overall estimated prevalence in China (0.058%), and injection drug use contributed to 60.0% of overall HIV infections in Xichang, the Capital city of Liangshan. With one national methadone clinic and three outpatient service sites, and three NEP sites, the HIV prevalence among people who inject drugs (PWID) in Xichang was estimated as 18.0% (2.8 times of national HIV prevalence among PWID) in 2012. Face-to-face questionnaire interviews were used in a cross-sectional study to assess experience, attitudes, possibility and acceptability of implementing 8 pharmacy-delivered services among PWID (n=403). The concordance of attitudes, possibility and acceptability between PWID and pharmacy staff (n=50) was examined. Rather than medical facility (23.1%), and NEP (8.9%), pharmacies were the main source of syringes for PWID in the last 12 months (82.1%), PWID (63.5%) reported syringes could be bought in single piece and at the price of $0.16 USD (59.3%). In the last 30 days, only 1 PWID brought used syringes back to a pharmacy. Pharmacy staffs' attitudes were generally negative but nearly neutral (average score -0.18), discrimination/ business concerns against pharmacy-delivered services existed, and 4 of 5 compared attitude questions between PWID and pharmacy staff were statistically different ($p<0.01$). 5 of 8 pharmacy-delivered services were available for PWID at low level (≤ 16.9%). Pharmacy staffs' supportive perception for pharmacy-delivered services focused on pharmacies' initiate roles targeting on general population more than on PWID. PWID were more supportive and optimistic than pharmacy staff toward potential usage of pharmacy-delivered services ($p<0.05$).Pharmacy-delivered services for PWID in Xichang were partly in reality, and could be feasible. It is urgently needed to address the legal requirements and remuneration for pharmacies. Pharmacy staff should receive additional training on services related knowledge and skills, cultural sensitivity toward PWID. Successful pharmacy-delivered services would benefit from identifying mutual interest and benefit between pharmacies and PWID.

Projected Outcomes Of Nurse-Family Partnership Home Visitation During 1996-2013, USA Miller TR. Prev Sci. 2015; 16(6): 765-777.
Nurse-Family Partnership (NFP) targets intensive prenatal and postnatal home visitation by registered nurses to low-income first-time mothers. Through 2013, 177,517 pregnant women enrolled in NFP programs. This article projects how NFP will affect their lives and the lives of their babies. NFP has been evaluated in six randomized trials and several more limited analyses of operational programs. The authors systematically reviewed evaluation findings on 21 outcomes and calculated effects on three more. They added outcome data from the NFP national data system and personal communications that filled outcome data gaps on some trials. The authors assumed effectiveness in replication declined by 21.8 %, proportionally with the decline in mean visits per family from trials to operational programs. By 2031, NFP program enrollments in 1996-2013 will prevent an estimated 500 infant deaths, 10,000 preterm births, 13,000 dangerous closely spaced second births, 4700 abortions, 42,000 child maltreatment incidents, 36,000 intimate partner violence incidents, 90,000 violent crimes by youth, 594,000 property and public order crimes (e.g., vandalism, loitering) by youth, 36,000 youth arrests, and 41,000 person-years of youth substance abuse. They will reduce smoking during pregnancy, pregnancy complications, childhood injuries,

and use of subsidized child care; improve language development; increase breast-feeding; and raise compliance with immunization schedules. They will eliminate the need for 4.8 million person-months of child Medicaid spending and reduce estimated spending on Medicaid, TANF, and food stamps by $3.0 billion (present values in 2010 dollars). By comparison, NFP cost roughly $1.6 billion. Thus, NFP appears to be a sound investment. It saves money while enriching the lives of participating low-income mothers and their offspring and benefiting society more broadly by reducing crime and safety net demand.

Structure Of the University Personality Inventory For Chinese College Students Zhang J, Lanza S, Zhang M, Su B. Psychol Rep. 2015; 116(3): 821-839.
The University Personality Inventory, a mental health instrument for college students, is frequently used for screening in China. However, its unidimensionality has been questioned. This study examined its dimensions to provide more information about the specific mental problems for students at risk. Four subsamples were randomly created from a sample (N = 6,110; M age = 19.1 yr.) of students at a university in China. Principal component analysis with Promax rotation was applied on the first two subsamples to explore dimension of the inventory. Confirmatory factor analysis was conducted on the third subsample to verify the exploratory dimensions. Finally, the identified factors were compared to the Symptom Checklist-90 (SCL-90) to support validity, and sex differences were examined, based on the fourth subsample. Five factors were identified: Physical Symptoms, Cognitive Symptoms, Emotional Vulnerability, Social Avoidance, and Interpersonal Sensitivity, accounting for 60.3% of the variance. All the five factors were significantly correlated with the SCL-90. Women scored significantly higher than men on Cognitive Symptoms and Interpersonal Sensitivity.

Coalition Formation To Address Structural Determinants Of Methamphetamine Use In Thailand Willard N, Srirojn B, Thomson N, Aramrattana A, Sherman S, Galai N, Celentano DD, Ellen JM. Health Promot Int. 2015; 30(3): 782-792.
Despite two recent government-sponsored wars on drugs', methamphetamine use continues to be a pervasive problem in Thailand. Out of concern for reported human rights abuses, there has been a call from the international community to take a different approach from the government zero tolerance. This paper describes the adaptation of the Connect to Protect® coalition formation process from urban U.S. cities to three districts in northern Thailand's Chiang Mai province, aimed to reduce methamphetamine use by altering the risk environment. Project materials, including manuals and materials (e.g. key actor maps and research staff memos), were reviewed to describe partnering procedures and selection criteria. Potential community partners were identified from various government and community sectors with a focus on including representatives from health, police district, and sub-district government officials. Of the 64 potential partners approached, 59 agreed to join one of three district-level coalitions. Partner makeup included 25% from the health sector, 22% who were sub-district government officials and 10% were representatives from the police sector. Key partners necessary for endorsement of and commitment to the coalition work included district-level governors, police chiefs and hospital directors for each district. Initial coalition strategic planning has resulted in policies and programs to address school retention, youth development initiatives and establishment of a new drug treatment and rehabilitation clinic in addition to other developing interventions. Similarities in building coalitions, such as the need to strategically develop buy-in with key constituencies, as well as differences of whom and how partners were identified are explored.

Early-Life Adversity and Physical and Emotional Health Across The Lifespan: A Neuroimmune Network Hypothesis Nusslock R, Miller GE. Biol Psychiatry. 2015.
Children who experience chronic stressors are vulnerable to emotional and physical health problems across the lifespan. This phenomenon raises questions for scientists and clinicians alike. How does adversity get under the skin of the developing child? Through what mechanisms does it confer vulnerability to a heterogeneous set of mental and physical illnesses? And how does it instantiate risk across different life stages, engendering vulnerability to conditions that develop shortly after stressor exposure-like depression-and conditions that manifest decades later, like heart disease? Although answers to these questions have started to emerge, research has typically focused on single diseases or organ systems. To understand the plethora of health problems associated with childhood adversity, the authors argue that the field needs a second generation of research that recognizes multidirectional transactions among biological systems. To help facilitate this process, they propose a neuroimmune network hypothesis as a heuristic framework for organizing knowledge from disparate literatures and as a springboard for generating integrative research. Drawing on existing data, the authors argue that early-life adversity amplifies crosstalk between peripheral inflammation and neural circuitries subserving threat-related, reward-related, and executive control-related processes. This crosstalk results in chronic low-grade inflammation, thereby contributing to adiposity, insulin resistance, and other predisease states. In the brain, inflammatory mediators act on cortico-amygdala threat and cortico-basal ganglia reward, circuitries in a manner that predisposes individuals to self-medicating behaviors like smoking, drug use, and consumption of high-fat diets. Acting in concert with inflammation, these behaviors accelerate the pathogenesis of emotional and physical health problems.

Understanding How Mindful Parenting May Be Linked To Mother-Adolescent Communication Lippold MA, Duncan LG, Coatsworth JD, Nix RL, Greenberg MT. J Youth Adolesc. 2015; 44(9): 1663-1673.
Researchers have sought to understand the processes that may promote effective parent-adolescent communication because of the strong links to adolescent adjustment. Mindfulness, a relatively new construct in Western psychology that derives from ancient Eastern traditions, has been shown to facilitate communication and to be beneficial when applied in the parenting context. In this article, the authors tested if and how mindful parenting was linked to routine adolescent disclosure and parental solicitation within a longitudinal sample of rural and suburban, early adolescents and their mothers (n = 432; mean adolescent age = 12.14, 46% male, 72% Caucasian). The authors found that three factors-negative parental reactions to disclosure, adolescent feelings of parental over-control, and the affective quality of the parent-adolescent relationship-mediated the association between mindful parenting and adolescent disclosure and parental solicitation. Results suggest that mindful parenting may improve mother-adolescent communication by reducing parental negative reactions to information, adolescent perceptions of over-control, and by improving the affective quality of the parent-adolescent relationship. The discussion highlights intervention implications and future directions for research.

Bringing Female Substance Users To the Center Of the Global HIV Response El-Bassel N, Strathdee SA. J Acquir Immune Defic Syndr. 2015; 69 Suppl 2: S94-95.
The Global Burden of Disease Study Group estimates that one-third of the world's substance users are female, including approximately 3.8 million women who injected drugs in 2010. Prevalence and patterns of substance use vary widely by region and by drug type and administration route. In many countries with high-HIV prevalence among people who inject drugs, HIV prevalence is often higher

among injecting females when compared with injecting males. Even noninjection drug use (i.e., snorting, smoking, inhalation, and ingestion) has been linked to increased risk for HIV acquisition because of increases in unprotected sex, genderbased violence, and related-structural barriers (poverty, unemployment, stigma, aggressive policing, and human rights violations)

Tuberculosis Report Among Injection Drug Users and Their Partners In Kazakhstan
Hermosilla S, El-Bassel N, Aifah A, Terlikbayeva A, Zhumadilov Z, Berikkhanova K, Darisheva M, Gilbert L, Schluger N, Galea S. Public Health. 2015; 129(5): 569-575.
Tuberculosis (TB) is a major threat to global public health. Kazakhstan has the second highest percentage of multidrug-resistant tuberculosis (MDR-TB) cases among incident tuberculosis cases in the world (WHO 2013). A high burden of MDR-TB suggests TB prevention, control, and treatment programs are failing. This study provides an epidemiologic profile of TB among injection drug users (IDUs), a high-risk and chronically underserved population, in Kazakhstan Cross-sectional study. The authors studied the characteristics and risk environment of IDUs with self-reported previous active TB and their primary sexual partners in Almaty, Kazakhstan. 728 individuals (364 couples) participated in a couple-based study in 2009.16.75% of participants reported at least one positive TB test (x-ray) in their lifetime. In a multivariable logistic regression adjusting for couple-based sampling, persons with positive TB test were significantly more likely to be older (odds ratio (OR) 7.26, 95% confidence interval (CI): 1.73, 30.43), male (OR 5.53, 95% CI: 2.74, 11.16), have a shorter duration of injection drug use (OR 0.17, 95% CI: 0.04, 0.65), have received high social support from their significant other (OR 2.13, 95% CI: 1.03, 4.40) and more likely (non-significantly) to have been incarcerated (OR 7.03, 95% CI: 0.64, 77.30).Older men with a history of incarceration and recent injection drug use were more likely to have positive TB test in Kazakhstan. Social network support, while potentially positive for many aspects of population health, may increase risk of TB among IDUs in this context. Public health policies that target high-risk populations and their at-risk networks may be necessary to stem the rise of MDR-TB in Central Asia.

The Role Of Decision-making In Cannabis-related Problems Among Young Adults Gonzalez R, Schuster RM, Mermelstein RM, Diviak KR. Drug Alcohol Depend. 2015; 154: 214-221.
Deficits in decision-making and episodic memory are often reported among heavy cannabis users, yet little is known on how they influence negative consequences from cannabis use. Individual differences in decision-making may explain, in part, why some individuals experience significant problems from their cannabis use whereas others do not. The authors hypothesized that poor decision-making would moderate relationships between amount of cannabis use and problems from cannabis use whereas episodic memory performance would not. Young adult cannabis users (n=52) with cannabis as their drug of choice and with minimal comorbidities completed semi-structured interviews, self-report questionnaires, and measures of neurocognitive functioning, with decision-making accessed via the Iowa Gambling Task (IGT), episodic memory via the Hopkins Verbal Learning Test - Revised (HVLT) and problems from cannabis use with the Marijuana Problems Scale. Strong relationships were observed between amount of cannabis use (lifetime, 12-month, and 30-day) and problems reported from use, but only among participants with low (impaired) decision-making ($R(2)=.39$ to .51; $p<.01$). No significant relationships were observed among those with better (low average to high average) decision-making performance ($p>.05$). In contrast, episodic memory performance was not a significant moderator of the relationship between amount of cannabis use and cannabis problems ($p>.05$). Cannabis users with poor decision-making may be at greater risk for experiencing significant negative consequences from their cannabis use. These

results lend further support to emerging evidence of decision-making as a risk factor for addiction and extend these findings to cannabis users.

Family Economic Hardship, Corticotropin-Releasing Hormone Receptor Polymorphisms, and Depressive Symptoms In Rural African-American Youths Chen Y-F, Brody GH. J Adolesc Health. 2015; 57(2): 235-240.
The purpose of this study was to use pooled data from two independent studies of rural African-American youths to test the moderation effect of the corticotropin-releasing hormone receptor 1 gene (CRHR1) on the link between family economic hardship and trajectories of depressive symptoms. Two longitudinal studies were conducted involving African-Americans, aged 16 (N = 474) and 18 (N = 419) years, who were randomly recruited in rural Georgia. Family economic hardship and youths' depressive symptoms were assessed four times across 2.5 years. Genetic data also were collected. Haplotype analysis was performed on single-nucleotide polymorphisms of CRHR1; two haplotypes were aggregated to form a CRHR1 index. Growth curve models were executed to determine whether CRHR1 moderated the link between Wave 1 family economic hardship and youths' development of depression.CRHR1 × family economic hardship interactions significantly predicted youths' depressive symptoms. When exposed to family economic hardship 1 standard deviation above the mean at Wave 1, youths who scored 0 on the CRHR1 index showed high and increasing depressive symptoms across time, whereas those who scored 2 on the index showed a decrease in depressive symptoms. The CRHR1 gene reduces the risk for depressive symptoms among youths living in families undergoing high levels of economic hardship.

Quality Of Parent-Adolescent Conversations About Sex and Adolescent Sexual Behavior: An Observational Study Rogers AA, Ha T, Stormshak EA, Dishion TJ. J Adolesc Health. 2015; 57(2): 174-178.
Studies suggest that the quality of parent-adolescent communication about sex uniquely predicts adolescent sexual behavior. Previous studies have relied predominantly on self-report data. Observational methods, which are not susceptible to self-report biases, may be useful in examining the associations between the quality of parent-adolescent communication about sex and adolescent sexual behavior more objectively. With a sample of adolescents (N = 55, 58% male, 44% white, Mage = 15.8) and their parents, the authors used hierarchical logistic regression analyses to examine the associations between the observed quality of parent-adolescent communication about dating and sex and the likelihood of adolescents' sexual intercourse. The quality of parent-adolescent communication about dating and sex predicted sexual behavior. Specifically, lecturing was associated with a higher likelihood of adolescents having had sexual intercourse. The quality of parent-adolescent communication about sex is a unique correlate of adolescent sexual behavior and warrants further investigation. Thus, it serves as a potential target of preventive interventions that aim to foster adolescent sexual health behaviors.

Benefit-Cost Analysis Of A Randomized Evaluation Of Communities That Care: Monetizing Intervention Effects On the Initiation Of Delinquency and Substance Use Through Grade 12 Kuklinski MR, Fagan AA, Hawkins JD, Briney JS, Catalano RF. J Exp Criminol. 2015; 11(2): 165-192.
The aim of this study was to determine whether the Communities That Care (CTC) prevention system is a cost-beneficial intervention. Data were from a longitudinal panel of 4,407 youth participating in a randomized controlled trial including 24 towns in 7 states, matched in pairs within state and randomly assigned to condition. Significant differences favoring intervention youth in

sustained abstinence from delinquency, alcohol use, and tobacco use through Grade 12 were monetized and compared to economic investment in CTC.CTC was estimated to produce $4,477 in benefits per youth (discounted 2011 dollars). It cost $556 per youth to implement CTC for 5 years. The net present benefit was $3,920. The benefit-cost ratio was $8.22 per dollar invested. The internal rate of return was 21%. Risk that investment would exceed benefits was minimal. Investment was expected to be recouped within 9 years. Sensitivity analyses in which effects were halved yielded positive cost-beneficial results. CTC is a cost-beneficial, community-based approach to preventing initiation of delinquency, alcohol use, and tobacco use. CTC is estimated to generate economic benefits that exceed implementation costs when disseminated with fidelity in communities.

Blunted Feedback Processing During Risk-taking In Adolescents With Features Of Problematic Internet Use Yau YHC, Potenza MN, Mayes LC, Crowley MJ. Addict Behav. 2015; 45: 156-163.
While the conceptualization of problematic Internet use (PIU) as a "behavioral addiction" resembling substance-use disorders is debated, the neurobiological underpinnings of PIU remain understudied. This study examined whether adolescents displaying features of PIU (at-risk PIU; ARPIU) are more impulsive and exhibit blunted responding in the neural mechanisms underlying feedback processing and outcome evaluation during risk-taking. Event-related potentials (ERPs) elicited by positive (i.e. reward) and negative (i.e. loss) feedback were recorded during performance on a modified version of the Balloon Analogue Risk Task (BART) among ARPIU (n=39) and non-ARPIU subjects (n=27). Compared to non-ARPIU, ARPIU adolescents displayed higher levels of urgency and lack of perseverance on the UPPS Impulsive Behavior Scale. Although no between-group difference in BART performance was observed, ERPs demonstrated overall decreased sensitivity to feedback in ARPIU compared to non-ARPIU adolescents, as indexed by blunted feedback-related negativity (FRN) and P300 amplitudes to both negative and positive feedback. The present study provides evidence for feedback processing during risk-taking as a neural correlate of ARPIU. Given recent concerns regarding the growing prevalence of PIU as a health concern, future work should examine the extent to which feedback processing may represent a risk factor for PIU, a consequence of PIU, or possibly both.

Ovarian Hormones and Borderline Personality Disorder Features: Preliminary Evidence For Interactive Effects Of Estradiol and Progesterone Eisenlohr-Moul TA, DeWall CN, Girdler SS, Segerstrom SC. Biol Psychol. 2015; 109: 37-52.
Cyclical fluctuations in the ovarian hormones 17β-estradiol (E2; estrogen) and progesterone (P4) predict emotions, cognitive processes, and behaviors relevant to Borderline Personality Disorder (BPD); however, there are individual differences in sensitivity to normal hormone shifts. This study examined associations of naturally occurring hormonal changes with concurrent BPD feature expression. Forty women sampled for a flat distribution of the PAI-BOR (n=10 where T<50, n=10 where 50<T<60, n=10 where 60<T<70, and n=10 where T>70) provided four weekly saliva samples and psychological assessments. Across most outcomes (e.g., BPD features, felt rejection, anger rumination, negative urgency) P4 deviation (from one's person mean) moderated the effect of current E2 deviation (from one's person mean) among women high (+1 SD) in trait BPD features such that E2 deviation was negatively associated with symptoms only when P4 was higher-than-usual. Cyclical hormone changes (e.g., higher P4 in the luteal phase; E2 fluctuations at ovulation and in the luteal phase) may impact BPD feature expression among at-risk women.

The Role Of Sexual Expectancies Of Substance Use As A Mediator Between Adult Attachment and Drug Use Among Gay and Bisexual Men Starks TJ, Millar BM, Tuck AN, Wells BE. Drug Alcohol Depend. 2015; 153: 187-193.
Research exploring substance use in gay and bisexual men has increasingly paid attention to interpersonal dynamics and relational concerns associated with the use of substances. The current study explored the role of adult attachment style on drug use as well as the potential mediating role of sexual expectancies of substance use among gay and bisexual men. Online survey data were gathered from 122 gay and bisexual men across the U.S., with a mean age of 33 years. All participants were HIV-negative and identified their relationship status as single. Survey measures included attachment style, sexual expectancies of substance use, and recent drug use. While neither anxious or avoidant attachment were directly associated with the odds of recent drug use, they were positively associated with sexual expectancies of substance use (β =0.27, $p<0.01$, and β =0.21, $p<0.05$) which, in turn, were positively associated with the odds of drug use (expB=1.09, $p<0.01$). Bootstrapping tests of indirect effects revealed a significant indirect relationship between anxious attachment and drug use through sexual expectancies of substance use (β=0.11, $p<0.05$), but not for avoidant attachment. This study highlights the importance of interpersonal expectancies as motivators for drug use among gay and bisexual men. Sexual expectancies of substance use were associated with drug use and anxious adult attachment was associated indirectly with drug use through these sexual expectancies.

Intersectionality Of Internalized HIV Stigma and Internalized Substance Use Stigma: Implications For Depressive Symptoms Earnshaw VA, Smith LR, Cunningham CO, Copenhaver MM. J Health Psychol. 2015; 20(8): 1083-1089.
The authors adopted an intersectionality framework and examined whether the relationship between internalized HIV stigma and depressive symptoms is moderated by internalized substance use stigma. A total of 85 people living with HIV with a history of substance use in the Bronx, New York, completed a survey. Results revealed evidence of moderation: Participants who internalized HIV stigma experienced greater depressive symptoms only if they also internalized substance use stigma. Researchers should examine stigma associated with multiple socially devalued characteristics to best understand how stigma impacts mental health among people living with HIV. Healthcare providers should address stigma associated with the full range of socially devalued characteristics with which people living with HIV live.

Assessing Effects Of Prenatal Alcohol Exposure Using Group-wise Sparse Representation Of FMRI Data Lv J, Jiang X, Li X, Zhu D, Zhao S, Zhang T, Hu X, Han J, Guo L, Li Z, Coles C, Hu X, Liu T. Psychiatry Res. 2015; 233(2): 254-268.
Task-based fMRI activation mapping has been widely used in clinical neuroscience in order to assess different functional activity patterns in conditions such as prenatal alcohol exposure (PAE) affected brains and healthy controls. In this paper, the authors propose a novel, alternative approach of group-wise sparse representation of the fMRI data of multiple groups of subjects (healthy control, exposed non-dysmorphic PAE and exposed dysmorphic PAE) and assess the systematic functional activity differences among these three populations. Specifically, a common time series signal dictionary is learned from the aggregated fMRI signals of all three groups of subjects, and then the weight coefficient matrices (named statistical coefficient map (SCM)) associated with each common dictionary were statistically assessed for each group separately. Through inter-group comparisons based on the correspondence established by the common dictionary, the authors' experimental results have demonstrated that the group-wise sparse coding strategy and the SCM can

effectively reveal a collection of brain networks/regions that were affected by different levels of severity of PAE.

Social Exclusion Modulates Event-related Frontal Theta and Tracks Ostracism Distress In Children van Noordt SJR, White LO, Wu J, Mayes LC, Crowley MJ. Neuroimage. 2015; 118: 248-255.
Social exclusion is a potent elicitor of distress. Previous studies have shown that medial frontal theta oscillations are modulated by the experience of social exclusion. Using the Cyberball paradigm, the authors examined event-related dynamics of theta power in the EEG at medial frontal sites while children aged 8-12 years were exposed to conditions of fair play and social exclusion. Using an event-related design, they found that medial frontal theta oscillations (4-8Hz) increase during both early (i.e., 200-400ms) and late (i.e., 400-800ms) processing of rejection events during social exclusion relative to perceptually identical "not my turn" events during inclusion. Importantly, the authors show that only for the later time window (400-800ms) slow-wave theta power tracks self-reported ostracism distress. Specifically, greater theta power at medial frontal sites to "rejection" events predicted higher levels of ostracism distress. Alpha and beta oscillations for rejection events were unrelated to ostracism distress at either 200-400ms or 400-800ms time windows. These findings extend previous studies by showing that medial frontal theta oscillations for rejection events are a neural signature of social exclusion, linked to experienced distress in middle childhood.

Behavioral Impulsivity and Risk-Taking Trajectories Across Early Adolescence In Youths With and Without Family Histories Of Alcohol and Other Drug Use Disorders Dougherty DM, Lake SL, Mathias CW, Ryan SR, Bray BC, Charles NE, Acheson A. Alcohol Clin Exp Res. 2015; 39(8): 1501-1509.
Youths with family histories of alcohol and other drug use disorders (FH+) are at increased susceptibility for developing substance use disorders relative to those without such histories (FH-). This vulnerability may be related to impaired adolescent development of impulse control and elevated risk-taking. However, no previous studies have prospectively examined impulse control and risk-taking in FH+ youth across adolescence. A total of 386 pre-adolescents (305 FH+, 81 FH-; aged 10 to 12) with no histories of regular alcohol or other drug use were compared on behavioral measures of impulsivity including delay discounting, response initiation (Immediate Memory Task), response inhibition impulsivity (GoStop Impulsivity Paradigm), and risk-taking (Balloon Analogue Risk Task-Youth). Youths completed these laboratory tasks every 6 months, allowing for the examination of 10- to 15-year-olds. Hierarchical linear modeling was used to characterize the development of impulse control and risk-taking as shown in performance of these tasks throughout adolescence. The authors found that (i) FH+ youths had increased levels of delay discounting and response inhibition impulsivity at study entry; (ii) regardless of FH status, all youths had relatively stable delay discounting across time, improvements in response inhibition and response initiation impulsivity, and increased risk-taking; and (iii) although FH+ youths had increased response inhibition impulsivity at pre-adolescence, these differences were negligible by mid-adolescence. Heightened delay discounting in FH+ pre-adolescents coupled with normal adolescent increases in risk-taking may contribute to their increased susceptibility toward problem substance use in adolescence.

Non-HIV-related Health Care Utilization, Demographic, Clinical and Laboratory Factors Associated With Time To Initial Retention In HIV Care Among HIV-positive Individuals Linked To HIV Care Louren L, Nohpal A, Shopin D, Colley G, Nosyk B, Montaner J, Lima VD, Seek and Treat for Optimal Prevention of HIV/AIDS (STOP HIV/AIDS) Study Group. HIV Med. 2015.

The aim of the study was to explore non-HIV-related health care service (NHRHS) utilization, demographic, clinical and laboratory factors associated with timely initial "retention" in HIV care among individuals "linked" to HIV care in British Columbia (BC), Canada. The authors conducted a Weibull time-to-initial-retention analysis among BC Seek and Treat for Optimal Prevention of HIV/AIDS (STOP HIV/AIDS) cohort participants linked in 2000-2010, who had 1 year of follow-up. The authors defined "linked" as the first HIV-related service accessed following HIV diagnosis and "retained" as having, within a calendar year, either: (i) at least two HIV-related physician visits/diagnostic tests or (ii) at least two antiretroviral therapy (ART) dispensations, 3 months apart. Individuals were followed until they were retained, died, their last contact date, or until 31 December 2011, whichever occurred first. Of 5231 linked individuals (78% male; median age 39: (Q1-Q3: 32-46) years], 4691 (90%) were retained [median time to initial retention of 9 (Q1-Q3: 5-13) months] by the end of follow-up and 540 (10%) were not. Eighty-four per cent of not retained and 96% of retained individuals used at least one type of NHRHS during follow-up. Individuals who saw a specialist for NHRHS during follow-up had a shorter time to initial retention than those who did not [adjusted hazard ratio (aHR) 2.79; 95% confidence interval (CI): 2.47-3.16]. However, those who saw a general practitioner (GP) for NHRHS (aHR 0.79; 95% CI: 0.74-0.84) and those admitted to the hospital for NHRHS (aHR 0.60; 95% CI: 0.54-0.67), versus those who did/were not, respectively, had longer times to initial retention, as did female patients, people who inject drugs (PWID) and individuals < 40 years old. Overall, 84% of not retained individuals used some type of NHRHS during follow-up. Given that 71% of not retained individuals used GP NHRHS, our results suggest that GP-targeted interventions may be effective in improving time to initial retention.

Live To Tell: Narratives Of Methamphetamine-using Women Taken Hostage By Their Intimate Partners In San Diego, CA Ludwig-Barron N, Syvertsen JL, Lagare T, Palinkas LA, Stockman JK. Int J Drug Policy. 2015; 26(9): 843-850.

Hostage-taking, an overlooked phenomenon in public health, constitutes a severe form of intimate partner violence and may be a precursor to female homicide within relationships characterized by substance use. Criminal justice studies indicate that most hostage incidents are male-driven events with more than half of all cases associated with a prior history of violence and substance use. Methamphetamine use increases a woman's' risk of partner violence, with methamphetamine-using individuals being up to nine times more likely to commit homicide. As homicide is the most lethal outcome of partner violence and methamphetamine use, this study aims to characterize the potential role of hostage-taking within these intersecting epidemics. Methamphetamine-using women enrolled in an HIV behavioural intervention trial (FASTLANE-II) who reported experiences of partner violence were purposively selected to participate in qualitative sub-studies (Women's Study I & II). Twenty-nine women, ages 26-57, participated in semi-structured interviews that discussed relationship dynamics, partner violence, drug use and sexual practices. Findings indicated four cases of women being held hostage by a partner, with two women describing two separate hostage experiences. Women discussed partner jealousy, drug withdrawal symptoms, heightened emotional states from methamphetamine use, and escalating violent incidents as factors leading up to hostage-taking. Factors influencing lack of reporting incidents to law enforcement included having a criminal record, fear of partner retaliation, and intentions to terminate the relationship when the

partner is incarcerated. Educating women on the warning signs of hostage-taking within the context of methamphetamine use and promoting behaviour change among male perpetrators can contribute to reducing the risk of homicide. Furthermore, bridging the gap between health services and law enforcement agencies and providing comprehensive services that address the needs of methamphetamine-using women in violent relationships can prevent or minimize potential harm to vulnerable women.

Reasons For Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Nicotine Tob Res. 2015; 17(7): 847-854.
Understanding why young people try and stop electronic cigarette (e-cigarette) use is critical to inform e-cigarette regulatory efforts. The authors conducted 18 focus groups (N = 127) in 1 middle school (MS), 2 high schools (HSs), and 2 colleges in Connecticut to assess themes related to e-cigarette experimentation and discontinuation. They then conducted surveys to evaluate these identified themes in 2 MSs, 4 HSs, and 1 college (N = 1,175) to explore whether reasons for e-cigarette experimentation and/or discontinuation differed by school level or cigarette smoking status. From the focus groups, the authors identified experimentation themes (i.e., curiosity, flavors, family/peer influence, easy access, and perceptions of e-cigarettes as "cool" and as a healthier/better alternative to cigarettes) and discontinuation themes (i.e., health concerns, loss of interest, high cost, bad taste, and view of e-cigarettes as less satisfying than cigarettes). The survey data showed that the top reasons for experimentation were curiosity (54.4%), appealing flavors (43.8%), and peer influences (31.6%), and the top reasons for discontinuation were responses related to losing interest (23.6%), perceiving e-cigarettes as "uncool" (16.3%), and health concerns (12.1%). Cigarette smokers tried e-cigarettes because of the perceptions that they can be used anywhere and to quit smoking and discontinued because they were not as satisfying as cigarettes. School level differences were detected. E-cigarette prevention efforts toward youth should include limiting e-cigarette flavors, communicating messages emphasizing the health risks of use, and changing social norms surrounding the use of e-cigarettes. The results should be interpreted in light of the limitations of this study.

Importance Of Women's Relative Socioeconomic Status Within Sexual Relationships In Communication About Safer Sex and HIV/STI Prevention Muchomba FM, Chan C, El-Bassel N. J Urban Health. 2015; 92(3): 559-571.
The socioeconomic status (SES) of women is increasingly considered an important factor for HIV/STI risk. The HIV/STI literature has largely focused on womens' absolute levels of SES, and therefore, the importance of their SES relative to their male sexual partners remains understudied. This paper examines the association between women's relative SES and frequency of safer sex communication among heterosexual couples. A convenience sample of 342 couples (N = 684) recruited in New York City was asked about frequency of discussions with their partner about the need to use male condoms, about HIV prevention, and about STI prevention in the previous 90 days. Differences between partners in education, income, employment, housing, and incarceration history were combined using principal component analysis to form an index of women's relative SES. Negative binomial regression models assessed associations between woman's relative SES and communication frequency controlling for age, sex, race, ethnicity, education, and relationship type using a generalized estimating equation framework. On average, participants had 2.5, 4.2, and 4.8 discussions regarding the need to use male condoms, about HIV prevention, and about STI prevention, respectively. A one standard deviation increase in a woman's relative SES score was

associated with increased frequency of discussions about male condom use (adjusted rate ratio [aRR], 1.15; 95% confidence interval [CI], 1.03-1.29), about HIV prevention (aRR, 1.25; CI, 1.14-1.37), and about STI prevention (aRR, 1.29; CI, 1.18-1.41). Women's relative SES may be an important factor for sexual communication, and further research on its role in HIV/STI risk may uncover avenues for intervention.

Perceived Barriers To Treatment For Alcohol Problems: A Latent Class Analysis Schuler MS, Puttaiah S, Mojtabai R, Crum RM. Psychiatr Serv. 2015; 66(11): 1221-1228.
Low rates of alcohol treatment seeking have been shown to be associated with perceived barriers to treatment, but heterogeneity in patterns of perceived barriers has not been explored. The study analyzed data from a population-based sample of adults with alcohol abuse and dependence in order to describe latent classes of individuals who reported one or more of 15 perceived barriers to seeking alcohol treatment and to identify characteristics associated with class membership. Data were from the National Epidemiologic Survey on Alcohol and Related Conditions (2001-2002). Analyses were restricted to treatment-naive adults with alcohol abuse or dependence who reported a perceived treatment need (N=1,053). Latent class analysis was performed to identify subgroups with respect to barriers to treatment. Latent class regression identified variables associated with each subgroup. Two subgroups emerged: the low-barriers class (87%), characterized primarily by attitudinal barriers, and the high-barriers class (13%), characterized by significant attitudinal, financial, stigma, and readiness-for-change barriers. In both classes, the most frequently endorsed barrier was the attitudinal belief that "I should be strong enough" to handle the problem without treatment. Univariate analyses showed strong associations between membership in the high-barriers class and comorbid psychiatric disorders, alcohol dependence (compared with abuse), and a family history of alcohol problems. Multivariate analyses found significant associations with a lifetime anxiety disorder and with education level. Attitudinal barriers were most prevalent. Findings revealed a notable subgroup with multiple barriers, including financial and stigma-related barriers. This subgroup may require additional resources and support to enter treatment.

Optimization Of Multicomponent Behavioral and Biobehavioral Interventions For the Prevention and Treatment Of HIV/AIDS Collins LM, Kugler KC, Gwadz MV. AIDS Behav. 2015.
To move society toward an AIDS-free generation, behavioral interventions for prevention and treatment of HIV/AIDS must be not only effective, but also cost-effective, efficient, and readily scalable. The purpose of this article is to introduce to the HIV/AIDS research community the multiphase optimization strategy (MOST), a new methodological framework inspired by engineering principles and designed to develop behavioral interventions that have these important characteristics. Many behavioral interventions comprise multiple components. In MOST, randomized experimentation is conducted to assess the individual performance of each intervention component, and whether it's presence/absence/setting has an impact on the performance of other components. This information is used to engineer an intervention that meets a specific optimization criterion, defined a priori in terms of effectiveness, cost, cost-effectiveness, and/or scalability. MOST will enable intervention science to develop a coherent knowledge base about what works and does not work. Ultimately this will improve behavioral interventions systematically and incrementally.

Initiation Of Antiretroviral Therapy At High CD4+ Cell Counts Is Associated With Positive Treatment Outcomes Lima VD, Reuter A, Harrigan PR, Louren L, Chau W, Hull M, Mackenzie L, Guillemi S, Hogg RS, Barrios R, Montaner JSG. AIDS. 2015; 29(14): 1871-1882.
There is limited research investigating the possible mechanisms of how starting combination antiretroviral therapy (cART) at a higher CD4 cell count decreases mortality. This study investigated the association between initiating cART with short-term and long-term achievement of viral suppression; emergence of any drug resistance and of an AIDS-defining illness (ADI); long-term treatment adherence; and all-cause mortality. This retrospective cohort study included 4120 naive patients who initiated cART between 2000 and 2012. Patients were followed until 2013, death or until the last contact date (varied by outcome). The main exposure was the interaction between period of cART initiation (2000-2006 and 2007-2012) and CD4 cell count at cART initiation (<500 versus ≥500 cells/μl). We considered both baseline and longitudinal covariates. We fitted different multivariable models using cross-sectional and longitudinal statistical methods, depending on the outcome. Patients who initiated cART with a CD4 cell count at least 500 cells/μl in 2007-2012 had an increased likelihood of achieving viral suppression at 9 months and of maintaining an adherence level of at least 95% over time, and the lowest probability of developing any resistance and an ADI during follow-up. These patients were not the ones with the highest likelihood of maintaining viral suppression over time, most likely due to viral load blips experienced during the follow-up. The outcomes in this study likely play an important role in explaining the positive impact of early cART initiation on mortality. These results should alleviate some of the concerns clinicians may have when initiating cART in patients with high CD4s as recommended by current treatment guidelines.

Declines In Highly Active Antiretroviral Therapy Initiation At CD4 Cell Counts 200 ≤ and the Contribution Of Diagnosis Of HIV At CD4 Cell Counts 200 ≤ In British Columbia, Canada Louren L, Samji H, Nohpal A, Chau W, Colley G, Lepik K, Barrios R, Lima V, Hogg RS, Montaner J, Kesselring S, Moore DM. HIV Med. 2015; 16(6): 337-345.
The aim of the study was to examine trends in initiating highly active antiretroviral therapy (HAART) with a CD4 count ≤ 200 cells/μL and the contribution of having a CD4 count ≤ 200 cells/μL at the time of diagnosis to these trends, in British Columbia (BC), Canada. The authors included in the analysis treatment- naïve BC residents aged 19 years who initiated HAART from 2003 to 2012. Participants were classified as follows: Group 1: diagnosed and initiated HAART with a CD4 count > 200 cells/μL; Group 2: diagnosed with a CD4 count > 200 cells/μL and initiated HAART with a CD4 count ≤ 200 cells/μL; and Group 3: diagnosed and initiated HAART with a CD4 count ≤ 200 cells/μL. We measured trends in initiating HAART with a CD4 count ≤ 200 cells/μL and used logistic regression models to measure factors associated with initiating HAART with a CD4 count ≤ 200 cells/μL, stratified by having a CD4 count ≤ 200 cells/μL or > 200 cells/μL at the time of diagnosis. Between 2003 and 2012, 3506 BC residents initiated HAART. Of these, 44% (1558 of 3506) initiated HAART with a CD4 count ≤ 200 cells/μL. This proportion declined from 69% (198 of 287) in 2003 to 21% (81 of 330) in 2012 ($P < 0.001$). The proportion of those in Group 3 increased from 49% (97 of 198) in 2003 to 69% (56 of 81) in 2012 ($P < 0.001$). Overall, 56% (1948), 22% (776) and 22% (782) made up Groups 1, 2, and 3, respectively. In adjusted analyses, seeing a specialist was significantly associated with being in Group 3. Using injection drugs and seeing a specialist were associated with being in Group 2. In recent years, among individuals who ever initiated HAART in BC, being diagnosed with low CD4 cell counts has become a greater contributor to initiating HAART with low CD4 cell counts.

Differential Patterns Of Amygdala and Ventral Striatum Activation Predict Gender-specific Changes In Sexual Risk Behavior Victor EC, Sansosti AA, Bowman HC, Hariri AR. J Neurosci. 2015; 35(23): 8896-8900.
Although the initiation of sexual behavior is common among adolescents and young adults, some individuals express this behavior in a manner that significantly increases their risk for negative outcomes including sexually transmitted infections. Based on accumulating evidence, the authors have hypothesized that increased sexual risk behavior reflects, in part, an imbalance between neural circuits mediating approach and avoidance in particular as manifest by relatively increased ventral striatum (VS) activity and relatively decreased amygdala activity. Here, the authors test their hypothesis using data from seventy 18- to 22-year-old university students participating in the Duke Neurogenetics Study. The authors found a significant three-way interaction between amygdala activation, VS activation, and gender predicting changes in the number of sexual partners over time. Although relatively increased VS activation predicted greater increases in sexual partners for both men and women, the effect in men was contingent on the presence of relatively decreased amygdala activation and the effect in women was contingent on the presence of relatively increased amygdala activation. These findings suggest unique gender differences in how complex interactions between neural circuit function contributing to approach and avoidance may be expressed as sexual risk behavior in young adults. As such, these findings have the potential to inform the development of novel, gender-specific strategies that may be more effective at curtailing sexual risk behavior.

Intergenerational Continuity In Parents' and Adolescents' Externalizing Problems: The Role Of Life Events and Their Interaction With GABRA2 Salvatore JE, Meyers JL, Yan J, Aliev F, Lansford JE, Pettit GS, Bates JE, Dodge KA, Rose RJ, Pulkkinen L, Kaprio J, Dick DM. J Abnorm Psychol. 2015; 124(3): 709-728.
The authors examine whether parental externalizing behavior has an indirect effect on adolescent externalizing behavior via elevations in life events, and whether this indirect effect is further qualified by an interaction between life events and adolescents' GABRA2 genotype (rs279871). They use data from 2 samples: the Child Development Project (CDP; n = 324) and FinnTwin12 (n = 802). In CDP, repeated measures of life events, mother-reported adolescent externalizing, and teacher-reported adolescent externalizing were used. In FinnTwin12, life events and externalizing were assessed at age 14. Parental externalizing was indexed by measures of antisocial behavior and alcohol problems or alcohol dependence symptoms in both samples. In CDP, parental externalizing was associated with more life events, and the association between life events and subsequent adolescent externalizing varied as a function of GABRA2 genotype ($p \leq .05$). The association between life events and subsequent adolescent externalizing was stronger for adolescents with 0 copies of the G minor allele compared to those with 1 or 2 copies of the minor allele. Parallel moderation trends were observed in FinnTwin12 ($p \leq .11$). The discussion focuses on how the strength of intergenerational pathways for externalizing psychopathology may differ as a function of adolescent-level individual differences.

Brief Family-Based Intervention For Substance Abusing Adolescents Hernandez L, Rodriguez AM, Spirito A. Child Adolesc Psychiatr Clin N Am. 2015; 24(3): 585-599.
Research has shown that a lack of parental involvement in their children's activities predicts initiation and escalation of substance use. Parental monitoring and supervision, parent-child communication including communication regarding beliefs and disapproval of substance use, positive parenting, and family management strategies, have been shown to protect against adolescent substance abuse and related problems. Family and parenting approaches to preventing

and intervening on adolescent substance abuse have received support in the literature. This article discusses the theoretical foundations as well as the application of the Family Check-up, a brief, family-based intervention for adolescent substance use.

Time Since Release From Incarceration and HIV Risk Behaviors Among Women: The Potential Protective Role Of Committed Partners During Re-entry Hearn LE, Whitehead NE, Khan MR, Latimer WW. AIDS Behav. 2015; 19(6): 1070-1077.
After release from incarceration, former female inmates face considerable stressors, which may influence drug use and other risk behaviors that increase risk for HIV infection. Involvement in a committed partnership may protect women against re-entry stressors that may lead to risky behaviors. This study measured the association between time since release from incarceration (1-6 months ago, and >6 months ago versus never incarcerated) and HIV risk behaviors and evaluated whether these associations differed by involvement in a committed partnership. Women released within the past 6 months were significantly more likely to have smoked crack cocaine, used injection drugs and engaged in transactional sex in the past month compared to never-incarcerated women and women released more distally. Stratified analyses indicated that incarceration within the past 6 months was associated with crack cocaine smoking, injection drug use and transactional sex among women without a committed partner yet unassociated with these risk behaviors among those with a committed partner.

The Family Check Up and Adolescent Depression: An Examination Of Treatment Responders and Non-Responders Connell AM, Stormshak E, Dishion T, Fosco G, Van Ryzin M. Prev Sci. 2015.
The Family Check Up (FCU) is a family-centered intervention for reducing children's problem behavior through improving parenting skills and family interactions. Although the FCU was designed to prevent conduct problems, the authors have also found the program to be effective in preventing escalating symptoms of depression in early adolescence. The current analyses examine heterogeneous patterns of response to treatment in an effort to identify factors associated with differential response to family intervention. The authors examined heterogeneity in trajectories of youth-reported depressive symptoms from grades 6 to 9, using a Latent Growth Mixture Modeling framework to identify patterns of treatment response and non-response. Three symptom trajectories were identified, including the following: (1) a large class exhibiting stable, low symptom levels, (2) a class exhibiting high and stable depressive symptoms, and (3) a class exhibiting low initial symptoms that increased over time. Significant intervention effects were identified only among the third class, as a preventive effect on depression from 7th to 9th grade for youth with low initial symptoms. No effect of intervention was observed in the other two classes. Comparisons of classes 2 and 3 suggested that class 3 members were more likely to be females with high baseline antisocial behavior, but lower initial levels of depression. The findings suggest the importance of exploring heterogeneity within a prevention design, as well as the importance of tailored approaches to the prevention of adolescent depression.

Retrospective Chart Review Of Obesity and Episodic and Chronic Illness Among Rural Mexican-American Adolescents Accessing Rural Health Clinic Services Champion JD, Pierce S, Collins JL. Int J Nurs Pract. 2015; 21(3): 328-336.
Obesity impacts the physical and psychological health of children and adolescents, and is a risk factor for development of episodic and chronic illness. Rural Mexican-American adolescents are at risk for obesity and associated chronic illnesses. The study used a retrospective chart review of data

collected routinely in a rural health clinic setting from 1 January 2005 to 31 December 2010 to assess incidence of overweight/obesity status and episodic or chronic illness among Mexican-American adolescents aged 12-18 years. Analyses included body mass index, age, gender, and episodic or chronic illness diagnoses. Two hundred twelve charts were audited; women (n =114, 53.8%), men (n =46.2%); normal (n =105, 49.5%), overweight/obese (n =107, 50.5%). There were more female normal (n=61, 53.5%) vs. overweight/obese (n = 53, 46.5%). More male overweight/obese (n = 54, 55.1%) than normal weight (n = 44, 44.9%). Age at first documented overweight/obesity status occurred in early adolescence (median =13 years, mode = 12 years). Chronic illness incidence was higher among men than women, and overweight/obese vs. normal weight adolescents and in sub-categorizations by weight and specific illness. Incidence of episodic illness was higher among women than men, with variation by weight and specific illness. Disproportionately high incidence of episodic or chronic illness and overweight/obesity identified among rural Mexican-American adolescents compels intervention modification to improve effectiveness.

Long-Term Effects Of Childhood Risk Factors On Cardiovascular Health During Adulthood Shrestha R, Copenhaver. Clin Med Rev Vasc Health. 2015; 7: 1-5.

The primary purpose of this article is to provide a broad overview of the research on the long-term effects of childhood risk factors on cardiovascular diseases (CVDs) during adulthood and to outline recommendations for prevention of CVDs based on evidence-based interventions (EBIs). CVDs are the leading cause of death and a major cause of disability in the United States and globally. Risk factors for CVDs are already identifiable in children and youth, and include both modifiable factors (e.g., unhealthy diet, physical inactivity, tobacco smoking), and factors that cannot be changed (e.g., age, heredity, sex). A fundamental issue has been the severity of the long-term effects of childhood risk factors (i.e., behavioral and intermediate risk factors) on subsequent cardiovascular health. It is clear from the empirical evidence that risk factors for CVDs can develop during childhood and adolescence. These risk factors in childhood have been linked to adverse health outcomes, including CVDs, during adulthood. The findings thus far suggest that, in order to be effective and reduce the risk of adulthood CVDs, intervention strategies should begin during childhood. The findings also underscore the importance of adopting a healthy lifestyle as early in life as possible.

A Family-Based Intervention For Improving Children's Emotional Problems Through Effects On Maternal Depressive Symptoms Reuben JD, Shaw DS, Brennan LM, Dishion TJ, Wilson MN. J Consult Clin Psychol. 2015.

This study focused on whether a brief family-based intervention for toddlers, the Family Check-Up (FCU), designed to address parent management skills and prevent early conduct problems, would have collateral effects on maternal depressive symptoms and subsequent child emotional problems. Parents with toddlers were recruited from the Women, Infants, and Children Nutritional Supplement Program based on the presence of socioeconomic, family, and child risk (N = 731). Families were randomly assigned to the FCU intervention or control group with yearly assessments beginning at child age 2. Maternal depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale at child ages 2 and 3. Child internalizing problems were collected from primary caregivers, alternative caregivers, and teachers using the Child Behavior Checklist at ages 7.5 and 8.5. Structural equation models revealed that mothers in families randomly assigned to the FCU showed lower levels of depressive symptoms at child age 3, which in turn were related to lower levels of child depressed/withdrawal symptoms as reported by primary caregivers, alternative caregivers, and teacher at ages 7.5-8.5.Findings suggest that a brief, preventive intervention

improving maternal depressive symptoms can have enduring effects on child emotional problems that are generalizable across contexts. As there is a growing emphasis for the use of evidence-based and cost-efficient interventions that can be delivered in multiple delivery settings serving low-income families and their children, clinicians and researchers welcome evidence that interventions can promote change in multiple problem areas. The FCU appears to hold such promise.

Suicide Attempts and Childhood Maltreatment Among Street Youth: A Prospective Cohort Study Hadland SE, Wood E, Dong H, Marshall BDL, Kerr T, Montaner JS, DeBeck K. Pediatrics. 2015; 136(3): 440-449.
Although suicide is a known leading cause of death among street youth, few prospective studies have explored childhood experiences as risk factors for future suicide attempt in this population. The authors examined the risk of attempted suicide in relation to childhood maltreatment among street youth. From September 2005 to November 2013, data were collected from the At Risk Youth Study (ARYS), a prospective cohort of street youth in Vancouver, Canada. Inclusion criteria were age 14 to 26 years, past-month illicit drug use, and street involvement. Participants completed the Childhood Trauma Questionnaire, an instrument measuring self-reported sexual, physical, and emotional abuse and physical and emotional neglect. Suicide attempts were assessed semiannually. Using Cox regression, we examined the association between the 5 types of maltreatment and suicide attempts. Of 660 participants, 68.2% were male and 24.6% were Aboriginal. Median age was 21.5 years. The prevalence of moderate to extreme childhood maltreatment ranged from 16.8% (sexual abuse) to 45.2% (emotional abuse). Participants contributed 1841 person-years, with suicide attempts reported by 35 (5.3%) individuals (crude incidence density: 1.9 per 100 person-years; 95% confidence interval [CI]: 1.4-2.6 per 100 person-years). In adjusted analyses, types of maltreatment associated with suicide attempts included physical abuse (adjusted hazard ratio [HR]: 4.47; 95% CI: 2.12-9.42), emotional abuse (adjusted HR: 4.92; 95% CI: 2.11-11.5), and emotional neglect (adjusted HR: 3.08; 95% CI: 1.05-9.03).Childhood maltreatment is associated with subsequent risk of suicidal behavior among street youth. Suicide prevention efforts should be targeted toward this marginalized population and delivered from a trauma-informed perspective.

Associations Of Contextual Risk and Protective Factors With Fathers' Parenting Practices In the Postdeployment Environment Davis L, Hanson SK, Zamir O, Gewirtz AH, DeGarmo DS. Psychol Serv. 2015; 12(3): 250-260.
Deployment separation and reunifications are salient contexts that directly impact effective family functioning and parenting for military fathers. Yet, little is known about determinants of postdeployed father involvement and effective parenting. The present study examined hypothesized risk and protective factors of observed parenting for 282 postdeployed fathers who served in the National Guard/Reserves. Preintervention data were employed from fathers participating in the After Deployment, Adaptive Parenting Tools randomized control trial. Parenting practices were obtained from direct observation of father-child interaction and included measures of problem solving, harsh discipline, positive involvement, encouragement, and monitoring. Risk factors included combat exposure, negative life events, months deployed, and posttraumatic stress disorder symptoms. Protective factors included education, income, dyadic adjustment, and social support. Results of a structural equation model assessing risk and protective factors for an effective parenting construct indicated that months deployed, income, and father age were most related to observed parenting, explaining 16% of the variance. The authors are aware of no other study using direct parent-child observations of fathers' parenting skills following overseas deployment. Implications for practice and preventive intervention are discussed.

Examination Of Substance Use, Risk Factors, and Protective Factors On Student Academic Test Score Performance Arthur MW, Brown EC, Briney JS, Hawkins JD, Abbott RD, Catalano RF, Becker L, Langer M, Mueller MT. J Sch Health. 2015; 85(8): 497-507.
School administrators and teachers face difficult decisions about how best to use school resources to meet academic achievement goals. Many are hesitant to adopt prevention curricula that are not focused directly on academic achievement. Yet, some have hypothesized that prevention curricula can remove barriers to learning and, thus, promote achievement. The authors examined relationships among school levels of student substance use and risk and protective factors that predict adolescent problem behaviors and achievement test performance. Hierarchical generalized linear models were used to predict associations involving school-averaged levels of substance use and risk and protective factors and students' likelihood of meeting achievement test standards on the Washington Assessment of Student Learning, statistically controlling for demographic and economic factors known to be associated with achievement. Levels of substance use and risk/protective factors predicted the academic test score performance of students. Many of these effects remained significant even after controlling for model covariates. Implementing prevention programs that target empirically identified risk and protective factors has the potential to have a favorable effect on students' academic achievement.

Early Sexual Debut: A Risk Factor For STIs/HIV Acquisition Among A Nationally Representative Sample Of Adults In Nepal Shrestha R, Karki P, Copenhaver M. J Community Health. 2015.
While early sexual debut is highly prevalent in Nepal, its link to sexually transmitted infections (STIs/HIV) risk factors has not been explored at a national level. The objective of this study was to assess potential association between early sexual debut and risk factors for STIs/HIV acquisition, including sexual risk behaviors, sexual violence, and teenage pregnancy among adults in Nepal. Data were taken from the nationally representative Nepal Demographic Health Survey (2011), which employed a two-stage complex design to collect data. A sample of 12,756 adults (ages 15-49 years) were included. Multivariate logistic models were conducted, adjusted for demographic characteristics, to assess the association between early sexual debut and STIs/HIV-related risk factors. The prevalence of early sexual debut in this sample was 39.2 %, with a mean age of coital debut at 17.9 years. After adjusting for potential confounders, individuals with early sexual debut were significantly more likely to report a history of STIs (aOR 1.19; 95 % CI 1.06-1.35) and had a significantly higher risk profile, including having multiple sex partner (aOR 2.14; 95 % CI 1.86-2.47), inconsistent condom use (aOR 0.72; 95 % CI 0.61-0.86), paid for sex (aOR 1.61; 95 % CI 1.14-2.27), a history of sexual violence (aOR 1.99; 95 % CI 1.63-2.43), and teenage pregnancy (aOR 12.87; 95 % CI 11.62-14.26). Individuals who have early sexual debut are more likely to engage in risk behaviors that place them at increased risk of STIs/HIV acquisition. STIs/HIV prevention strategies should aim at delaying sexual debut to decrease the disproportionate burden of adverse health outcomes, including STIs/HIV, among individuals in Nepal.

Stigma Toward Men Who Have Sex With Men Among Future Healthcare Providers In Malaysia: Would More Interpersonal Contact Reduce Prejudice? Earnshaw VA, Jin H, Wickersham JA, Kamarulzaman A, John J, Lim SH, Altice FL. AIDS Behav. 2015.
Men who have sex with men (MSM) living in countries with strong stigma toward MSM are vulnerable to HIV and experience significant barriers to HIV care. Research is needed to inform interventions to reduce stigma toward MSM in these countries, particularly among healthcare providers. A cross-sectional survey of 1158 medical and dental students was conducted at seven

Malaysian universities in 2012. Multivariate analyses of variance suggest that students who had interpersonal contact with MSM were less prejudiced toward and had lower intentions to discriminate against MSM. Path analyses with bootstrapping suggest stereotypes and fear mediate associations between contact with prejudice and discrimination. Intervention strategies to reduce MSM stigma among healthcare providers in Malaysia and other countries with strong stigma toward MSM may include facilitating opportunities for direct, in-person or indirect, media-based prosocial contact between medical and dental students with MSM.

Buffering Effect Of Positive Parent-child Relationships On Adolescent Risk Taking: A Longitudinal Neuroimaging Investigation Qu Y, Fuligni AJ, Galvan A, Telzer EH. Dev Cogn Neurosci. 2015; 15: 26-34.
Adolescence is marked by a steep increase in risk-taking behavior. The serious consequences of such heightened risk taking raise the importance of identifying protective factors. Despite its dynamic change during adolescence, family relationships remain a key source of influence for teenagers. Using a longitudinal fMRI approach, we scanned 23 adolescents twice across a 1.5-year period to examine how changes in parent-child relationships contribute to changes in adolescent risk taking over time via changes in adolescents' neural reactivity to rewards. Results indicate that although parent-child relationships are not associated with adolescent risk taking concurrently, increases in positive parent-child relationships contribute to declines in adolescent risk taking. This process is mediated by longitudinal decreases in ventral striatum activation to rewards during risk taking. Findings highlight the neural pathways through which improvements in positive parent-child relationships serve to buffer longitudinal increases in adolescent risk taking.

Neighborhood Poverty, College Attendance, and Diverging Profiles Of Substance Use and Allostatic Load In Rural African American Youth Chen E, Miller GE, Brody GH, Lei MK. Clin Psychol Sci. 2015; 3(5): 675-685.
A subset of African American youth who live in impoverished neighborhoods display resilient profiles academically and behaviorally. The authors hypothesized that this resilience might be "skin-deep," in that the ongoing efforts needed to achieve success might take a physiological toll on these youth. At age 19, 452 rural African American youth were assessed on broader contextual risk (neighborhood poverty) and external indicators of success (college attendance). One year later, participants were assessed on substance use and cumulative physiological risk (allostatic load). African American youth from more disadvantaged neighborhoods who attended college had lower levels of substance use, but higher levels of allostatic load compared to those from less disadvantaged neighborhoods who attended college, or to those who did not attend college. These findings indicate that a subset of African American youth from poor neighborhoods exhibits a profile of "skin-deep resilience," characterized by external successes combined with heightened internal physiological risk.

Changing Friend Selection In Middle School: A Social Network Analysis Of A Randomized Intervention Study Designed To Prevent Adolescent Problem Behavior DeLay D, Ha T, Van Ryzin M, Winter C, Dishion TJ. Prev Sci. 2015.
Adolescent friendships that promote problem behavior are often chosen in middle school. The current study examines the unintended impact of a randomized school-based intervention on the selection of friends in middle school, as well as on observations of deviant talk with friends 5 years later. Participants included 998 middle school students (526 boys and 472 girls) recruited at the onset of middle school (age 11-12Â years) from three public middle schools participating in the

Family Check-up model intervention. The current study focuses only on the effects of the SHAPe curriculum-one level of the Family Check-up model-on friendship choices. Participants nominated friends and completed measures of deviant peer affiliation. Approximately half of the sample (n = 500) was randomly assigned to the intervention, and the other half (n = 498) comprised the control group within each school. The results indicate that the SHAPe curriculum affected friend selection within school 1 but not within schools 2 or 3. The effects of friend selection in school 1 translated into reductions in observed deviancy training 5 years later (age 16-17 years). By coupling longitudinal social network analysis with a randomized intervention study, the current findings provide initial evidence that a randomized public middle school intervention can disrupt the formation of deviant peer groups and diminish levels of adolescent deviance 5 years later.

Model-Free Feature Screening For Ultrahigh Dimensional Discriminant Analysis Cui H, Li R, Zhong W. J Am Stat Assoc. 2015; 110(510): 630-641.
This work is concerned with marginal sure independence feature screening for ultra-high dimensional discriminant analysis. The response variable is categorical in discriminant analysis. This enables us to use conditional distribution function to construct a new index for feature screening. In this paper, we propose a marginal feature screening procedure based on empirical conditional distribution function. The authors establish the sure screening and ranking consistency properties for the proposed procedure without assuming any moment condition on the predictors. The proposed procedure enjoys several appealing merits. First, it is model-free in that its implementation does not require specification of a regression model. Second, it is robust to heavy-tailed distributions of predictors and the presence of potential outliers. Third, it allows the categorical response having a diverging number of classes in the order of $O(n^{\kappa})$ with some $\kappa \geq 0$. The authors assess the finite sample property of the proposed procedure by Monte Carlo simulation studies and numerical comparison. They further illustrate the proposed methodology by empirical analyses of two real-life data sets.

Prenatal Cocaine Exposure and Child Outcomes: A Conference Report Based On A Prospective Study From Cleveland Singer LT, Minnes S, Min MO, Lewis BA, Short EJ. Hum Psychopharmacol. 2015; 30(4): 285-289.
The study aims to describe developmental outcomes from a longitudinal prospective cohort (Cleveland study) of prenatally cocaine-exposed (CE) infants. Two hundred eighteen CE and 197 nonexposed infants were enrolled at birth and followed through mid-adolescence. Birth CE status was determined by interview and biologic measures. Multiple demographic, drug, and environmental correlates were controlled. Standardized, normative, reliable measures of fetal growth, intelligence quotient (IQ), behavior, executive function, and language were given at each age and risk for substance misuse assessed in adolescence. A subset of children received volumetric magnetic resonance imaging (MRI) at 7 years and functional MRI at 14 years. The effect of CE was determined through multiple regression analyses controlling for confounders. Cocaine exposed had significant negative effects on fetal growth, attention, executive function, language, and behavior, while overall IQ was not affected. CE had significant negative effects on perceptual reasoning IQ and visual-motor skills and predicted lower volume of corpus callosum and decreased gray matter in the occipital and parietal lobes. CE children had higher risk for substance misuse. Confounding risk factors had additive effects on developmental outcomes. Prenatal exposure to cocaine was related to poorer perceptual organization IQ, visual-spatial information processing, attention, language, executive function, and behavior regulation through early adolescence.

Trends Among U.S. High School Seniors In Recent Marijuana Use and Associations With Other Substances: 1976-2013 Lanza ST, Vasilenko SA, Dziak JJ, Butera NM. J Adolesc Health. 2015; 57(2): 198-204.
The purpose of this study was to describe historical trends in rates of recent substance use and associations between marijuana and other substances, among U.S. high school seniors by race and gender. Data from Monitoring the Future (1976-2013; N= 599,109) were used to estimate historical trends in alcohol use, heavy episodic drinking (HED), cigarette use, and marijuana use. The authors used time-varying effect models to flexibly estimate changes in associations of substance use behaviors. Past-month marijuana use rates peaked in the 1970s, declined through 1990, then rose again to reach levels of use of more than 20% for both black and white participants. Recent years show increasing disparities across groups such that males, and in particular black youth, are on a trajectory toward higher use. This rise in marijuana use is particularly concerning among black youth, with rates far exceeding those for cigarette use and HED. The association of marijuana use with both cigarette use and HED is particularly high in recent years among black adolescents. Substance use recently declined among high school seniors, except for marijuana use, particularly among black youth. The increasing association between marijuana and other substances among black adolescents suggests future amplification in critical health disparities.

Examining Reciprocal Influences Among Family Climate, School Attachment, and Academic Self-Regulation: Implications For School Success Xia M, Fosco GM, Feinberg ME. J Fam Psychol. 2015.
Guided by family systems and ecological theories, this study examined the multicontextual implications of family, school, and individual domains for adolescents' school success. The first goal of this study was to examine reciprocal influences among family climate, school attachment, and academic self-regulation (ASR) during the middle school years. The second goal was to test the relative impact of each of these domains on adolescents' school adjustment and academic achievement after the transition to high school. The authors applied a cross-lag structural equation modeling approach to longitudinal data from 979 students in the 6th grade and their families, followed over 5 measurement occasions, from 6th through 9th grade. Controlling for family income, parent education, and adolescent gender, the results revealed reciprocal relationships between the family climate and school attachment over time; both of these factors were related to increases in ASR over time. In turn, ASR was a robust predictor of academic success, with unique associations with school adjustment and academic achievement. Family climate and school adjustment had modest to marginal associations with school adjustment, and no association with academic achievement. Applications of these findings for family school interventions are discussed.

Correlates Of Sex Trading Among Drug-Involved Women In Committed Intimate Relationships: A Risk Profile Jiwatram-Negan T, El-Bassel N. Womens Health Issues. 2015; 25(4): 420-428.
Despite a slight decline in new human immunodeficiency virus (HIV) infections in New York, marked increases and concentrated epidemics continue among subsets of the population, including women engaged in sex trading. The authors examined the prevalence and correlates of sex trading among 346 low-income, HIV-negative women in HIV-concordant intimate relationships. Women and their long-term main partners were recruited to participate in an HIV prevention intervention. Baseline data were used in this article. Of the 346 women in the study, 28% reported sex trading during the prior 90 days. Multivariate analyses showed increased relative risk of sex trading by lifetime experience of severe intimate partner violence (IPV), drug, and alcohol use, and marginal

significance for mental health hospitalization, partner drug dependency, and homelessness. These findings suggest an urgent need for HIV prevention and intervention efforts targeted toward women in intimate relationships who trade sex for money or drugs, with an emphasis on IPV, mental health, history of incarceration, and substance abuse.

Modeling Intensive Longitudinal Data With Mixtures Of Nonparametric Trajectories and Time-Varying Effects Dziak JJ, Li R, Tan X, Shiffman S, Shiyko MP. Psychol Methods. 2015.
Behavioral scientists increasingly collect intensive longitudinal data (ILD), in which phenomena are measured at high frequency and in real time. In many such studies, it is of interest to describe the pattern of change over time in important variables as well as the changing nature of the relationship between variables. Individuals' trajectories on variables of interest may be far from linear, and the predictive relationship between variables of interest and related covariates may also change over time in a nonlinear way. Time-varying effect models (TVEMs; see Tan, Shiyko, Li, Li, & Dierker, 2012) address these needs by allowing regression coefficients to be smooth, nonlinear functions of time rather than constants. However, it is possible that not only observed covariates but also unknown, latent variables may be related to the outcome. That is, regression coefficients may change over time and also vary for different kinds of individuals. Therefore, the authors describe a finite mixture version of TVEM for situations in which the population is heterogeneous and in which a single trajectory would conceal important, interindividual differences. This extended approach, MixTVEM, combines finite mixture modeling with non- or semiparametric regression modeling, to describe a complex pattern of change over time for distinct latent classes of individuals. The usefulness of the method is demonstrated in an empirical example from a smoking cessation study. The authors provide a versatile SAS macro and R function for fitting MixTVEMs.

PROSPER Partnership Delivery System: Effects On Adolescent Conduct Problem Behavior Outcomes Through 6.5 Years Past Baseline Spoth RL, Trudeau LS, Redmond C, Shin C, Greenberg MT, Feinberg ME, Hyun G-H. J Adolesc. 2015; 45: 44-55.
The authors report long-term effects of the PROSPER delivery system for universal evidence-based preventive interventions on adolescent conduct problem behaviors (CPBs). A cluster randomized trial included 28 school districts assigned to PROSPER or a control condition. Community-based teams in PROSPER condition school districts selected evidence-based interventions-a family-focused intervention in sixth grade and a school-based intervention the next year; follow-up assessments were conducted through 12th grade. CPBs were measured with 12 self-report items derived from the National Youth Survey. Intervention-control differences were tested via a multi-level Zero-Inflated Poisson (ZIP) model. Differences were significant from 9th through 12th grades; Relative Reduction Rates were between 10.1% and 14.5%. The intervention group was delayed in reaching a 10th grade reference level of CPBs by 10.7 months. Moderation analyses indicated stronger effects for early substance initiators. Findings suggest that the PROSPER delivery system has the potential to reduce CPBs in general populations.

Brain Activation To Negative Stimuli Mediates A Relationship Between Adolescent Marijuana Use and Later Emotional Functioning Heitzeg MM, Cope LM, Martz ME, Hardee JE, Zucker RA. Dev Cogn Neurosci. 2015.
This work investigated the impact of heavy marijuana use during adolescence on emotional functioning, as well as the brain functional mediators of this effect. Participants (n=40) were recruited from the Michigan Longitudinal Study (MLS). Data on marijuana use were collected prospectively beginning in childhood as part of the MLS. Participants were classified as heavy

marijuana users (n=20) or controls with minimal marijuana use. Two facets of emotional functioning-negative emotionality and resiliency (a self-regulatory mechanism)-were assessed as part of the MLS at three time points: mean age 13.4, mean age 19.6, and mean age 23.1. Functional neuroimaging data during an emotion-arousal word task were collected at mean age 20.2. Negative emotionality decreased and resiliency increased across the three time points in controls but not heavy marijuana users. Compared with controls, heavy marijuana users had less activation to negative words in temporal, prefrontal, and occipital cortices, insula, and amygdala. Activation of dorsolateral prefrontal cortex to negative words mediated an association between marijuana group and later negative emotionality. Activation of the cuneus/lingual gyrus mediated an association between marijuana group and later resiliency. Results support growing evidence that heavy marijuana use during adolescence affects later emotional outcomes.

Correlates Of Smoking Status Among Women Experiencing Intimate Partner Violence: Substance Use, Posttraumatic Stress, and Coping Sullivan TP, Flanagan JC, Dudley DN, Holt LJ, Mazure CM, McKee SA. Am J Addict. 2015; 24(6): 546-553.
Smoking prevalence among women who experience intimate partner violence (IPV) is two to three times higher than the prevalence among women nationally. Yet, research on cigarette smoking among this population of women is scarce. This study examined differences between daily smokers and non-smokers among a sample of 186 IPV-victimized women. Comparing these groups may identify key factors that could inform future research, and ultimately, smoking cessation interventions to improve women's health. Results showed that smokers and non-smokers differed in terms of alcohol and drug use problem severity, posttraumatic stress symptom severity, psychological and physical IPV victimization severity, and severity of use of psychological and physical IPV. Smokers fared worse on all domains where differences emerged. Findings of a logistic regression demonstrated that alcohol problem severity was related to daily smoking status; post hoc analysis revealed that the effect of alcohol problem severity was moderated by the level of Posttraumatic stress disorder (PTSD) avoidance symptom severity. Findings suggest a sub-population of women experiencing IPV who smoke and incur additional risk for psychiatric symptom severity and maladaptive behaviors. This study suggests the need to examine factors such as IPV and its negative sequelae to inform smoking cessation research for women. This study contributes to the scarce literature examining the intersections of PTSD, alcohol and drug use, and smoking. Examining these factors in the context of IPV, which is a highly prevalent problem, is critical to informing future treatment development investigations.

Trainee and Client Experiences Of Therapeutic Assessment In A Required Graduate Course: A Qualitative Analysis Smith JD, Egan KN. J Pers Assess. 2015; 1-10.
Surveys indicate that practice and training in psychological assessment, and personality assessment (PA) to a lesser degree, has been stable or increasing over the past quarter-century. However, its future arguably remains threatened due to changes in doctoral training programs and beliefs in the field concerning the utility of PA for treatment success. To increase interest in and use of PA, studies of training methods that include trainees' perspectives are needed. This study evaluated the experiences of 10 graduate trainees and their clients who were trained in and conducted a brief Therapeutic Assessment (TA). Qualitative responses to a self-evaluation administered post-TA were coded using directed content analysis. Results indicated that trainees viewed TA/PA as having clinical utility; they had positive feelings about TA/PA, and they desired or intended to use or continue learning about TA/PA. Clients' responses reflected positive feelings about the TA, having gained new self-awareness or understanding, and having a positive relationship with the assessor.

The findings suggest that teaching PA from a TA perspective could produce positive benefits for psychology trainees.

The Impact Of Alcohol Use and Related Disorders On the HIV Continuum Of Care: A Systematic Review : Alcohol and the HIV Continuum Of Care Vagenas P, Azar MM, Copenhaver MM, Springer SA, Molina PE, Altice FL. Curr HIV/AIDS Rep. 2015.
Alcohol use is highly prevalent globally with numerous negative consequences to human health, including HIV progression, in people living with HIV (PLH). The HIV continuum of care, or treatment cascade, represents a sequence of targets for intervention that can result in viral suppression, which ultimately benefits individuals and society. The extent to which alcohol impacts each step in the cascade, however, has not been systematically examined. International targets for HIV treatment as prevention aim for 90% of PLH to be diagnosed, 90% of them to be prescribed with antiretroviral therapy (ART), and 90% to achieve viral suppression; currently, only 20% of PLH are virally suppressed. This systematic review, from 2010 through May 2015, found 53 clinical research papers examining the impact of alcohol use on each step of the HIV treatment cascade. These studies were mostly cross-sectional or cohort studies and from all income settings. Most (77%) found a negative association between alcohol consumption on one or more stages of the treatment cascade. Lack of consistency in measurement, however, reduced the ability to draw consistent conclusions. Nonetheless, the strong negative correlations suggest that problematic alcohol consumption should be targeted, preferably using evidence-based behavioral and pharmacological interventions, to indirectly increase the proportion of PLH achieving viral suppression, to achieve treatment as prevention mandates, and to reduce HIV transmission.

Variability In Medical Marijuana Laws In the United States Bestrashniy J, Winters KC. Psychol Addict Behav. 2015; 29(3): 639-642.
Marijuana use and its distribution raise several complex health, social, and legal issues in the United States. Marijuana is prohibited in only 23 states and promarijuana laws are likely to be introduced in these states in the future. Increased access to and legalization of medical marijuana may have an impact on recreational marijuana use and perception through increased availability and decreased restrictiveness around the drug. The authors undertook an analysis to characterize the policy features of medical marijuana legislation, including an emphasis on the types of medical conditions that are included in medical marijuana laws. A high degree of variability in terms of allowable medical conditions, limits on cultivation and possession, and restrictiveness of policies was discovered. Further research is needed to determine if this variability impacts recreational use in those states.

Parental Involvement In Brief Interventions For Adolescent Marijuana Use Piehler TF, Winters KC. Psychol Addict Behav. 2015; 29(3): 512-521.
Adolescents (aged 12-18 years) identified in a school setting as abusing marijuana and other drugs were randomly assigned to complete 1 of 2 brief interventions (BIs). Adolescents and their parent (N = 259) were randomly assigned to receive either a 2-session adolescent only (BI-A) or a 2-session adolescent and additional parent session (BI-AP). Interventions were manualized and delivered in a school setting by trained counselors. Adolescents were assessed at intake and at 6 months following the completion of the intervention. Using a latent construct representing 6-month marijuana use outcomes, current findings supported previous research that BI-AP resulted in superior outcomes when compared to BI-A. The presence of a marijuana dependence diagnosis at baseline predicted poorer outcomes when compared to youth without a diagnosis. Both baseline

diagnostic status and co-occurring conduct problems interacted with intervention condition in predicting marijuana use outcomes. A marijuana dependence diagnosis resulted in poorer marijuana use outcomes within the BI-A condition when compared to BI-AP. Co-occurring conduct problems were associated with poorer marijuana use outcomes within the BI-AP intervention when compared to BI-A. Implications for implementing BIs given diagnostic status, parent involvement, and co-occurring conduct problems are discussed.

Temporal Variation In Facilitator and Client Behavior During Group Motivational Interviewing Sessions Houck JM, Hunter SB, Benson JG, Cochrum LL, Rowell LN, D'Amico EJ. Psychol Addict Behav. 2015.
There is considerable evidence for motivational interviewing (MI) in changing problematic behaviors. Research on the causal chain for MI suggests influence of facilitator speech on client speech. This association has been examined using macro (session-level) and micro (utterance-level) measures; however, effects across sessions have largely been unexplored, particularly with groups. The authors evaluated a sample of 129 adolescent Group MI sessions, using a behavioral coding system and timing information to generate information on facilitator and client speech (CT; change talk) within 5 successive segments (quintiles) of each group session. They hypothesized that facilitator speech (open-ended questions and reflections of CT) would be related to subsequent CT. Repeated measures analysis indicated significant quadratic and cubic trends for facilitator and client speech across quintiles. Across quintiles, cross-lagged panel analysis using a zero-inflated negative binomial model showed minimal evidence of facilitator speech on client CT, but did indicate several effects of client CT on facilitator speech, and of client CT on subsequent client CT. Results suggest that session-level effects of facilitator speech on client speech do not arise from long-duration effects of facilitator speech; instead, we detected effects of facilitator speech on client speech only at the beginning and end of sessions, when open questions, respectively, suppressed and enhanced client expressions of CT. Findings suggest that clinicians must remain vigilant to client CT throughout the group session, reinforcing it when it arises spontaneously and selectively employing open-ended questions to elicit it when it does not, particularly toward the end of the session.

Can Marijuana Make It Better? Prospective Effects Of Marijuana and Temperament On Risk For Anxiety and Depression Grunberg VA, Cordova KA, Bidwell LC, Ito TA. Psychol Addict Behav. 2015; 29(3): 590-602.
Increases in marijuana use in recent years highlight the importance of understanding how marijuana affects mental health. Of particular relevance is the effect of marijuana use on anxiety and depression given that marijuana use is highest among late adolescents/early adults, the same age range in which risk for anxiety and depression is the highest. Here the authors examine how marijuana use moderates the effects of temperament on level of anxiety and depression in a prospective design in which baseline marijuana use and temperament predict anxiety and depression 1 year later. The authors found that harm avoidance (HA) is associated with higher anxiety and depression a year later, but only among those low in marijuana use. Those higher in marijuana use show no relation between HA and symptoms of anxiety and depression. Marijuana use also moderated the effect of novelty seeking (NS), with symptoms of anxiety and depression increasing with NS only among those with high marijuana use. NS was unrelated to symptoms of anxiety and depression among those low in marijuana use. The temperament dimension of reward dependence was unrelated to anxiety and depression symptoms. These results suggest that marijuana use does

not have an invariant relationship with anxiety and depression, and that the effects of relatively stable temperament dimensions can be moderated by other contextual factors.

Opportunities and Challenges Of Digital Technology For HIV Treatment and Prevention Simoni JM, Kutner BA, Horvath KJ. Curr HIV/AIDS Rep. 2015.
Novel eHealth interventions are creating exciting opportunities for health promotion along the continuum of HIV care and prevention. Reviews of recent work indicate the use of multiple platforms (e.g., smartphones, social media), with trends toward individualized approaches and real-time assessments. However, the field needs more rigorous investigations to provide evidence of long-term impact on clinical indicators and should expand its targets beyond men who have sex with men and medication adherence. Challenges to the field include working within restricted funding timelines and disseminating eHealth interventions to those most in need.

The Emergence Of Parent-Child Coercive Processes In Toddlerhood Chang H, Shaw DS. Child Psychiatry Hum Dev. 2015.
Parent-child coercion typically emerges in toddlerhood with the child's first acts of willful defiance and the parent's first disciplinary attempts. The authors explored how parents and children may contribute to this process by examining bidirectional and interactive effects between child and maternal negative behavior in 310 low-income, ethnically diverse boys. Using multiple informants and methods, child negative emotionality and maternal negative control were assessed at 18 months and child disruptive behavior and maternal negative control were measured at 24 months. Indicative of parent effects, maternal negative control at 18 months amplified the relation between children's negative emotionality at 18 months and disruptive behavior at 24 months. Child effects were found in an unexpected direction such that children's negative emotionality at 18 months predicted decreases in mother's negative control at 24 months. Findings are discussed within a transactional framework that emphasizes mutual influence of children and parents over the course of development.

Preventing Adolescent Depression With The Family Check-Up: Examining Family Conflict As A Mechanism Of Change Fosco GM, Van Ryzin MJ, Connell AM, Stormshak EA. J Fam Psychol. 2015.
Family-centered prevention programs are understudied for their effects on adolescent depression, despite considerable evidence that supports their effectiveness for preventing escalation in youth problem behavior and substance use. This study was conducted with 2 overarching goals: (a) replicate previous work that has implicated the Family Check-Up (FCU), a multilevel, gated intervention model embedded in public middle schools, as an effective strategy for preventing growth in adolescent depressive symptoms and (b) test whether changes in family conflict may be an explanatory mechanism for the long-term, protective effects of the FCU with respect to adolescent depression. This trial was conducted with 593 ethnically diverse families who were randomized to intervention (offered the FCU) or middle school as usual. Complier average causal effect (CACE) analysis revealed that engagers in the FCU evidenced less growth in depressive symptoms and family conflict from 6th through 9th grade, and post hoc analyses indicated that the FCU is related to lower rates of major depressive disorder. The second set of analyses examined family conflict as a mechanism of change for families who participated in the FCU. Families who reported short-term intervention benefits had significantly less escalation in family conflict over the middle school years; in turn, growth in family conflict explained risk for adolescent depressive symptoms.

The Longitudinal Relationship Between Employment and Substance Use Among At-risk Adolescents Osilla KC, Miles JNV, Hunter SB, D'Amico EJ. J Child Adolesc Behav. 2015; 3(3).
This paper explores the longitudinal association between employment and alcohol/other drug (AOD) use and consequences among an at-risk youth sample with a first-time AOD offense. This study extends previous research by examining the effects of more stable employment over time. Participants were adolescents referred to a diversion program (N=193) for a first-time AOD offense. Mean age was 16.6 (SD=1.1), 67% of the sample was male; and 45% Hispanic or Latino/a, 45% white; 10% other. The authors examined work intensity at program intake with AOD use, AOD-related consequences and risky social environment 180 days after the first survey. Greater work intensity was associated with greater peak drinks per occasion 180 days later and time spent around teens who use alcohol and marijuana; when controlling for age, gender, and race/ethnicity, work intensity was only associated with increased contact with teens who use marijuana. Work stability was not found to be associated with AOD-related use, outcomes, or reports of a risky social environment. Understanding how employment uniquely affects at-risk youth can help us determine policies and practices that may be needed to monitor the amount of time teens work.

Promoting Positive Future Expectations During Adolescence: The Role Of Assets Stoddard SA, Pierce J. Am J Community Psychol. 2015.
Positive future expectations can facilitate optimal development and contribute to healthier outcomes for youth. Researchers suggest that internal resources and community-level factors may influence adolescent future expectations, yet little is known about the processes through which these benefits are conferred. The present study examined the relationship between contribution to community, neighborhood collective efficacy, purpose, hope and future expectations, and tested a mediation model that linked contribution to community and collective efficacy with future expectations through purpose and hope in a sample of 7th grade youth (N = 196; Mage =Â 12.39; 60 % female; 40% African American; 71 % economically disadvantaged). Greater collective efficacy and contribution to community predicted higher levels of hope and purpose. Higher levels of hope and purpose predicted more positive future expectations. Contribution to community and neighborhood collective efficacy indirectly predicted future expectations via hope. Implications of the findings and suggestions for future research are discussed.

Socio-structural and Behavioral Risk Factors Associated With Trafficked History Of Female Bar/spa Entertainers In the Sex Trade In the Philippines Urada LA, Halterman S, Raj A, Tsuyuki K, Pimentel-Simbulan N, Silverman JG. Int J Gynaecol Obstet. 2015.
The aim of this study was to explore factors associated with trafficking (deceptive/coercive entry to sex trade) among female bar/spa entertainers who traded sex in the Philippines. Female bar/spa entertainers who traded sex in the past 6 months were recruited from 25 bar/spa venues in Metro Manila (April 2009-January 2010) and assessed via cross-sectional survey data collection for HIV-risk-related socio-structural factors associated with deceptive/coercive entry into the sex trade. The study employed hierarchical linear modeling. Of 166 bar/spa entertainers assessed, 19 (11.4%) reported being deceived/coerced (i.e. trafficked) into their first jobs. Trafficking history was independently associated with current drug use (adjusted odds ratio [AOR] 2.05; 95% confidence interval [CI] 1.00-3.97) decreased availability of condoms at venues for entertainers (AOR 0.18; 95% CI 0.05-0.71) and, conversely, increased peer support for practicing safer sex behaviors (AOR 3.08; 95% CI 1.63-5.09). Those deceived/coerced into their positions were more likely than non-trafficked women to have been recruited by an agency who came to their rural province (AOR 12.07; 95% CI 1.77-82.25) as opposed to getting the job from advertisement (AOR 0.10; 95% CI

0.02-0.65) or a friend/acquaintance (AOR 0.02; 95% CI 0.00-0.48).The findings have implications for designing interventions to prevent and target trafficked women in the Philippines who may be more vulnerable to substance use and, potentially, HIV infection.

Police Encounters Among Needle Exchange Clients In Baltimore: Drug Law Enforcement As A Structural Determinant Of Health Beletsky L, Cochrane J, Sawyer AL, Serio-Chapman C, Smelyanskaya M, Han J, Robinowitz N, Sherman SG. Am J Public Health. 2015; 105(9): 1872-1879.
The authors piloted a monitoring mechanism to document police encounters around programs targeting people who inject drugs (PWID), and assessed their demographic predictors at 2 Baltimore, Maryland, needle exchange program (NEP) sites. In a brief survey, 308 clients quantified, characterized, and sited recent police encounters. Multivariate linear regression determined encounter predictors, and we used geocoordinate maps to illustrate clusters. Within the past 6 months, clients reported a median of 3 stops near NEP sites (interquartile range [IQR] = 0-7.5) and a median of 1 arrest in any location (IQR= 0-2). Three respondents reported police referral to the NEP. Being younger (P = .009), being male (P = .033), and making frequent NEP visits (P = .02) were associated with reported police stops. Among clients reporting arrest or citation for syringe possession, Whites were significantly less likely than non-Whites to report being enroute to or from an NEP (P < .001). Reported encounters were clustered around NEPs. Systematic surveillance of structural determinants of health for PWID proved feasible when integrated into service activities. Improved monitoring is critical to informing interventions to align policing with public health, especially among groups subject to disproportionate levels of drug law enforcement.

Prescription Disposal Practices: A 2-Year Ecological Study Of Drug Drop Box Donations In Appalachia Gray J, Hagemeier N, Brooks B, Alamian A. Am J Public Health. 2015; 105(9): e89-94.
The authors quantified controlled substance donations via permanent drug donation boxes over 2 years in a region with high prescription abuse, assessing medication characteristics, time between dispensing and donation, and weight of medications donated per capita. In partnership with Drug Enforcement Administration and local law enforcement, we analyzed permanent drug donation box collections in 8 Northeast Tennessee locations from June 2012 to April 2014. The authors recorded controlled substance dosage units along with the product dispensing date. They collected 4841 pounds of pharmaceutical waste, 4.9% (238.5 pounds) of which were controlled substances, totaling 106,464 controlled substance doses. Analysis of dispensing dates for controlled substances indicated a median of 34 months lapsed from dispensing to donation (range = 1-484 months). The mean controlled substance donation rate was 1.39 pounds per 1000 residents. Communities with fewer than 10,000 residents had a statistically higher controlled substance donation rate (P = .002) compared with communities with 10,000 or more residents. Permanent drug donation boxes can be an effective mechanism to remove controlled substances from community settings. Rural and urban community residents should be provided convenient and timely access to drug disposal options.

Comparing Treatment Policies With Assistance From the Structural Nested Mean Model Lu X, Lynch KG, Oslin DW, Murphy S. Biometrics. 2015.
Treatment policies, also known as dynamic treatment regimes, are sequences of decision rules that link the observed patient history with treatment recommendations. Multiple, plausible, treatment policies are frequently constructed by researchers using expert opinion, theories, and reviews of the literature. Often these different policies represent competing approaches to managing an illness.

Here, the authors develop an "assisted estimator" that can be used to compare the mean outcome of competing treatment policies. The term "assisted" refers to the fact estimators from the Structural Nested Mean Model, a parametric model for the causal effect of treatment at each time point, are used in the process of estimating the mean outcome. This work is motivated by our work on comparing the mean outcome of two competing treatment policies using data from the ExTENd study in alcohol dependence.

Cost-effectiveness Of Population-level Expansion Of Highly Active Antiretroviral Treatment For HIV In British Columbia, Canada: A Modelling Study Nosyk B, Min JE, Lima VD, Hogg RS, Montaner JSG, STOP HIV/AIDS study group. Lancet HIV. 2015; 2(9): e393-400.
Widespread HIV screening and access to highly active antiretroviral treatment (ART) were cost effective in mathematical models, but population-level implementation has led to questions about cost, value, and feasibility. In 1996, British Columbia, Canada, introduced universal coverage of drug and other health-care costs for people with HIV/AIDS and began extensive scale-up in access to ART. The authors aimed to assess the cost-effectiveness of ART scale-up in British Columbia compared with hypothetical scenarios of constrained treatment access. Using comprehensive linked population-level data, they populated a dynamic, compartmental transmission model to simulate the HIV/AIDS epidemic in British Columbia from 1997 to 2010. The authors estimated HIV incidence, prevalence, mortality, costs (in 2010 CAN$), and quality-adjusted life-years (QALYs) for the study period, which was 1997-2010. They calculated incremental cost-effectiveness ratios from societal and third-party-payer perspectives to compare actual practice (true numbers of individuals accessing ART) to scenarios of constrained expansion (75% and 50% probability of accessing ART). They also investigated structural and parameter uncertainty. Actual practice resulted in 263 averted incident cases compared with 75% of observed access and 676 averted cases compared with 50% of observed access to ART. From a third-party-payer perspective, actual practice resulted in incremental cost-effectiveness ratios of $23 679 per QALY versus 75% access and $24 250 per QALY versus 50% access. From a societal perspective, actual practice was cost saving within the study period. When the model was extended to 2035, current observed access resulted in cumulative savings of $25·1 million compared with the 75% access scenario and $65·5 million compared with the 50% access scenario. ART scale-up in British Columbia has decreased HIV-related morbidity, mortality, and transmission. Resulting incremental cost-effectiveness ratios for actual practice, derived within a limited timeframe, were within established cost-effectiveness thresholds and were cost saving from a societal perspective.

Bayesian Group Lasso For Nonparametric Varying-Coefficient Models With Application To Functional Genome-Wide Association Studies Li J, Wang Z, Li R, Wu R. Ann Appl Stat. 2015; 9(2): 640-664.
Although genome-wide association studies (GWAS) have proven powerful for comprehending the genetic architecture of complex traits, they are challenged by a high dimension of single-nucleotide polymorphisms (SNPs) as predictors, the presence of complex environmental factors, and longitudinal or functional natures of many complex traits or diseases. To address these challenges, the authors propose a high-dimensional varying-coefficient model for incorporating functional aspects of phenotypic traits into GWAS to formulate a so-called functional GWAS or fGWAS. Bayesian group lasso and the associated MCMC algorithms are developed to identify significant SNPs and estimate how they affect longitudinal traits through time-varying genetic actions. The model is generalized to analyze the genetic control of complex traits using subject-specific sparse longitudinal data. The statistical properties of the new model are investigated through simulation

studies. The authors use the new model to analyze a real GWAS data set from the Framingham Heart Study, leading to the identification of several significant SNPs associated with age-specific changes of body mass index. The fGWAS model, equipped with Bayesian group lassso, will provide a useful tool for genetic and developmental analysis of complex traits or diseases.

The Downside Of Tobacco Control? Smoking and Self-stigma: A systematic Review Evans-Polce RJ, Castaldelli-Maia JM, Schomerus G, Evans-Lacko SE. Soc Sci Med. 2015; 145: 26-34.
Little is known about the consequences of tobacco smoking stigma on smokers and how smokers may internalize smoking-related stigma. This review summarizes existing literature on tobacco smoking self-stigma, investigating to what extent smokers are aware of negative stereotypes, agree with them and apply them to themselves. The authors carried out a systematic search of Pubmed/Web of Science/PsycInfo databases for articles related to smoking self-stigma through June 2013. Reference lists and citations of included studies were also checked and experts were contacted. After screening articles for inclusion/exclusion criteria the authors performed a quality assessment and summarized findings according to the stages of self-stigma as conceptualized in Corrigan progressive model of self-stigma (aware, agree, apply and harm). Initial searches yielded 570 articles. Thirty of these articles (18 qualitative and 12 quantitative studies) met criteria for our review. Awareness of smoking stigma was virtually universal across studies. Coping strategies for smoking stigma and the degree to which individuals who smoke internalized this stigma varied both within and across studies. There was considerable variation in positive, negative, and non-significant consequences associated with smoking self-stigma. Limited evidence was found for subgroup differences in smoking-related stigma. While there is some evidence that smoking self-stigma leads to reductions in smoking, this review also identified significant negative consequences of smoking self-stigma. Future research should assess the factors related to differences in how individuals respond to smoking stigma. Public health strategies which limit the stigmatization of smokers may be warranted.

Yoga In Public School Improves Adolescent Mood and Affect Felver JC, Butzer B, Olson KJ, Smith IM, Khalsa SBS. Contemp Sch Psychol. 2015; 19(3): 184-192.
The purpose of the present study was to directly compare the acute effects of participating in a single yoga class versus a single standard physical education (PE) class on student mood. Forty-seven high school students completed self-report questionnaires assessing mood and affect immediately before and after participating in a single yoga class and a single PE class one week later. Data were analyzed using paired-samples t tests and Wilcoxon-signed ranks tests and by comparing effect sizes between the two conditions. Participants reported significantly greater decreases in anger, depression, and fatigue from before to after participating in yoga compared to PE. Significant reductions in negative affect occurred after yoga but not after PE; however, the changes were not significantly different between conditions. In addition, after participating in both yoga and PE, participants reported significant decreases in confusion and tension, with no significant difference between groups. Results suggest that school-based yoga may provide unique benefits for students above and beyond participation in PE. Future research should continue to elucidate the distinct psychological and physiological effects of participating in yoga compared to PE activities.

Interrelationships Among Parental Family History Of Substance Misuse, Delay Discounting, and Personal Substance Use VanderBroek L, Acker J, Palmer AA, de Wit H, MacKillop J. Psychopharmacology (Berl). 2015.
Despite consistent evidence of the familiarity of substance misuse, the mechanisms by which family history (FH) increases the risk of addiction are not well understood. One behavioral trait that may mediate the risk for substance use and addiction is delay discounting (DD), which characterizes an individual's preferences for smaller immediate rewards compared to larger future rewards. The aim of this study is to examine the interrelationships among FH, DD, and diverse aspects of personal substance use, and to test DD as a mediator of the relationship between FH and personal substance use. The study used crowdsourcing to recruit a community sample of adults (N =732). Family history was assessed using a brief assessment of perceived parental substance use problems, personal substance use was assessed using the Alcohol Use Disorders Identification Test and a measure of frequency of use, and delay discounting was assessed using a latent index of discounting preferences across six reward magnitudes. Steeper discounting was significantly associated with personal alcohol, tobacco, and marijuana use, and level of substance experimentation. Steeper DD was also associated with a denser parental FH of alcohol, tobacco, and overall substance misuse. Parental FH density was significantly associated with several aspects of personal substance use, and these relationships were partially mediated by DD. The current study suggests that impulsivity, as measured by DD, is one proximal mechanism by which parental FH increases substance use later in life. The causal role of DD in this relationship will need to be established in future longitudinal studies.

Prevalence Of Marijuana and Other Substance Use Before and After Washington State's Change From Legal Medical Marijuana To Legal Medical and Non-Medical Marijuana: Cohort Comparisons In A Sample Of Adolescents Mason WA, Fleming CB, Ringle JL, Hanson K, Gross TJ, Haggerty KP. Subst Abus. 2015.
A growing number of states have new legislation extending prior legalization of medical marijuana by allowing non-medical marijuana use for adults. The potential influence of this change in legislation on adolescent marijuana and other substance use (e.g., spillover or substitution effects) is uncertain. The authors capitalize on an ongoing study to explore the prevalence of marijuana and other substance use in two cohorts of adolescents who experienced the non-medical marijuana law change in Washington State at different ages. Participants were 8(th) graders enrolled in targeted Tacoma, Washington public schools and recruited in two consecutive annual cohorts. The analysis sample was 238 students who completed a baseline survey in the 8(th) grade and a follow-up survey after the 9(th) grade. Between the two assessments, the second cohort experienced the Washington State non-medical marijuana law change, whereas the first cohort did not. Self-report survey data on lifetime and past month marijuana, cigarette, and alcohol use were collected. Multivariate multilevel modeling showed that cohort differences in the likelihood of marijuana use were significantly different from those for cigarette and alcohol use at follow-up (adjusting for baseline substance initiation). Marijuana use was higher for the second cohort than the first cohort, but this difference was not statistically significant. Rates of cigarette and alcohol use were slightly lower in the second cohort than in the first cohort. This exploratory study found that marijuana use was more prevalent among teens shortly after the transition from medical marijuana legalization only to medical and non-medical marijuana legalization, although the difference between cohorts was not statistically significant. The findings also provided some evidence of substitution effects. The analytic technique used here may be useful for examining potential long-term effects of non-medical marijuana laws on adolescent marijuana use and substitution or spillover effects in future studies.

The Syndemic Of HIV, HIV-related Risk and Multiple Co-morbidities Among Women Who Use Drugs In Malaysia: Important Targets For Intervention Loeliger KB, Marcus R, Wickersham JA, Pillai V, Kamarulzaman A, Altice FL. Addict Behav. 2015; 53: 31-39. Substance use and HIV are syndemic public health problems in Malaysia. Harm reduction efforts to reduce HIV transmission have primarily focused on men with substance use disorders. To explore HIV risk behaviors, substance use, and social factors associated with poor health outcomes among women who use drugs in Malaysia. A cross-sectional survey of 103 drug-using women in Kuala Lumpur, Malaysia were recruited to assess their medical, psychiatric and social comorbidity as well as their engagement in nationally recommended HIV testing and monitoring activities. One-third reported having ever injected drugs, with most (68.2%) having recently shared injection paraphernalia. Sex work (44.7%) and infrequent condom use (42.4%) were common as was underlying psychiatric illness and physical and sexual violence during childhood and adulthood. Most women (62.1%) had unstable living situations and suffered from an unmet need for social support and health services. HIV prevalence was high (20%) with only two thirds of women eligible for antiretroviral therapy having received it. Suboptimal HIV testing and/or monitoring was positively associated with interpersonal violence (AOR 2.73; 95% CI 1.04-7.14) and negatively associated with drug injection (AOR 0.28; 95% CI 0.10-0.77).Women who use drugs in Malaysia demonstrate considerable medical, psychiatric and social co-morbidity, which negatively contributes to optimal and crucial engagement in HIV treatment-as-prevention strategies. Mental health and social support may be key targets for future public health interventions aimed at drug-using women in Malaysia.

Self-control Forecasts Better Psychosocial Outcomes But Faster Epigenetic Aging In Low-SES Youth Miller GE, Yu T, Chen E, Brody GH. Proc Natl Acad Sci USA. 2015;112(33):10325-10230. There are persistent socioeconomic disparities in many aspects of child development in America. Relative to their affluent peers, children of low socioeconomic status (SES) complete fewer years of education, have a higher prevalence of health problems, and are convicted of more criminal offenses. Based on research indicating that low self-control underlies some of these disparities, policymakers have begun incorporating character-skills training into school curricula and social services. However, emerging data suggest that for low-SES youth, self-control may act as a "double-edged sword," facilitating academic success and psychosocial adjustment, while at the same time undermining physical health. Here, the authors examine this hypothesis in a five-wave study of 292 African American teenagers from rural Georgia. From ages 17 to 20 y, the authors assessed SES and self-control annually, along with depressive symptoms, substance use, aggressive behavior, and internalizing problems. At age 22 y, they obtained DNA methylation profiles of subject's peripheral blood mononuclear cells. These data were used to measure epigenetic aging, a methylation-derived biomarker reflecting the disparity between biological and chronological aging. Among high-SES youth, better mid-adolescent self-control presaged favorable psychological and methylation outcomes. However, among low-SES youth, self-control had divergent associations with these outcomes. Self-control forecasted lower rates of depressive symptoms, substance use, aggressive behavior, and internalizing problems but faster epigenetic aging. These patterns suggest that for low-SES youth, resilience is a "skin-deep" phenomenon, wherein outward indicators of success can mask emerging problems with health. These findings have conceptual implications for models of resilience, and practical implications for interventions aimed at ameliorating social and racial disparities.

Reducing Risks For Problem Behaviors During the High School Transition: Proximal Outcomes In The Common Sense Parenting Trial Mason WA, Fleming CB, Ringle JL, Thompson RW, Haggerty KP, Snyder JJ. J Child Fam Stud. 2015; 24(9): 2568-2578.
This study tests Common Sense Parenting (CSP)®, a widely used parent-training program, in its standard form and in a modified form known as CSP Plus, with low-income 8(th) graders and their families during the high school transition. The six-session CSP program proximally targets parenting and child emotion regulation skills. CSP Plus adds two sessions that include youth, and the eight-session program further targets skills for avoiding negative peers and activities in high school. Over two cohorts, 321 families were enrolled and randomly assigned to either CSP, CSP Plus, or minimal-contact control conditions. To date, pretest and posttest assessments have been completed, with 93% retention over about a 6-month interval. Here, analyses of preliminary outcomes from pretest to posttest focus on data collected from parents, who represent the primary proximal intervention targets. Intent-to-treat structural equation modeling analyses were conducted. CSP and CSP Plus had statistically significant effects on increased parent-reported child emotion regulation skills. CSP Plus further showed a statistically significant effect on increased parent perceptions of their adolescent being prepared for high school, but only in a model that excluded the CSP condition. Neither program had a significant proximal effect on parenting practices. Emotion regulation, one indicator of self-control, is a robust protective factor against problem behaviors. Intervention effects on this outcome may translate into reduced problems during high school. Moreover, CSP Plus showed some limited signs of added value for preparing families for the high school transition.

RESEARCH ON PHARMACOTHERAPIES FOR DRUG ABUSE

Long-Acting Cocaine Hydrolase For Addiction Therapy Chen X, Xue L, Hou S, Jin Z, Zhang T, Zheng F, Zhan CG. Proc Natl Acad Sci U S A. 2015 Dec 28. pii: 201517713. [Epub ahead of print].
Cocaine abuse is a world-wide public health and social problem without a US Food and Drug Administration-approved medication. An ideal anticocaine medication would accelerate cocaine metabolism, producing biologically inactive metabolites by administration of an efficient cocaine-specific exogenous enzyme. The authors' recent studies have led to the discovery of the desirable, highly efficient cocaine hydrolases (CocHs) that can efficiently detoxify and inactivate cocaine without affecting normal functions of the CNS. Preclinical and clinical data have demonstrated that these CocHs are safe for use in humans and are effective for accelerating cocaine metabolism. However, the actual therapeutic use of a CocH in cocaine addiction treatment is limited by its short biological half-life (e.g., 8 h or shorter in rats). Here the authors demonstrate a novel CocH form, a catalytic antibody analog, which is a fragment crystallizable (Fc)-fused CocH dimer (CocH-Fc) constructed by using CocH to replace the Fab region of human IgG1. The CocH-Fc not only has a high catalytic efficiency against cocaine but also, like an antibody, has a considerably longer biological half-life (e.g., ~107 h in rats). A single dose of CocH-Fc was able to accelerate cocaine metabolism in rats even after 20 d and thus block cocaine-induced hyperactivity and toxicity for a long period. Given the general observation that the biological half-life of a protein drug is significantly longer in humans than in rodents, the CocH-Fc reported in this study could allow dosing once every 2-4 wk, or longer, for treatment of cocaine addiction in humans.

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; 40(9): 2198-2206.
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.

Full Fatty Acid Amide Hydrolase Inhibition Combined With Partial Monoacylglycerol Lipase Inhibition: Augmented and Sustained Antinociceptive Effects With Reduced Cannabimimetic Side Effects In Mice Ghosh S, Kinsey SG, Liu Q-S, Hruba L, McMahon LR, Grim TW, Merritt CR, Wise LE, Abdullah RA, Selley DE, Sim-Selley LJ, Cravatt BF, Lichtman AH. J Pharmacol Exp Ther. 2015; 354(2): 111-120.
Inhibition of fatty acid amide hydrolase (FAAH) or monoacylglycerol lipase (MAGL), the primary hydrolytic enzymes for the respective endocannabinoids N-arachidonoylethanolamine (AEA) and 2-arachidonylglycerol (2-AG), produces antinociception but with minimal cannabimimetic side effects. Although selective inhibitors of either enzyme often show partial efficacy in various nociceptive models, their combined blockade elicits augmented antinociceptive effects, but side effects emerge. Moreover, complete and prolonged MAGL blockade leads to cannabinoid receptor type 1 (CB1) receptor functional tolerance, which represents another challenge in this potential therapeutic strategy. Therefore, the present study tested whether full FAAH inhibition combined with partial MAGL inhibition would produce sustained antinociceptive effects with minimal cannabimimetic side effects. Accordingly, the authors tested a high dose of the FAAH inhibitor PF-3845 (N-3-pyridinyl-4-[[3-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenyl]methyl]-1-piperidinecarboxamide; 10 mg/kg) given in combination with a low dose of the MAGL inhibitor JZL184 [4-nitrophenyl 4-(dibenzo[d][1,3]dioxol-5-yl(hydroxy)methyl)piperidine-1-carboxylate] (4 mg/kg) in mouse models of inflammatory and neuropathic pain. This combination of inhibitors elicited profound increases in brain AEA levels (>10-fold) but only 2- to 3-fold increases in brain 2-AG levels. This combination produced significantly greater antinociceptive effects than single enzyme inhibition and did not elicit common cannabimimetic effects (e.g., catalepsy, hypomotility, hypothermia, and substitution for Δ(9)-tetrahydrocannabinol in the drug-discrimination assay), although these side effects emerged with high-dose JZL184 (i.e., 100 mg/kg). Finally, repeated administration of this combination did not lead to tolerance to its antiallodynic actions in the carrageenan assay or CB1 receptor functional tolerance. Thus, full FAAH inhibition combined with partial MAGL inhibition reduces neuropathic and inflammatory pain states with minimal cannabimimetic effects.

Effects Of 7-day Continuous D-amphetamine, Methylphenidate, and Cocaine Treatment On Choice Between Methamphetamine And Food In Male Rhesus Monkeys Schwienteck KL, Banks ML. Drug Alcohol Depend. 2015; 155: 16-23.
Methamphetamine addiction is a significant public health problem for which no Food and Drug Administration-approved pharmacotherapies exist. Preclinical drug vs. food choice procedures have been predictive of clinical medication efficacy in the treatment of opioid and cocaine addiction. Whether preclinical choice procedures are predictive of candidate medication effects for other abused drugs, such as methamphetamine, remains unclear. The present study's aim was to determine continuous 7-day treatment effects with the monoamine releaser d-amphetamine and the monoamine uptake inhibitor methylphenidate on methamphetamine vs. food choice. In addition, 7-day cocaine treatment effects were also examined. Behavior was maintained under a concurrent schedule of food delivery (1-g pellets, fixed-ratio 100 schedule) and methamphetamine injections (0-0.32mg/kg/injection, fixed-ratio 10 schedule) in male rhesus monkeys (n=4). Methamphetamine choice dose-effect functions were determined daily before and during 7-day periods of continuous intravenous treatment with d-amphetamine (0.01-0.1mg/kg/h), methylphenidate (0.032-

0.32mg/kg/h), or cocaine (0.1-0.32mg/kg/h).During saline treatment, increasing methamphetamine doses resulted in a corresponding increase in methamphetamine vs. food choice. Continuous 7-day treatments with d-amphetamine, methylphenidate or cocaine did not significantly attenuate methamphetamine vs. food choice up to doses that decreased rates of operant responding. However, 0.1mg/kg/h d-amphetamine did eliminate methamphetamine choice in two monkeys. The present subchronic treatment results support the utility of preclinical methamphetamine choice to evaluate candidate medications for methamphetamine addiction. Furthermore, these results confirm and extend previous results demonstrating differential pharmacological mechanisms between cocaine choice and methamphetamine choice.

Nicotinic Ligands As Multifunctional Agents For the Treatment Of Neuropsychiatric Disorders Terry Jr, AV, Callahan PM, Hernandez CM. Biochem Pharmacol. 2015; 97(4): 388-398.
The challenges associated with developing more effective treatments for neurologic and psychiatric illness such as Alzheimer's disease and schizophrenia are considerable. Both the symptoms and the pathophysiology of these conditions are complex and poorly understood and the clinical presentations across different patients can be very heterogeneous. Moreover, it has become apparent that the reductionist approach to drug discovery for these illnesses that has dominated the field for decades (i.e., the development of highly selective compounds or other treatment modalities focused on a very specific pathophysiologic target) has not been widely successful. Accordingly, a variety of new strategies have emerged including the development of "multitarget-directed ligands" (MTDLs), the development and/or identification of compounds that exhibit "multifunctional" activity (e.g., pro-cognitive plus neuroprotective, pro-cognitive plus antipsychotic activity), "repurposing" strategies for existing compounds that have other clinical indications, and novel "adjunctive" treatment strategies that might enhance the efficacy of the currently available treatments. Interestingly, a variety of ligands at nicotinic acetylcholine receptors (nAChRs) appear to have the potential to fulfill one or more of these desirable properties (i.e., multifunctional, repurposing, or adjunctive treatment potential). The purpose of this review (while not all-inclusive) is to provide an overview of a variety of nAChR ligands that demonstrate potential in these categories, particularly, "multifunctional" properties. Due to their densities in the mammalian brain and the amount of literature available, the review will focus on ligands of the high affinity α4β2 nAChR and the low affinity α7 nAChR.

Effects Of Self-administered Methamphetamine On Discrimination Learning and Reversal In Nonhuman Primates Kangas BD, Bergman J. Psychopharmacology (Berl). 2015.
Frequent exposure to methamphetamine has been reported to adversely influence cognitive behavior and, in particular, inhibitory control processes.The present studies were conducted in squirrel monkeys to assess the effects of daily intravenous methamphetamine self-administration on touch screen-based repeated acquisition and discrimination reversal tasks thought to reflect behavioral dimensions of, respectively, learning and response inhibition. First, stable methamphetamine-maintained behavior was established in each subject (0.35-1.6 mg/kg/session), and subsequently, a second daily session of discrimination learning was conducted (20 h later). Subjects first learned to discriminate between two simultaneously presented stimuli (acquisition) and, subsequently, to re-learn the discrimination with the contingencies switched (reversal). The role of the interval between self-administration and touch screen sessions was evaluated, as well as the effects of abrupt methamphetamine discontinuation.Results indicate that daily methamphetamine self-administration markedly disrupted the development of discrimination learning, initially requiring nearly twice the number of trials to master discriminations. The magnitude of adverse effects in individual subjects

correlated to the level of daily methamphetamine intake. Importantly, however, behavioral disruption of discrimination learning was surmounted following remedial training. Once criterion levels of discrimination performance were achieved, subsequent development of reversal performance was largely unaffected except when the interval between self-administration and touch screen session was short and, thus, likely a result of methamphetamine's direct effects. Discontinuation of methamphetamine produced no disruption in acquisition or reversal.These results indicate that self-administered methamphetamine can markedly disrupt learning processes and highlight key differences in its effects on different aspects of discrimination learning.

Knock-In Mice With NOP-eGFP Receptors Identify Receptor Cellular and Regional Localization Ozawa A, Brunori G, Mercatelli D, Wu J, Cippitelli A, Zou B, Xie XS, Williams M, Zaveri NT, Low S, Scherrer G, Kieffer BL, Toll L. J Neurosci. 2015; 35(33): 11682-11693.
The nociceptin/orphanin FQ (NOP) receptor, the fourth member of the opioid receptor family, is involved in many processes common to the opioid receptors including pain and drug abuse. To better characterize receptor location and trafficking, knock-in mice were created by inserting the gene encoding enhanced green fluorescent protein (eGFP) into the NOP receptor gene (Oprl1) and producing mice expressing a functional NOP-eGFP C-terminal fusion in place of the native NOP receptor. The NOP-eGFP receptor was present in brain of homozygous knock-in animals in concentrations somewhat higher than in wild-type mice and was functional when tested for stimulation of [(35)S]GTPγS binding in vitro and in patch-clamp electrophysiology in dorsal root ganglia (DRG) neurons and hippocampal slices. Inhibition of morphine analgesia was equivalent when tested in knock-in and wild-type mice. Imaging revealed detailed neuroanatomy in brain, spinal cord, and DRG and was generally consistent with in vitro autoradiographic imaging of receptor location. Multicolor immunohistochemistry identified cells coexpressing various spinal cord and DRG cellular markers, as well as coexpression with μ-opioid receptors in DRG and brain regions. Both in tissue slices and primary cultures, the NOP-eGFP receptors appear throughout the cell body and in processes. These knock-in mice have NOP receptors that function both in vitro and in vivo and appear to be an exceptional tool to study receptor neuroanatomy and correlate with NOP receptor function.The NOP receptor, the fourth member of the opioid receptor family, is involved in pain, drug abuse, and a number of other CNS processes. The regional and cellular distribution has been difficult to determine due to lack of validated antibodies for immunohistochemical analysis. To provide a new tool for the investigation of receptor localization, the authors have produced knock-in mice with a fluorescent-tagged NOP receptor in place of the native NOP receptor. These knock-in mice have NOP receptors that function both in vitro and in vivo and have provided a detailed characterization of NOP receptors in brain, spinal cord, and DRG neurons. They appear to be an exceptional tool to study receptor neuroanatomy and correlate with NOP receptor function.

Par-4 Secretion: Stoichiometry Of 3-arylquinoline Binding To Vimentin Sviripa VM, Burikhanov R, Obiero JM, Yuan Y, Nickell JR, Dwoskin LP, Zhan C-G, Liu C, Tsodikov OV, Rangnekar VM, Watt DS. Org Biomol Chem. 2015.
Advanced prostate tumors usually metastasize to the lung, bone, and other vital tissues and are resistant to conventional therapy. Prostate apoptosis response-4 protein (Par-4) is a tumor suppressor that causes apoptosis in therapy-resistant prostate cancer cells by binding specifically to a receptor, Glucose-regulated protein-78 (GRP78), found only on the surface of cancer cells. 3-Arylquinolines or "arylquins" induce normal cells to release Par-4 from the intermediate filament protein, vimentin and promote Par-4 secretion that targets cancer cells in a paracrine manner. A structure-activity study identified arylquins that promote Par-4 secretion, and an evaluation of

arylquin binding to the hERG potassium ion channel using a [(3)H]-dofetilide binding assay permitted the identification of structural features that separated this undesired activity from the desired Par-4 secretory activity. A binding study that relied on the natural fluorescence of arylquins and that used the purified rod domain of vimentin (residues 99-411) suggested that the mechanism behind Par-4 release involved arylquin binding to multiple sites in the rod domain.

Effects Of *t*he Nicotinic Agonist Varenicline On the Performance Of Tasks Of Cognition In Aged and Middle-aged Rhesus and Pigtail Monkeys Terry Jr, AV, Plagenhoef M, Callahan PM. Psychopharmacology (Berl). 2015.
Due to the rising costs of drug development especially in the field of neuropsychiatry, there is increasing interest in efforts to identify new clinical uses for existing approved drugs (i.e., drug repurposing). The purpose of this work was to evaluate in animals the smoking cessation agent, varenicline, a partial agonist at α4β2 and full agonist at α7 nicotinic acetylcholine receptors, for its potential as a repurposed drug for disorders of cognition.Oral doses of varenicline ranging from 0.01 to 0.3 mg/kg were evaluated in aged and middle-aged monkeys for effects on the following: working/short-term memory in a delayed match to sample (DMTS) task, distractibility in a distractor version of the DMTS (DMTS-D), and cognitive flexibility in a ketamine-impaired reversal learning task.In dose-effect studies in the DMTS and DMTS-D tasks, varenicline was not associated with statistically significant effects on performance. However, individualized "optimal doses" were effective when repeated on a separate occasion (i.e., improving DMTS accuracy at long delays and DMTS-D accuracy at short delays by approximately 13.6 and 19.6 percentage points above baseline, respectively). In reversal learning studies, ketamine impaired accuracy and increased perseverative responding, effects that were attenuated by all three doses of varenicline that were evaluated. While the effects of varenicline across the different behavioral tasks were modest, these data suggest that varenicline may have potential as a repurposed drug for disorders of cognition associated with aging (e.g., Alzheimer's disease), as well as those not necessarily associated with advanced age (e.g., schizophrenia).

Addiction Pharmacogenetics: A Systematic Review Of the Genetic Variation Of the Dopaminergic System Patriquin MA, Bauer IE, Soares JC, Graham DP, Nielsen DA. Psychiatr Genet. 2015; 25(5): 181-193.
Substance use disorders have significant personal, familial, and societal consequences. Despite the serious consequences of substance use, only a few therapies are effective in treating substance use disorders, thus highlighting a need for improved treatment practices. Substance use treatment response depends on multiple factors such as genetic, biological, and social factors. It is essential that each component is represented in treatment plans. The dopaminergic system plays a critical role in the pharmacotherapy for addictions, and an understanding of the role of variation of genes involved in this system is essential for its success. This review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement guidelines. A computerized literature search was conducted using PubMed and Scopus (all databases). Articles published up to April 2015 that examined the role of dopaminergic gene variation in the pharmacotherapy of alcohol, opioid, and cocaine use disorders were reviewed. Search terms were dopamine, gene, polymorphism, substance abuse, treatment, and response. Polymorphisms of the DRD2, ANKK1, DAT1, DBH, and DRD4 genes have been found to moderate the effects of pharmacotherapy of alcohol, opioid, and cocaine use disorders. The integration of genetic information with clinical data will inform health professionals of the most efficacious pharmacotherapeutic intervention for substance use disorders. More studies are needed to confirm and extend these findings.

A Double-Blind, Placebo-Controlled Trial To Evaluate the Safety, Tolerability, and Pharmacokinetics Of Single, Escalating Oral Doses Of JDTic Buda JJ, Carroll FI, Kosten TR, Swearingen D, Walters BB. Neuropsychopharmacology. 2015; 40(9): 2059-2065.
Animal studies suggest that kappa opioid receptor antagonists (KORAn) potentially could treat a wide variety of addictive and depressive disorders. The authors assessed the KORAn JDTic for safety, tolerability, and pharmacokinetics in a double-blind, placebo-controlled, randomized trial evaluating single oral doses in healthy adult males. Predose and postdose safety assessments included orthostatic vital signs; 6-lead continuous telemetry monitoring (approximately 16 h predose to 24 h postdose); 12-lead electrocardiograms (ECGs); clinical chemistry, hematology, coagulation, and urinalysis; psychomotor functioning (using the Wayne Saccadic Fixator (WSF)); and adverse events. As a potential indicator of JDTic effects on affect, the POMS Standard instrument was administered predose and daily postdose Days 1-6. At 1 mg, 2 of the 6 JDTic (and 0/6 placebo) subjects experienced a single, asymptomatic event of multiple beats of nonsustained ventricular tachycardia (NSVT). Their events were temporally similar with respect to time postdose (and the postdose timing of an NSVT event in a monkey). These events triggered a study stopping rule. No differences were observed between the placebo and JDTic subjects with respect to clinical chemistry, hematology, coagulation, urinalysis, orthostatic vital signs, WSF, or 12-lead ECG parameters. Plasma JDTic levels were below the lower limit of quantitation (0.1 nM) in all subjects. There were no significant differences in POMS scores between the placebo and JDTic groups. Although the evidence is circumstantial, it suggests that NSVT is a potential JDTic toxicity in humans. Given the therapeutic potential of KORAn, further investigation is needed to determine whether a significant JDTic human cardiac effect indeed exists, and if so, whether it is specific to JDTic or represents a KORAn class effect.

Synthesis, Nicotinic Acetylcholine Receptor Binding, In Vitro and In Vivo Pharmacology Properties Of 3'-(substituted Pyridinyl)-deschloroepibatidine Analogs Ondachi PW, Ye Z, Castro AH, Luetje CW, Damaj MI, Mascarella SW, Navarro HA, Carroll FI. Bioorg Med Chem. 2015; 23(17): 5693-5701.
Over the last several years the authors have synthesized and studied the in vitro and in vivo nAChR pharmacological properties of epibatidine (4) analogs. In this study they report the synthesis, nAChR in vitro and in vivo pharmacological properties of 3';-(substituted pyridinyl)-deschloroepibatidine analogs (5a-e and 6a-e). All of the analogs had high binding affinity for α4β2(∗)-nAChRs. Several of the analogs were potent antagonists of α4β2-nAChRs in in vitro efficacy tests and were potent antagonists of nicotine-induced antinociception in the mouse tail-flick test. Compound 6b had a Ki = 0.13 nM in the binding assay, 25- and 46-fold selectivity for the α4β2(∗)-nAChR relative to the α3β4- and α7-nAChR, respectively, in the in vitro efficacy test and an AD50 = 0.13 μg/kg in the tail-flick test. Combined with favorable calculated physiochemical properties compared to varenicline, these findings suggest that 6b should be considered for development as a potential pharmacotherapy for treating nicotine addiction and other CNS disorders.

Characterization Of Kappa Opioid Receptor Mediated, Dynorphin-stimulated [(35)S]GTPγS Binding In Mouse Striatum For the Evaluation Of Selective KOR Ligands In An Endogenous Setting Zhou L, Stahl EL, Lovell KM, Frankowski KJ, Prisinzano TE, Aubé J, Bohn LM. Neuropharmacology. 2015; 99: 131-141.
Differential modulation of kappa opioid receptor (KOR) signaling has been a proposed strategy for developing therapies for drug addiction and depression by either activating or blocking this

receptor. Hence, there have been significant efforts to generate ligands with diverse pharmacological properties including partial agonists, antagonists, allosteric modulators as well as ligands that selectively activate some pathways while not engaging others (biased agonists). It is becoming increasingly evident that G protein coupled receptor signaling events are context dependent and that what may occur in cell based assays may not be fully indicative of signaling events that occur in the naturally occurring environment. As new ligands are developed, it is important to assess their signaling capacity in relevant endogenous systems in comparison to the performance of endogenous agonists. Since KOR is considered the cognate receptor for dynorphin peptides we have evaluated the selectivity profiles of dynorphin peptides in wild-type (WT), KOR knockout (KOR-KO), and mu opioid receptor knockout (MOR-KO) mice using [(35)S]GTPγS binding assay in striatal membrane preparations. The authors find that while the small molecule KOR agonist U69,593, is very selective for KOR, dynorphin peptides promiscuously stimulate G protein signaling in striatum. Furthermore, these studies demonstrate that norBNI and 5';GNTI are highly nonselective antagonists as they maintain full potency and efficacy against dynorphin signaling in the absence of KOR. Characterization of a new KOR antagonist, which may be more selective than NorBNI and 5's;GNTI, is presented using this approach.

Galectin-1 Suppresses Methamphetamine Induced Neuroinflammation In Human Brain Microvascular Endothelial Cells: Neuroprotective Role In Maintaining Blood Brain Barrier Integrity Parikh NU, Aalinkeel R, Reynolds JL, Nair BB, Sykes DE, Mammen MJ, Schwartz SA, Mahajan SD. Brain Res. 2015; 1624: 175-187.
Methamphetamine (Meth) abuse can lead to the breakdown of the blood-brain barrier (BBB) integrity leading to compromised CNS function. The role of Galectins in the angiogenesis process in tumor-associated endothelial cells (EC) is well established; however no data are available on the expression of Galectins in normal human brain microvascular endothelial cells and their potential role in maintaining BBB integrity. The authors evaluated the basal gene/protein expression levels of Galectin-1, -3 and -9 in normal primary human brain microvascular endothelial cells (BMVEC) that constitute the BBB and examined whether Meth altered Galectin expression in these cells, and if Galectin-1 treatment impacted the integrity of an in-vitro BBB. These results showed that BMVEC expressed significantly higher levels of Galectin-1 as compared to Galectin-3 and -9. Meth treatment increased Galectin-1 expression in BMVEC. Meth induced decrease in TJ proteins ZO-1, Claudin-3 and adhesion molecule ICAM-1 was reversed by Galectin-1. These data suggests that Galectin-1 is involved in BBB remodeling and can increase levels of TJ proteins ZO-1 and Claudin-3 and adhesion molecule ICAM-1 which helps maintain BBB tightness thus playing a neuroprotective role. Galectin-1 is thus an important regulator of immune balance from neurodegeneration to neuroprotection, which makes it an important therapeutic agent/target in the treatment of drug addiction and other neurological conditions.

High Affinity A3β4 Nicotinic Acetylcholine Receptor Ligands AT-1001 And AT-1012 Attenuate Cocaine-induced Conditioned Place Preference and Behavioral Sensitization In Mice Khroyan TV, Yasuda D, Toll L, Polgar WE, Zaveri NT. Biochem Pharmacol. 2015; 97(4): 531-541.
Cholinergic signaling via the nicotinic acetylcholine receptors (nAChRs) in the mesolimbic circuitry is involved in the rewarding effects of abused drugs such as cocaine and opioids. In mouse studies, nonselective nAChR antagonist mecamylamine blocks cocaine-induced conditioned place preference (CPP) and behavioral sensitization. Among subtype-selective nAChR antagonists, the β2-selective antagonist dihydrobetaerythroidine and α7 antagonist methyllycaconitine (MLA), but

not MLA alone prevent behavioral sensitization to cocaine. Since the role of the α3β4 nAChR subtype in the rewarding and behavioral effects of cocaine is unknown, the present study investigated the effect of two potent and selective α3β4 nAChR ligands, AT-1001 and AT-1012, on the acquisition of cocaine-induced CPP and behavioral sensitization in mice. At 5-30mg/kg, cocaine produced robust CPP, whereas behavioral sensitization of locomotor activity was only observed at the higher doses (20-30mg/kg). Pretreatment with AT-1001 (1-10mg/kg) or AT-1012 (3-10mg/kg) blocked CPP induced by 5mg/kg cocaine, but not by 30mg/kg cocaine. Lower doses of AT-1001 (0.3-1mg/kg) and AT-1012 (1-3mg/kg) did not affect the increase in locomotor activity induced by 5 or 30mg/kg cocaine. But AT-1001, at these doses, blocked locomotor sensitization induced by 30mg/kg cocaine. These results indicate that the α3β4 nAChR play a role in the rewarding and behavioral effects of cocaine, and that selective α3β4 nAChR ligands can attenuate cocaine-induced behavioral phenomena. Since the selective α3β4 nAChR functional antagonist AT-1001 has also been shown to block nicotine self-administration in rats, the present results suggest that α3β4 nAChRs may be a target for the treatment of cocaine addiction as well as for cocaine-nicotine comorbid addiction.

Reward and Toxicity Of Cocaine Metabolites Generated By Cocaine Hydrolase Murthy V, Geng L, Gao Y, Zhang B, Miller JD, Reyes S, Brimijoin S. Cell Mol Neurobiol. 2015; 35(6): 819-826.
Butyrylcholinesterase (BChE) gene therapy is emerging as a promising concept for treatment of cocaine addiction. BChE levels after gene transfer can rise 1000-fold above those in untreated mice, making this enzyme the second most abundant plasma protein. For months or years, gene transfer of a BChE mutated into a cocaine hydrolase (CocH) can maintain enzyme levels that destroy cocaine within seconds after appearance in the blood stream, allowing little to reach the brain. Rapid enzyme action causes a sharp rise in plasma levels of two cocaine metabolites, benzoic acid (BA) and ecgonine methyl ester (EME), a smooth muscle relaxant that is mildly hypotensive and, at best, only weakly rewarding. The present study, utilizing Balb/c mice, tested reward effects and cardiovascular effects of administering EME and BA together at molar levels equivalent to those generated by a given dose of cocaine. Reward was evaluated by conditioned place preference. In this paradigm, cocaine (20 mg/kg) induced a robust positive response but the equivalent combined dose of EME + BA failed to induce either place preference or aversion. Likewise, mice that had undergone gene transfer with mouse CocH (mCocH) showed no place preference or aversion after repeated treatments with a near-lethal 80 mg/kg cocaine dose. Furthermore, a single administration of that same high cocaine dose failed to affect blood pressure as measured using the noninvasive tail-cuff method. These observations confirm that the drug metabolites generated after CocH gene transfer therapy are safe even after a dose of cocaine that would ordinarily be lethal.

Design, Synthesis, and Pharmacological Evaluation Of JDTic Analogs To Examine the Significance Of the 3- and 4-methyl Substituents Carroll FI, Gichinga MG, Kormos CM, Maitra R, Runyon SP, Thomas JB, Mascarella SW, Decker AM, Navarro HA. Bioorg Med Chem. 2015; 23(19): 6379-6388.
The design and discovery of JDTic as a potent and selective kappa opioid receptor antagonist used the N-substituted trans-3,4-dimethyl-4-(3-hydroxyphenyl) piperidine pharmacophore as the lead structure. In order to determine if the 3-methyl or 4-methyl groups were necessary in JDTic and JDTic analogs for antagonistic activity, compounds 4a-c, and 4d-f which have either the 3-methyl or both the 3- and 4-methyl groups removed, respectively, from JDTic and analogs were synthesized and evaluated for their in vitro opioid receptor antagonist activities using a

[(35)S]GTPγS binding assay. Other ADME properties were also assessed for selected compounds. These studies demonstrated that neither the 3-methyl or 3,4-dimethyl groups present in JDTic and analogs are required to produce potent and selective κ opioid receptor antagonists.

The New Psychoactive Substances 5-(2-aminopropyl)indole (5-IT) and 6-(2-aminopropyl)indole (6-IT) Interact With Monoamine Transporters In Brain Tissue Marusich JA, Antonazzo KR, Blough BE, Brandt SD, Kavanagh PV, Partilla JS, Baumann MH. Neuropharmacology. 2015; 101: 68-75.
In recent years, use of psychoactive synthetic stimulants has grown rapidly. 5-(2-Aminopropyl) indole (5-IT) is a synthetic drug associated with a number of fatalities, that appears to be one of the newest 3,4-methylenedioxymethamphetamine (MDMA) replacements. Here, the monoamine-releasing properties of 5-IT, its structural isomer 6-(2-aminopropyl)indole (6-IT), and MDMA were compared using in vitro release assays at transporters for dopamine (DAT), norepinephrine (NET), and serotonin (SERT) in rat brain synaptosomes. In vivo pharmacology was assessed by locomotor activity and a functional observational battery (FOB) in mice. 5-IT and 6-IT were potent substrates at DAT, NET, and SERT. In contrast with the non-selective releasing properties of MDMA, 5-IT displayed greater potency for release at DAT over SERT, while 6-IT displayed greater potency for release at SERT over DAT. 5-IT produced locomotor stimulation and typical stimulant effects in the FOB similar to those produced by MDMA. Conversely, 6-IT increased behaviors associated with 5-HT toxicity. 5-IT likely has high abuse potential, which may be somewhat diminished by its slow onset of in vivo effects, whereas 6-IT may have low abuse liability, but enhanced risk for adverse effects. Results indicate that subtle differences in the chemical structure of transporter ligands can have profound effects on biological activity. The potent monoamine-releasing actions of 5-IT, coupled with its known inhibition of MAO A, could underlie its dangerous effects when administered alone, and in combination with other monoaminergic drugs or medications. Consequently, 5-IT and related compounds may pose substantial risk for abuse and serious adverse effects in human users.

Structure-activity Relationship Studies Of Functionally Selective Kappa Opioid Receptor Agonists That Modulate ERK 1/2 Phosphorylation While Preserving G Protein Over Barrestin2 Signaling Bias Lovell KM, Frankowski KJ, Stahl EL, Slauson SR, Yoo E, Prisinzano TE, Aubé J, Bohn LM. ACS Chem Neurosci. 2015; 6(8): 1411-1419.
Kappa opioid receptor (KOR) modulation is a promising target for drug discovery efforts due to KOR involvement in pain, depression, and addiction behaviors. The authors recently reported a new class of triazole KOR agonists that displays significant bias toward G protein signaling over βarrestin2 recruitment; interestingly, these compounds also induce less activation of ERK1/2 map kinases than the balanced agonist, U69,593. They have identified structure-activity relationships around the triazole scaffold that allows for decreasing the bias for G protein signaling over ERK1/2 activation while maintaining the bias for G protein signaling over βarrestin2 recruitment. The development of novel compounds, with different downstream signaling outcomes, independent of G protein/βarrestin2 bias, provides a more diverse pharmacological toolset for use in defining complex KOR signaling and elucidating the significance of KOR-mediated signaling.

Negatively Charged Carbon Nanohorn Supported Cationic Liposome Nanoparticles: A Novel Delivery Vehicle For Anti-Nicotine Vaccine Zheng H, Hu Y, Huang W, de Villiers S, Pentel P, Zhang J, Dorn H, Ehrich M, Zhang C. J Biomed Nanotechnol. 2015; 11(12): 2197-2210.
Tobacco addiction is the second-leading cause of death in the world. Due to the nature of nicotine (a small molecule), finding ways to combat nicotine's deleterious effects has been a constant challenge to the society and the medical field. In the present work, a novel anti-nicotine vaccine based on nanohorn supported liposome nanoparticles (NsL NPs) was developed. The nano-vaccine was constructed by using negatively charged carbon nanohorns as a scaffold for the assembly of cationic liposomes, which allow the conjugation of hapten conjugated carrier proteins. The assembled bio-nanoparticles are stable. Mice were immunized subcutaneously with the nano-vaccine, which induced high titer and high affinity of nicotine specific antibodies in mice. Furthermore, no evidence of clinical signs or systemic toxicity followed multiple administrations of NsL-based anti-nicotine vaccine. These results suggest that NsL-based anti-nicotine vaccine is a promising candidate in treating nicotine dependence and could have potential to significantly contribute to smoking cessation.

The Frequency Of Early-activated Hapten-specific B Cell Subsets Predicts the Efficacy Of Vaccines For Nicotine Dependence Laudenbach M, Tucker AM, Runyon SP, Carroll FI, Pravetoni M. Vaccine. 2015; 33(46): 6332-6339.
Therapeutic vaccines for nicotine addiction show pre-clinical efficacy. Yet, clinical evaluation of the first-generation nicotine vaccines did not meet expectations because only a subset of immunized subjects achieved effective serum antibody levels. Recent studies suggest that vaccine design affects B cell activation, and that the frequency of the hapten-specific B cell subsets contributes to vaccine efficacy against drugs of abuse. To extend this hypothesis to nicotine immunogens, the authors synthesized a novel hapten containing a carboxymethylureido group at the 2-position of the nicotine structure (2CMUNic) and compared its efficacy to the previously characterized 6CMUNic hapten. Haptens were conjugated to the keyhole limpet hemocyanin (KLH) carrier protein, and evaluated for efficacy against nicotine in mice using the clinically approved alum adjuvant. Using a novel fluorescent antigen-based magnetic enrichment strategy paired with multicolor flow cytometry analysis, polyclonal hapten-specific B cell subsets were measured in mice immunized with either 6CMUNic-KLH or 2CMUNic-KLH. The 6CMUNic-KLH showed significantly greater efficacy than 2CMUNic-KLH on nicotine distribution to serum and to the brain. The 6CMUNic-KLH elicited higher anti-nicotine serum antibody titers, and greater expansion of hapten-specific B cells than 2CMUNic-KLH. Within the splenic polyclonal B cell population, a higher number of hapten-specific IgM(high) and germinal centre B cells predicted greater vaccine efficacy against nicotine distribution. These early pre-clinical findings suggest that hapten structure affects activation of B cells, and that variations in the frequency of early-activated hapten-specific B cell subsets underlie individual differences in vaccine efficacy.

Synthesis and Characterization Of 5-Hydroxy-2-(2-phenylethyl)chromone (5-HPEC) and Its Analogues As Non-nitrogenous 5-HT2B Ligands Williams DA, Zaidi SA, Zhang Y. J Nat Prod. 2015; 78(8): 1859-1867.
The involvement of the neurotransmitter serotonin (5-HT) in numerous physiological functions is often attributed to the diversity of receptors with which it interacts. Ligands targeting serotonin receptor 2B (5-HT2B) have received renewed interest for their potential to help understand the role of 5-HT2B in migraines, drug abuse, neurodegenerative diseases, and irritable bowel syndrome. To date, most of the ligands targeting 5-HT2B have been nitrogen-containing compounds. The natural

product 5-hydroxy-2-(2-phenylethyl) chromone (5-HPEC, 5) has been shown previously to act as a non-nitrogenous antagonist for the 5-HT2B receptor (pKi = 5.6). This report describes further progress on the study of the structure-activity relationship of both naturally occurring and synthetic compounds bearing the 2-(2-phenylethyl)chromone scaffold at the 5-HT2B receptor. The inhibitory activity of the newly synthesized compounds (at 10 μM) was tested against each of the 5-HT2 receptors. Following this assay, the binding affinity and antagonism of the most promising compounds were then evaluated at 5-HT2B. Among all the analogues, 5-hydroxy-2-(2-phenylpropyl)chromone (5-HPPC, 22h) emerged as a new lead compound, showing a 10-fold improvement in affinity (pKi = 6.6) over 5-HPEC with reasonable antagonist properties at 5-HT2B. Additionally, ligand docking studies have identified a putative binding pocket for 5-HPPC and have helped understand its improved affinity.

Effects Of Fatty Acid Amide Hydrolase (FAAH) Inhibitors On Working Memory In Rats
Panlilio LV, Thorndike EB, Nikas SP, Alapafuja SO, Bandiera T, Cravatt BF, Makriyannis A, Piomelli D, Goldberg SR, Justinova Z. Psychopharmacology (Berl). 2015.
Manipulations of the endocannabinoid system could potentially produce therapeutic effects with minimal risk of adverse cannabis-like side effects. Inhibitors of fatty acid amide hydrolase (FAAH) increase endogenous levels of the cannabinoid-receptor agonist, anandamide, and show promise for treating a wide range of disorders. However, their effects on learning and memory have not been fully characterized.The authors determined the effects of five structurally different FAAH inhibitors in an animal model of working memory known to be sensitive to impairment by delta-9 tetrahydrocannabinol (THC).A delayed nonmatching-to-position procedure was used in rats. Illuminated nosepoke holes were used to provide cues (left versus right) and record responses (correct versus incorrect) after delays ranging from 0 to 28 s. Various test drugs were given acutely up to two times per week before daily sessions. One FAAH inhibitor, AM3506 (3 mg/kg), decreased accuracy in the memory task. Four other FAAH inhibitors (URB597, URB694, PF-04457845, and ARN14633) and a monoacylglycerol lipase inhibitor (JZL184, which blocks the degradation of the endocannabinoid 2-arachidonoylglycerol) had no effect. Testing of AM3506 in combination with antagonists for receptors known to be affected by anandamide and other fatty acid amides indicated that the impairment induced by AM3506 was mediated by cannabinoid CB1 receptors, and not by alpha-type peroxisome proliferator-activated receptors (PPAR-alpha) or vanilloid transient receptor potential cation channels (TRPV1).FAAH inhibitors differ with respect to their potential for memory impairment, abuse liability, and probably other cannabis-like effects, and they should be evaluated individually for specific therapeutic and adverse effects.

Associations Between Adrenocortical Activity and Nicotine Response In Female Smokers By Menstrual Phase Huttlin EA, Allen AM, Tosun NL, Allen SS, al'Absi M. Addict Behav. 2015; 50: 135-139.
Previous research suggests that menstrual phase may influence smoking-related symptomatology. The present study analyzes the relationship between menstrual phase and salivary cortisol with subjective responses to nicotine among female smokers during ad libitum smoking. The authors hypothesize higher cortisol levels would be associated with increased positive and decreased negative subjective responses to nicotine. The authors also expected that these associations would vary by menstrual phase. Females aged 18-40 who smoke at least five cigarettes/day, reported regular menstrual cycles and did not use exogenous hormones or psychotropic medications were enrolled into a controlled cross-over trial. Participants completed identical data collection procedures during follicular (F) and luteal (L) phases; including self-collected salivary cortisol

samples and completion of a nicotine response lab session involving administration of nicotine nasal spray and monitoring of subjective response to nicotine via the Subjective State Scale and Visual Analog Scale. Participants (n = 116) were 29.1 ± 6.9 years old and smoked an average of 12.3 ± 5.5 cigarettes daily. During F phase, higher morning cortisol was associated with decreased negative affect ($r = -0.21$, $p = 0.03$), withdrawal ($r = -0.30$, $p < 0.01$) and increased relaxation ($r = 0.24$, $p = 0.02$) after administration of nicotine nasal spray. Conversely, during L phase, higher morning cortisol was associated with a decrease in head rush ($r = -0.26$, $p = 0.01$) and urge to smoke ($r = -0.21$, $p = 0.04$) after administration of nicotine nasal spray. Similar associations between greater diurnal cortisol variation and response to nicotine were seen. These observations indicate that cortisol may have a phase-specific association with some subjective responses to nicotine in female smokers. Additional research should explore how these relationships may influence smoking cessation efforts.

Medication Nonadherence, "Professional Subjects," and Apparent Placebo Responders
McCann DJ, Petry NM, Bresell A, Isacsson E, Wilson E, Alexander R.
Nonadherence is a major problem in clinical trials of new medications. To evaluate the extent of nonadherence, this study evaluated pharmacokinetic sampling from 1765 subjects receiving active therapy across 8 psychiatric trials conducted between 2001 and 2011. With nonadherence defined as greater than 50% of plasma samples below the limit of quantification for study drug, the percentage of nonadherent subjects ranged from 12.8% to 39.2%. There was a trend towards increased nonadherence in studies with greater numbers of subjects, but an association with nonadherence was not apparent for other study design parameters or subject characteristics. For 2 trials with multiple recruitment sites in geographical proximity, several subjects attempted to simultaneously enroll at separate site locations. The construct of "professional subjects" those who enroll in trials only for financial gain, is gaining attention and we therefore modeled the impact of professional subjects on medication efficacy trials. The results indicate that enrollment of professional subjects who are destined to success (those who will appear to achieve treatment success regardless of study drug assignment) can substantially increase both the apparent placebo response rate and the sample size requirement for statistical power, while decreasing the observed effect size. The overlapping nature of nonadherence, professional subjects, and placebo response suggests that these issues should be considered and addressed together. Following this approach, we describe a novel clinical trial design to minimize the adverse effects of professional subjects on trial outcomes and discuss methods to monitor adherence.

Measures Of Outcome For Stimulant Trials: ACTTION Recommendations and Research Agenda Kiluk BD, Carroll KM, Duhig A, Falk DE, Kampman K, Lai S, Litten RZ, McCann DJ, Montoya ID, Preston KL, Skolnick P, Weisner C, Woody G, Chandler R, Detke MJ, Dunn K, Dworkin RH, Fertig J, Gewandter J, Moeller FG, Ramey T, Ryan M, Silverman K, Strain EC.
The development and approval of an efficacious pharmacotherapy for stimulant use disorders has been limited by the lack of a meaningful indicator of treatment success, other than sustained abstinence. In March, 2015, a meeting sponsored by Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) was convened to discuss the current state of the evidence regarding meaningful outcome measures in clinical trials for stimulant use disorders. Attendees included members of academia, funding and regulatory agencies, pharmaceutical companies, and healthcare organizations. The goal was to establish a research agenda for the development of a meaningful outcome measure that may be used as an endpoint in clinical trials for stimulant use disorders. Based on guidelines for the selection of clinical trial

endpoints, the lessons learned from prior addiction clinical trials, and the process that led to identification of a meaningful indicator of treatment success for alcohol use disorders, several recommendations for future research were generated. These include a focus on the validation of patient reported outcome measures of functioning, the exploration of patterns of stimulant abstinence that may be associated with physical and/or psychosocial benefits, the role of urine testing for validating self-reported measures of stimulant abstinence, and the operational definitions for reduction-based measures in terms of frequency rather than quantity of stimulant use. These recommendations may be useful for secondary analyses of clinical trial data, and in the design of future clinical trials that may help establish a meaningful indicator of treatment success.

Quinine As A Potential Tracer For Medication Adherence: A Pharmacokinetic and Pharmacodynamic Assessment Of Quinine Alone and In Combination With Oxycodone In Humans Babalonis S, Hampson AJ, Lofwall MR, Nuzzo PA, Walsh SL. J Clin Pharmacol. 2015 Jun 1. doi: 10.1002/jcph.557. [Epub ahead of print].
Effective strategies to monitor pharmacotherapy adherence are necessary, and sensitive biological markers are lacking. This study examined a subtherapeutic dose of quinine as a potential adherence tracer. Primary aims included examination of the plasma and urinary pharmacokinetic profile of once-daily quinine; secondary aims assessed pharmacokinetic/pharmacodynamic interactions with oxycodone (a CYP3A and CYP2D substrate). Healthy, nondependent opioid users (n = 9) were enrolled in this within-subject, double-blind, placebo-controlled inpatient study. Participants received the following oral doses: day 1, oxycodone (30 mg); days 2-4, quinine (80 mg); day 5, quinine and oxycodone (2 hours postquinine). Blood and 24-hour urine samples were collected throughout the study, and pharmacodynamic outcomes were assessed during experimental sessions (days 1, 4, 5). Quinine displayed a plasma Tmax ~2 hours and t1/2 ~10 hours. Oxycodone and noroxycodone parameters (Tmax , Cmax , t1/2) were similar with or without quinine present, although drug exposure (AUC) was slightly greater when combined with quinine. No pharmacodynamic interactions were detected, and doses were safely tolerated. During washout, quinine urinary concentrations steadily declined (elimination t1/2 ~16 hours), with a 94% decrease observed 72 hours postdose. Overall, low-dose quinine appears to be a good candidate for a medication additive to monitor adherence for detection of missed medication.

Mood and Anxiety Regulation By Nicotinic Acetylcholine Receptors: A Potential Pathway To Modulate Aggression and Related Behavioral States Picciotto MR, Lewis AS, van Schalkwyk GI, Mineur YS. Neuropharmacology. 2015; 96(Pt B): 235-243.
The co-morbidity between smoking and mood disorders is striking. Preclinical and clinical studies of nicotinic effects on mood, anxiety, aggression, and related behaviors, such as irritability and agitation, suggest that smokers may use the nicotine in tobacco products as an attempt to self-medicate symptoms of affective disorders. The role of nicotinic acetylcholine receptors (nAChRs) in circuits regulating mood and anxiety is beginning to be elucidated in animal models, but the mechanisms underlying the effects of nicotine on aggression-related behavioral states (ARBS) are still not understood. Clinical trials of nicotine or nicotinic medications for neurological and psychiatric disorders have often found effects of nicotinic medications on ARBS, but few trials have studied these outcomes systematically. Similarly, the increase in ARBS resulting from smoking cessation can be resolved by nicotinic agents, but the effects of nicotinic medications on these types of mental states and behaviors in non-smokers are less well understood. Here the authors review the literature on the role of nAChRs in regulating mood and anxiety, and subsequently on the closely

related construct of ARBS. They suggest avenues for future study to identify how nAChRs and nicotinic agents may play a role in these clinically important areas.

E-Cigarettes and Smoking Cessation: Insights and Cautions From A Secondary Analysis Of Data From A Study Of Online Treatment-Seeking Smokers Pearson JL, Stanton CA, Cha S, Niaura RS, Luta G, Graham AL. Nicotine Tob Res. 2015; 17(10): 1219-1227.
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, Fagerström 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.

Naltrexone Maintenance Decreases Cannabis Self-Administration and Subjective Effects In Daily Cannabis Smokers Haney M, Ramesh D, Glass A, Pavlicova M, Bedi G, Cooper, ZD. Neuropsychopharmacology. 2015; 40(11): 2489-2498.
Given that cannabis use is increasing in the United States, pharmacological treatment options to treat cannabis use disorder are needed. Opioid antagonists modulate cannabinoid effects and may offer a potential approach to reducing cannabis use. In this double-blind, placebo-controlled human laboratory study, the authors assessed the effects of naltrexone maintenance on the reinforcing, subjective, psychomotor, and cardiovascular effects of active and inactive cannabis. Nontreatment-seeking, daily cannabis smokers were randomized to receive naltrexone (50 mg: n=18 M and 5 F) or placebo (0 mg; n=26 M and 2 F) capsules for 16 days. Before, during, and after medication maintenance, participants completed 10 laboratory sessions over 4-6 weeks, assessing cannabis; behavioral and cardiovascular effects. Medication compliance was verified by observed capsule administration, plasma naltrexone, and urinary riboflavin. Relative to placebo, maintenance on naltrexone significantly reduced both active cannabis self-administration and its positive subjective effects. Participants in the placebo group had 7.6 times (95% CI: 1.1-51.8) the odds of self-administering active cannabis compared with the naltrexone group. This attenuation of reinforcing and positive subjective effects also influenced cannabis use in the natural ecology. Naltrexone had intrinsic effects: decreasing ratings of friendliness, food intake, and systolic blood pressure, and increasing spontaneous reports of stomach upset and headache, yet dropout rates were comparable between groups. In summary, the authors show for the first time that maintenance on naltrexone decreased cannabis self-administration and ratings of 'good effect' in nontreatment-seeking daily

cannabis smokers. Clinical studies in patients motivated to reduce their cannabis use are warranted to evaluate naltrexone's efficacy as a treatment for cannabis use disorder.

Smoking and Cardiac Rehabilitation Participation: Associations With Referral, Attendance and Adherence Gaalema DE, Cutler AY, Higgins ST, Ades PA. Prev Med. 2015; 80: 67-74.
Continued smoking after a cardiac event greatly increases mortality risk. Smoking cessation and participation in cardiac rehabilitation (CR) are effective in reducing morbidity and mortality. However, these two behaviors may interact; those who smoke may be less likely to access or complete CR. This review explores the association between smoking status and CR referral, attendance, and adherence. A systematic literature search was conducted examining associations between smoking status and CR referral, attendance and completion in peer-reviewed studies published through July 1st, 2014. For inclusion, studies had to report data on outpatient CR referral, attendance or completion rates and smoking status had to be considered as a variable associated with these outcomes. Fifty-six studies met inclusion criteria. In summary, a history of smoking was associated with an increased likelihood of referral to CR. However, smoking status also predicted not attending CR and was a strong predictor of CR dropout. Continued smoking after a cardiac event predicts lack of attendance in, and completion of CR. The issue of smoking following a coronary event deserves renewed attention.

Contraceptive Use and Method Choice Among Women With Opioid and Other Substance Use Disorders: A Systematic Review Terplan M, Hand DJ, Hutchinson M, Salisbury-Afshar E, Heil, Sarah H. Prev Med. 2015; 80: 23-31.
The aims of this study were to systematically review the literature on contraceptive use by women with opioid and other substance use disorders in order to estimate overall contraceptive use and to examine method choice given the alarmingly high rate of unintended pregnancy in this population. Pubmed (1948-2014) and PsycINFO (1806-2014) databases were searched for peer-reviewed journal articles using a systematic search strategy. Only articles published in English and reporting contraceptive use within samples of women with opioid and other substance use disorders were eligible for inclusion. Out of 580 abstracts reviewed, 105 articles were given a full-text review, and 24 studies met the inclusion criteria. The majority (51%) of women in these studies reported using opioids, with much smaller percentages reporting alcohol and cocaine use. Across studies, contraceptive prevalence ranged widely, from 6%-77%, with a median of 55%. Results from a small subset of studies (N=6) suggest that women with opioid and other substance use disorders used contraception less often than non-drug-using comparison populations (56% vs. 81%, respectively). Regarding method choice, condoms were the most prevalent method, accounting for a median of 62% of contraceptives used, while use of more effective methods, especially implants and intrauterine devices (IUDs), was far less prevalent 8%.Women with opioid and other substance use disorders have an unmet need for contraception, especially for the most effective methods. Offering contraception services in conjunction with substance use treatment and promoting use of more effective methods could help meet this need and reduce unintended pregnancy in this population.

Neural Activation During Risky Decision-making In Youth At High Risk For Substance Use Disorders Hulvershorn LA, Hummer TA, Fukunaga R, Leibenluft E,; Finn P, Cyders MA, Anand A, Overhage L, Dir A, Brown J. Psychiatry Res. 2015; 233(2): 102-111.
Risky decision-making, particularly in the context of reward-seeking behavior, is strongly associated with the presence of substance use disorders (SUDs). However, there has been little research on the neural substrates underlying reward-related decision-making in drug-naïve youth

who are at elevated risk for SUDs. Participants comprised 23 high-risk (HR) youth with a well-established SUD risk phenotype and 27 low-risk healthy comparison (HC) youth, aged 10-14. Participants completed the balloon analog risk task (BART), a task designed to examine risky decision-making, during functional magnetic resonance imaging. The HR group had faster reaction times, but otherwise showed no behavioral differences from the HC group. HR youth experienced greater activation when processing outcome, as the chances of balloon explosion increased, relative to HC youth, in ventromedial prefrontal cortex (vmPFC). As explosion probability increased, group-by-condition interactions in the ventral striatum/anterior cingulate and the anterior insula showed increasing activation in HR youth, specifically on trials when explosions occurred. Thus, atypical activation increased with increasing risk of negative outcome (i.e., balloon explosion) in a cortico-striatal network in the HR group. These findings identify candidate neurobiological markers of addiction risk in youth at high familial and phenotypic risk for SUDs.

Relationships Of PROP Taste Phenotype, Taste Receptor Genotype, and Oral Nicotine Replacement Use Ahijevych K, Tepper BJ, Graham MC, Holloman C, Matcham WA. Nicotine Tob Res. 2015; 17(9): 1149-1155.
Recommended dosage of oral nicotine replacement therapy (NRT) product is often not achieved in smoking cessation attempts. n-6-propylthiouracil (PROP) bitter taste phenotype may be a potential risk factor for non-adherence to oral NRT products due to their bitter taste. There is limited literature on this phenotype in the context of smoking and none in relation to oral NRT pharmacotherapy. The association of PROP taste phenotype with NRT usage and sensory response to products was examined. In a cross-over experimental design, 120 participants received a 1 week supply of nicotine inhalers and 1 week of nicotine lozenges with random assignment to order. Mixed effects linear model analyses were conducted. PROP taste phenotype and taste receptor genotype were not associated with NRT usage or sensory response to NRT, after adjusting for other factors. However, PROP non-tasters used a higher number of lozenges per day (continuous exposure) than nicotine cartridges (intermittent exposure). Unexpectedly, half of baseline PROP non-tasters shifted to taster phenotype 2 weeks after smoking cessation or reduction. Menthol cigarette smokers identified higher NRT strength of sensation scores than nonmenthol smokers. Taste receptor genotype was related to PROP taste phenotype (Kendall $\tau = .591$, $p = .0001$).A nonsignificant relationship of PROP phenotype and NRT usage may be associated with NRT under-dosing and limited variance in the outcome variable. PROP non-tasters; greater use of lozenges is consistent with nicotine exposure being less aversive to non-tasters. Further research of this and other factors impacting NRT usage are warranted to effectively inform smoking cessation pharmacotherapy.

Pharmacological, Sensorimotor, and Expectancy Effects On Tobacco Withdrawal: A Preliminary Study Guillot CR, Stone MD, Geary BA, Kirkpatrick MG, Tidey JW, Cook JW, Leventhal AM. Hum Psychopharmacol. 2015; 30(5): 364-371.
Research designs for parsing the mechanisms underlying tobacco withdrawal are scant. This study introduced a novel research design that simultaneously manipulated three tobacco withdrawal mechanisms: pharmacological (nicotine dissipation), sensorimotor (elimination of the smoking ritual), and expectancy (activation of beliefs regarding the effects of nicotine deprivation), permitting examination of the effects of each mechanism while holding the other two mechanisms constant. Following overnight abstinence, 32 regular cigarette smokers were randomized in a 2 (expectancy: told patch contains nicotine versus told placebo patch) × 2 (drug: receive 21-mg transdermal nicotine patch versus receive placebo patch) × 2 (sensorimotor: smoke very low

nicotine content cigarettes versus no smoking) full factorial between-subjects design. Participants repeatedly completed measures of craving, affect, and anticipated pleasure from and desire for rewarding experiences, followed by a smoking lapse analog task. Receiving nicotine (versus placebo) increased positive affect and anticipated pleasure from and desire for reward. Expecting nicotine (versus placebo) reduced negative affect and increased smoking delay. Sensorimotor stimulation from smoking (versus no smoking) reduced smoking urge and behavior. Results provided initial validation of this novel three-mechanism design. This design can be used in the future to advance understanding and treatment of tobacco withdrawal.

The Effects Of Dronabinol During Detoxification and The Initiation Of Treatment With Extended Release Naltrexone Bisaga A, Sullivan MA, Glass A, Mishlen K, Pavlicova M, Haney M, Raby WN, Levin FR, Carpenter KM, Mariani JJ, Nunes EV. Drug Alcohol Depend. 2015;154: 38-45.
Evidence suggests that the cannabinoid system is involved in the maintenance of opioid dependence.The authors examined whether dronabinol, a cannabinoid receptor type 1 partial agonist, reduces opioid withdrawal and increases retention in treatment with extended release naltrexone (XR-naltrexone).Opioid dependent participants were randomized to receive dronabinol 30mg/d (n=40) or placebo (n=20), under double-blind conditions, while they underwent inpatient detoxification and naltrexone induction. Before discharge all participants received an injection of XR-naltrexone, with an additional dose given four weeks later. Dronabinol or placebo was given while inpatient and for 5 weeks afterwards. The primary outcomes were the severity of opioid withdrawal, measured with the Subjective Opioid Withdrawal Scale, and retention in treatment at the end of the inpatient phase and at the end of the 8-week trial.The severity of opioid withdrawal during inpatient phase was lower in the dronabinol group relative to placebo group (p=0.006). Rates of successful induction onto XR-naltrexone (dronabinol 66%, placebo 55%) and completion of treatment (dronabinol 35%, placebo 35%) were not significantly different. Post hoc analysis showed that the 32% of participants who smoked marijuana regularly during the outpatient phase had significantly lower ratings of insomnia and anxiety and were more likely to complete the 8-week trial. Dronabinol reduced the severity of opiate withdrawal during acute detoxification but had no effect on rates of XR-naltrexone treatment induction and retention. Participants who elected to smoke marijuana during the trial were more likely to complete treatment regardless of treatment group assignment.

Genetic Variation (CHRNA5), Medication (combination Nicotine Replacement Therapy Vs. Varenicline), and Smoking Cessation Chen L-S, Baker TB, Jorenby D, Piper M, Saccone N, Johnson E, Breslau N, Hatsukami D, Carney RM, Bierut LJ. Drug Alcohol Depend. 2015; 154: 278-282.
Recent evidence suggests that the efficacy of smoking cessation pharmacotherapy can vary across patients based on their genotypes. This study tests whether the coding variant rs16969968 in the CHRNA5 nicotinic receptor gene predicts the effects of combination nicotine replacement therapy (cNRT) and varenicline on treatment outcomes. In two randomized smoking cessation trials comparing cNRT vs. placebo, and varenicline vs. placebo, the authors used logistic regression to model associations between CHRNA5 rs16969968 and abstinence at end of treatment. For abstinence at end of treatment, there was an interaction between cNRT and rs16969968 (X(2)=8.15, df=2, omnibus-p=0.017 for the interaction); individuals with the high-risk AA genotype were more likely to benefit from cNRT. In contrast, varenicline increased abstinence, but its effect did not vary with CHRNA5. However, the genetic effects differed between the placebo control groups across

two trials (wald=3.94, df=1, p=0.047), this non-replication can alter the interpretation of pharmacogenetic findings. Results from two complementary smoking cessation trials demonstrate inconsistent genetic results in the placebo arms. This evidence highlights the need to compare the most effective pharmacotherapies with the same placebo control to establish pharmacogenetic evidence to aid decisions on medication choice for patients trying to quit smoking.

Barriers To Telephone Quitline Use Among Methadone-Maintained Smokers Griffin JL, Segal KS, Nahvi S. Nicotine Tob Res. 2015; 17(8): 931-936.
Drug users have high rates of tobacco use and tobacco-related disease. Telephone quitlines promote smoking cessation, but their reach among drug users is unknown. The authors thus aimed to assess utilization of and barriers to telephone quitlines among methadone-maintained smokers. Subjects were opioid-dependent smokers in Bronx, New York, methadone treatment programs who were enrolled in a clinical trial of varenicline. All subjects were offered referral to a free, proactive quitline. The authors examined quitline records, surveyed barriers to quitline use, and queried reasons for declining referral. Of the 112 subjects enrolled, 47% were male, 54% were Hispanic, and 28% were Black. All subjects were offered referral, and 25 (22% of study participants) utilized the quitline. Quitline utilizers (vs. nonutilizers) were significantly more likely to have landline phone service (72 vs. 42%, p = .01), interest in quitline participation (92 vs. 62%, p < .01), and willingness to receive calls (96 vs. 76%, p = .02). Nonutilizers were significantly more likely to report cell phone service lapse (38 vs. 14%, p = .04), and difficulty charging cell phones (19 vs. 0%, p = .02). Reasons for quitline refusal included: (a) skepticism of quitline efficacy; (b) aversion to telephone communication; (c) competing life demands (e.g., drug treatment, shelter); and (d) problems with cell phone service or minutes. Despite several limitations to quitline access among methadone-maintained smokers, routine quitline referral was associated with 22% utilization. To expand provision of smoking cessation treatment to opioid-dependent smokers, interventions to promote routine quitline referral in substance abuse treatment programs warrant investigation.

Anti-saccade Error Rates As A Measure Of Attentional Bias In Cocaine Dependent Subjects
Dias NR, Schmitz JM, Rathnayaka N,Red SD, Sereno AB, Moeller FG, Lane SD. Behav Brain Res. 2015; 292: 493-499.
Cocaine-dependent (CD) subjects show attentional bias toward cocaine-related cues, and this form of cue-reactivity may be predictive of craving and relapse. Attentional bias has previously been assessed by models that present drug-relevant stimuli and measure physiological and behavioral reactivity (often reaction time). Studies of several CNS diseases outside of substance use disorders consistently report anti-saccade deficits, suggesting a compromise in the interplay between higher-order cortical processes in voluntary eye control (i.e., anti-saccades) and reflexive saccades driven more by involuntary midbrain perceptual input (i.e., pro-saccades). Here, the authors describe a novel attentional-bias task developed by using measurements of saccadic eye movements in the presence of cocaine-specific stimuli, combining previously unique research domains to capitalize on their respective experimental and conceptual strengths. CD subjects (N = 46) and healthy controls (N = 41) were tested on blocks of pro-saccade and anti-saccade trials featuring cocaine and neutral stimuli (pictures). Analyses of eye-movement data indicated (1) greater overall anti-saccade errors in the CD group; (2) greater attentional bias in CD subjects as measured by anti-saccade errors to cocaine-specific (relative to neutral) stimuli; and (3) no differences in pro-saccade error rates. Attentional bias was correlated with scores on the obsessive-compulsive cocaine scale. The results demonstrate increased saliency and differential attentional to cocaine cues by the CD group. The assay provides a sensitive index of saccadic (visual inhibitory) control, a specific index of

attentional bias to drug-relevant cues, and preliminary insight into the visual circuitry that may contribute to drug-specific cue reactivity.

Examination Of A Recommended Algorithm For Eliminating Nonsystematic Delay Discounting Response Sets White TJ, Redner R, Skelly JM, Higgins ST. Drug Alcohol Depend. 2015; 154: 300-303.
The aims of this study were to examine (1) whether use of a recommended algorithm (Johnson and Bickel, 2008) improves upon conventional statistical model fit (R(2)) for identifying nonsystematic response sets in delay discounting (DD) data, (2) whether removing such data meaningfully effects research outcomes, and (3) to identify participant characteristics associated with nonsystematic response sets. Discounting of hypothetical monetary rewards was assessed among 349 pregnant women (231 smokers and 118 recent quitters) via a computerized task comparing $1000 at seven future time points with smaller values available immediately. Nonsystematic response sets were identified using the algorithm and conventional statistical model fit (R(2)). The association between DD and quitting was analyzed with and without nonsystematic response sets to examine whether the inclusion or exclusion impacts this relationship. Logistic regression was used to examine whether participant sociodemographics were associated with nonsystematic response sets. The algorithm excluded fewer cases than the R(2) method (14% vs. 16%), and was not correlated with logk as is R(2). The relationship between logk and the clinical outcome (spontaneous quitting) was unaffected by exclusion methods; however, other variables in the model were affected. Lower educational attainment and younger age were associated with nonsystematic response sets. The algorithm eliminated data that were inconsistent with the nature of discounting and retained data that were orderly. Neither method impacted the smoking/DD relationship in this data set. Nonsystematic response sets are more likely among younger and less educated participants, who may need extra training or support in DD studies.

Variations In Opioid Receptor Genes In Neonatal Abstinence Syndrome Wachman EM, Hayes MJ, Sherva R, Brown MS, Davis JM, Farrer LA, Nielsen DA. Drug Alcohol Depend. 2015; 155: 253-259.
There is significant variability in the severity of neonatal abstinence syndrome (NAS) due to in-utero opioid exposure. The authors wanted to determine if single nucleotide polymorphisms (SNPs) in key candidate genes contribute to this variability. Full-term opioid-exposed newborns and their mothers (n=86 pairs) were studied. DNA was genotyped for 80 SNPs from 14 genes utilizing a custom designed microarray. The association of each SNP with NAS outcomes was evaluated. SNPs in two opioid receptor genes in the infants were associated with worse NAS severity: (1) The PNOC rs732636 A allele (OR=3.8, p=0.004) for treatment with 2 medications and a longer hospital stay (LOS) of 5.8 days (p=0.01), and (2) The OPRK1 rs702764 C allele (OR=4.1, p=0.003) for treatment with 2 medications. The OPRM1 rs1799971 G allele (β=-6.9 days, p=0.02) and COMT rs740603 A allele (β=-5.3 days, p=0.01) were associated with shorter LOS. The OPRD1 rs204076 A allele in the mothers was associated with a longer LOS by 6.6 days (p=0.008). Results were significant point-wise but did not meet the experiment-wide significance level. These findings suggest that SNPs in opioid receptor and the PNOC genes are associated with NAS severity. However, further testing in a large sample is warranted. This has important implications for prenatal prediction and personalized treatment regimens for infants at highest risk for severe NAS.

Effects Of Oxytocin On Aggressive Responding In Healthy Adult Men Alcorn 3rd, JL, Green CE, Schmitz J, Lane SD. Behav Pharmacol. 2015; 26(8 Spec No): 798-804.
This study investigated the acute effects of oxytocin (OT) on human aggression using a well-established laboratory measure of state (reactive) aggression to test the hypothesis that OT would decrease the frequency of aggressive responding. In a within-subject design, 17 healthy male volunteers received placebo or 24 IU of intranasal OT. Aggression was measured using the Point Subtraction Aggression Paradigm at 30 min before and 30, 60, and 90 min after dose. Acute OT did not produce a significant main effect on aggressive behavior. OT attenuated the expected rise in diastolic blood pressure from morning to early afternoon observed under placebo, providing a possible indication of biological activity. Examination of individual differences showed that aggressive responding following OT dosing (but not placebo) was positively correlated with psychometric measures of interpersonal manipulation and anger (Pearson's r=0.57), indicating that higher scores on these antisocial personality traits were related to increased aggressive behavior following OT administration. These preliminary results stand in contrast to previous work on the prosocial effects of OT and highlight the need for further understanding of individual differences in aggression following OT administration. Such individual differences may have implications for the therapeutic use of OT in individuals with psychiatric disorders and dysfunctional social behavior.

Greater Reductions In Nicotine Exposure While Smoking Very Low Nicotine Content Cigarettes Predict Smoking Cessation Dermody SS, Donny EC, Hertsgaard LA, Hatsukami DK. Tob Control. 2015; 24(6): 536-539.
Reducing the nicotine content of cigarettes is a potential regulatory strategy that may enable cessation. The present study investigated the effect of nicotine exposure while smoking very low nicotine content (VLNC) cigarettes on cessation outcomes. The roles of possible sources of nicotine were also explored, including the VLNC cigarette and co-use of cigarettes with normal nicotine content. A secondary data analysis of two analogous randomised trials of treatment seeking, adult daily smokers (n=112) who were instructed to smoke VLNC cigarettes for 6 weeks and then make a quit attempt. Controlling for baseline demographic and smoking features, the association between reductions in nicotine exposure during the 6-week trial, assessed by urinary total cotinine and biomarker-confirmed smoking abstinence 1 month later, was tested. Subsequent analyses controlled for the effects of the frequency of VLNC and normal nicotine content cigarette use and the nicotine yield of the VLNC cigarette (0.05 vs 0.09 mg).Greater reductions in nicotine exposure while smoking VLNC cigarettes predicted abstinence independent of individual differences in baseline smoking, cotinine, dependence, gender and study. Nicotine reduction was largest among individuals who were assigned to smoke a VLNC cigarette with lower nicotine yield and who smoked fewer normal nicotine content and VLNC cigarettes. In the context of nicotine regulations and corresponding research, factors that undermine nicotine reduction must be addressed, including the availability and use of cigarettes with normal nicotine content and not sufficiently reducing the nicotine yield of cigarettes.

Bridging Waitlist Delays With Interim Buprenorphine Treatment: Initial Feasibility Sigmon SC, C Meyer A, Hruska B, Ochalek T, Rose G, Badger GJ, Brooklyn JR, Heil SH, Higgins ST, Moore BA, Schwartz RP. Addict Behav. 2015; 51: 136-142.
Despite the effectiveness of agonist maintenance for opioid dependence, individuals can remain on waitlists for months, during which they are at significant risk for morbidity and mortality. Interim dosing, consisting of daily medication without counseling, can reduce these risks. In this pilot study, the authors examined the initial feasibility of a novel technology-assisted interim buprenorphine

treatment for waitlisted opioid-dependent adults. Following buprenorphine induction during Week 1, participants (n=10) visited the clinic at Weeks 2, 4, 6, 8, 10 and 12 to ingest their medication under staff observation, provide a urine specimen and receive their remaining doses via a computerized Med-O-Wheel Secure device. They also received daily monitoring via an Interactive Voice Response (IVR) platform, as well as random call-backs for urinalysis and medication adherence checks. The primary outcome was percent of participants negative for illicit opioids at each 2-week visit, with secondary outcomes of past-month drug use, adherence and acceptability. Participants achieved high levels of illicit opioid abstinence, with 90% abstinent at the Week 2 and 4 visits and 60% at Week 12. Significant reductions were observed in self-reported past-month illicit opioid use ($p<.001$), opioid withdrawal ($p<.001$), opioid craving ($p<.001$) and ASI Drug composite score ($p=.008$). Finally, adherence with buprenorphine administration (99%), daily IVR calls (97%) and random call-backs (82%) was high. Interim buprenorphine treatment shows promise for reducing patient and societal risks during delays to conventional treatment. A larger-scale, randomized clinical trial is underway to more rigorously examine the efficacy of this treatment approach.

Early Phase In the Development Of Cannabidiol As A Treatment For Addiction: Opioid Relapse Takes Initial Center Stage Hurd YL, Yoon M, Manini AF, Hernandez S, Olmedo R, Ostman M, Jutras-Aswad D. Neurotherapeutics. 2015; 12(4): 807-815.
Multiple cannabinoids derived from the marijuana plant have potential therapeutic benefits but most have not been well investigated, despite the widespread legalization of medical marijuana in the USA and other countries. Therapeutic indications will depend on determinations as to which of the multiple cannabinoids, and other biologically active chemicals that are present in the marijuana plant, can be developed to treat specific symptoms and/or diseases. Such insights are particularly critical for addiction disorders, where different phytocannabinoids appear to induce opposing actions that can confound the development of treatment interventions. Whereas Δ(9)-tetracannabinol has been well documented to be rewarding and to enhance sensitivity to other drugs, cannabidiol (CBD), in contrast, appears to have low reinforcing properties with limited abuse potential and to inhibit drug-seeking behavior. Other considerations such as CBD's anxiolytic properties and minimal adverse side effects also support its potential viability as a treatment option for a variety of symptoms associated with drug addiction. However, significant research is still needed as CBD investigations published to date primarily relate to its effects on opioid drugs, and CBD's efficacy at different phases of the abuse cycle for different classes of addictive substances remain largely understudied. This paper provides an overview of preclinical animal and human clinical investigations, and presents preliminary clinical data that collectively sets a strong foundation in support of the further exploration of CBD as a therapeutic intervention against opioid relapse. As the legal landscape for medical marijuana unfolds, it is important to distinguish it from "medical CBD" and other specific cannabinoids, that can more appropriately be used to maximize the medicinal potential of the marijuana plant.

Separate and Combined Effects Of Gabapentin and 9-tetrahydrocananbinol In Humans Discriminating 9-tetrahydrocananbinol Lile JA, Wesley MJ, Kelly TH, Hays LR. Behav Pharmacol. 2015.
The aim of the present study was to examine a potential mechanism of action of gabapentin to manage cannabis-use disorders by determining the interoceptive effects of gabapentin in cannabis users discriminating [ ]-tetrahydrocananbinol ([ ]-THC) using a pharmacologically selective drug-discrimination procedure. Eight cannabis users learned to discriminate 30 mg oral [ ]-THC from

placebo and then received gabapentin (600 and 1200 mg), [ ]-THC (5, 15, and 30 mg), and placebo alone and in combination. Self-report, task performance, and physiological measures were also collected. [ ]-THC served as a discriminative stimulus, produced positive subjective effects, elevated heart rate, and impaired psychomotor performance. Both doses of gabapentin substituted for the [ ]-THC discriminative stimulus and engendered subjective and performance-impairing effects that overlapped with those of [ ]-THC when administered alone. When administered concurrently, gabapentin shifted the discriminative-stimulus effects of [ ]-THC leftward/upward, and combinations of [ ]-THC and gabapentin generally produced larger effects on cannabinoid-sensitive outcomes relative to [ ]-THC alone. These results suggest that one mechanism by which gabapentin might facilitate cannabis abstinence is by producing effects that overlap with those of cannabinoids.

Dopamine D3 Receptor-preferring Agonist Enhances The Subjective Effects Of Cocaine In Humans Newton TF, Haile CN, Mahoney 3rd, JJ, Shah R, Verrico CD, De La Garza 2nd, R, Kosten TR. Psychiatry Res. 2015; 230(1): 44-49.
Pramipexole is a D3 dopamine receptor-preferring agonist indicated for the treatment of Parkinson disease. Studies associate pramipexole with pathological gambling and impulse control disorders suggesting a role for D3 receptors in reinforcement processes. Clinical studies showed pramipexole decreased cocaine craving and reversed central deficits in individuals with cocaine use disorder. Preclinical studies have shown acute administration of pramipexole increases cocaine's reinforcing effects whereas other reports suggest chronic pramipexole produces tolerance to cocaine. In a randomized, double-blind, placebo-controlled study the authors examined the impact of pramipexole treatment on the subjective effects produced by cocaine in volunteers with cocaine use disorder. Volunteers received pramipexole titrated up to 3.0mg/d or placebo over 15 days. Participants then received intravenous cocaine (0, 20 and 40mg) on day 15. Cardiovascular and subjective effects were obtained with visual analog scales at time points across the session. Pramipexole alone increased peak heart rate following saline and diastolic blood pressure following cocaine. Pramipexole produced upwards of two-fold increases in positive subjective effects ratings following cocaine. These results indicate that chronic D3 receptor activation increases the subjective effects of cocaine in humans. Caution should be used when prescribing pramipexole to patients that may also use cocaine.

Test-Retest Reliability and Stability Of the Nicotine Metabolite Ratio Among Treatment-Seeking Smokers Hamilton DA, Mahoney MC, Novalen M, Chenoweth MJ, Heitjan DF, Lerman C, Tyndale RF, Hawk Jr, LW. Nicotine Tob Res. 2015; 17(12): 1505-1509.
The nicotine metabolite ratio (NMR), the ratio of 3-hydroxycotinine to cotinine, is a biomarker used in smoking cessation research, with several retrospective studies suggesting that NMR predicts treatment outcome. To be maximally useful in tailoring treatment, estimates of NMR should be stable over time. The present study is the first to examine the short-term test-retest reliability of NMR among treatment-seeking smokers. Blood NMR was assessed at two time points, approximately 2-3 weeks apart and prior to intervention, among 72 healthy adult smokers (49% female; 35% non-White) enrolled in a cessation trial (http://ClinicalTrials.gov ID: NCT01314001). Mean NMR was stable from Time-1 to Time-2, with no significant change between assessments; test-retest reliability for NMR values was excellent (ICC[2,1] = 0.87). Test-retest reliability remained acceptable to high when NMR was categorized, as in recent clinical trials. Classification of participants as slow (quartile 1, NMR $\leq$ 0.24) or normal/fast NMR (quartiles 2-4, NMR $\geq$ 0.25) was consistent from Time-1 to Time-2 for 96% of participants (κ = 0.89). Though classification of

participants into NMR quartiles was less consistent from Time-1 to Time-2 (67% agreement; weighted $\kappa = 0.73$), all reclassifications occurred between adjacent quartiles. Overall, these data support the use of a single NMR assessment for association studies with smoking phenotypes and in smokers seeking to quit, and they encourage large-scale efforts to determine optimal NMR cutpoints for tailoring treatment selection.

Alcohol Administration Increases Cocaine Craving But Not Cocaine Cue Attentional Bias
Marks KR, Pike E, Stoops WW, Rush CR. Alcohol Clin Exp Res. 2015; 39(9): 1823-1831.
Alcohol consumption is a known antecedent to cocaine relapse. Through associative conditioning, it is hypothesized that alcohol increases incentive motivation for cocaine and thus the salience of cocaine-related cues, which are important in maintaining drug-taking behavior. Cocaine-using individuals display a robust cocaine cue attentional bias as measured by fixation time during the visual probe task. The purpose of this study was to evaluate the influence of alcohol administration on cocaine cue attentional bias using eye-tracking technology to directly measure attentional allocation. Twenty current cocaine users completed a double-blind, placebo-controlled, within-subjects study that tested the effect of 3 doses of alcohol (0.00, 0.325, and 0.65 g/kg) on cocaine cue attentional bias using the visual probe task with eye-tracking technology. The participant-rated and physiological effects of alcohol were also assessed. Participants displayed a robust cocaine cue attentional bias following both placebo and alcohol administration as measured by fixation time, but not response time. Alcohol administration did not influence cocaine cue attentional bias, but increased craving for cocaine in a dose-dependent manner. Alcohol produced prototypic psychomotor and participant-rated effects. Alcohol administration increases cocaine craving but not cocaine cue attentional bias. Alcohol-induced cocaine craving suggests that alcohol increases incentive motivation for cocaine but not the salience of cocaine-related cues.

A Double Blind, Placebo Controlled Trial Of Modafinil For the Treatment Of Cocaine Dependence Without Co-morbid Alcohol Dependence Kampman KM, Lynch KG, Pettinati HM, Spratt K, Wierzbicki MR, Dackis C, O'Brien CP. Drug Alcohol Depend. 2015; 155: 105-110.
Modafinil is a medication approved for narcolepsy and shift work sleep disorder. It has both dopaminergic and glutamatergic activity that could be useful for the treatment of cocaine dependence. Modafinil has reduced cocaine subjective effects and cocaine self-administration in human laboratory trials and has reduced cocaine use in cocaine dependent patients in some clinical trials. This was an 8-week, double blind, placebo controlled clinical trial involving 94 cocaine dependent subjects. Subjects received 300mg of modafinil or identical placebo daily along with weekly individual therapy. The primary outcome measure was cocaine use measured by self-report, and confirmed by twice weekly urine benzoylecgonine tests (UBT). Additional outcome measures included cocaine craving measured by the Brief Substance Craving Scale and global improvement measured by the Clinical Global Impression Scale (CGI).The odds ratio (OR) in favor of abstinence for modafinil vs. placebo was 2.54 (p=. 03) and modafinil-treated subjects were significantly more likely than placebo-treated subjects to be abstinent from cocaine during the last 3 weeks of the trial, 23% vs. 9%, $\chi(2)=3.9$, $p<.05$. Modafinil treated subjects were more likely to report very low levels of cocaine craving intensity and duration on the Brief Substance Craving Scale (OR=2.04, p=.03 and OR 1.06, p=.03 respectively). Modafinil-treated subjects were also more likely than placebo-treated subjects to rate themselves as "very much improved" on the CGI (OR=2.69, p=.03). Modafinil may be an efficacious treatment for cocaine dependence.

Buspirone Treatment Of Cannabis Dependence: A Randomized, Placebo-controlled Trial
McRae-Clark AL, Baker NL, Gray KM, Killeen TK, Wagner AM, Brady KT, DeVane CL, Norton J. Drug Alcohol Depend. 2015; 156: 29-37.
The purpose of this study was to evaluate the efficacy of buspirone, a partial 5-HT1A agonist, for treatment of cannabis dependence. One hundred seventy-five cannabis-dependent adults were randomized to receive either up to 60mg/day of buspirone (n=88) or placebo (n=87) for 12 weeks combined with a brief motivational enhancement therapy intervention and contingency management to encourage study retention. Cannabis use outcomes were assessed via weekly urine cannabinoid tests. Participants in both groups reported reduced cannabis craving over the course of the study; however, buspirone provided no advantage over placebo in reducing cannabis use. Significant gender by treatment interactions were observed, with women randomized to buspirone having fewer negative urine cannabinoid tests than women randomized to placebo (p=0.007), and men randomized to buspirone having significantly lower creatinine adjusted cannabinoid levels as compared to those randomized to placebo (p=0.023). An evaluation of serotonin allelic variations did not find an association with buspirone treatment response. Buspirone was not more efficacious than placebo in reducing cannabis use. Important gender differences were noted, with women having worse cannabis use outcomes with buspirone treatment. Considerations for future medication trials in this challenging population are discussed.

Profiles Of Urine Drug Test In Clinical Pain Patients Vs Pain Research Study Subjects Lee C-T, Vo TT, Cohen AS, Ahmed S, Zhang Y, Mao J, Chen L. Pain Med. 2015. The aim of this study was to examine similarities and differences in urine drug test (UDT) results in clinical pain patients and pain subjects participating in pain research studies. An observational study with retrospective chart review and data analysis. The authors analyzed 1,874 UDT results obtained from 1) clinical pain patients (Clinical Group; n = 1,529) and 2) pain subjects consented to participate in pain research studies (Research Group; n = 345). Since several medications such as opioids used in pain management are drugs of abuse (DOA) and can result in a positive UDT, we specifically identified those cases of positive UDT due to nonprescribed DOA and designated these cases as positive UDT with DOA (PUD).We found that 1) there was a higher rate of PUD in clinical pain patients (41.3%) than in pain research study subjects (14.8%); 2) although subjects in the Research Group were informed ahead of time that UDT will be conducted as a screening test, a substantial number (14.8%) of pain research study subjects still showed PUD; 3) there were different types of DOA between clinical pain patients (cannabinoids as the top DOA) and research study subjects (cocaine as the top DOA); and 4) a common factor associated with PUD was opioid therapy in both Clinical Group and Research Group. These results support previous findings that PUD is a common finding in clinical pain patients, particularly in those prescribed opioid therapy, and we suggest that UDT be used as routine screening testing in pain research studies.

A Randomized Controlled Trial Of The Effects Of Working Memory Training In Methadone Maintenance Patients Rass O, Schacht RL, Buckheit K, Johnson MW, Strain EC, Mintze, MZ. Drug Alcohol Depend. 2015; 156: 38-46.
Working memory impairment in individuals with chronic opioid dependence can play a major role in cognitive and treatment outcomes. Cognitive training targeting working memory shows promise for improved function in substance use disorders. To date, cognitive training has not been incorporated as an adjunctive treatment for opioid dependence. Methadone maintenance patients were randomly assigned to experimental (n=28) or active control (n=28) 25-session computerized training and run in parallel. Cognitive and drug use outcomes were assessed before and after

training. Participants in the experimental condition showed performance improvements on two of four working memory measures, and both groups improved on a third measure of working memory performance. Less frequent drug use was found in the experimental group than in the control group post-training. In contrast to previous findings with stimulant users, no significant effect of working memory training on delay discounting was found using either hypothetical or real rewards. There were no group differences on working memory outcome measures that were dissimilar from the training tasks, suggesting that another mechanism (e.g., increased distress tolerance) may have driven drug use results. Working memory training improves performance on some measures of working memory in methadone maintenance patients, and may impact drug use outcomes. Working memory training shows promise in patients with substance use disorders; however, further research is needed to understand the

Randomized Trial Of Reduced-Nicotine Standards For Cigarettes Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG, al'Absi M, Carmella SG, Cinciripini PM, Dermody SS, Drobes DJ, Hecht SS, Jensen J, Lane T, Le CT, McClernon FJ, Montoya ID, Murphy SE, Robinson JD, Stitzer ML, Strasser AA, Tindle H, Hatsukami DK. N Engl J Med. 2015; 373(14): 1340-1349.

The Food and Drug Administration can set standards that reduce the nicotine content of cigarettes. The authors conducted a double-blind, parallel, randomized clinical trial between June 2013 and July 2014 at 10 sites. Eligibility criteria included an age of 18 years or older, smoking of five or more cigarettes per day, and no current interest in quitting smoking. Participants were randomly assigned to smoke for 6 weeks either their usual brand of cigarettes or one of six types of investigational cigarettes, provided free. The investigational cigarettes had nicotine content ranging from 15.8 mg per gram of tobacco (typical of commercial brands) to 0.4 mg per gram. The primary outcome was the number of cigarettes smoked per day during week 6.A total of 840 participants underwent randomization, and 780 completed the 6-week study. During week 6, the average number of cigarettes smoked per day was lower for participants randomly assigned to cigarettes containing 2.4, 1.3, or 0.4 mg of nicotine per gram of tobacco (16.5, 16.3, and 14.9 cigarettes, respectively) than for participants randomly assigned to their usual brand or to cigarettes containing 15.8 mg per gram (22.2 and 21.3 cigarettes, respectively; $P<0.001$). Participants assigned to cigarettes with 5.2 mg per gram smoked an average of 20.8 cigarettes per day, which did not differ significantly from the average number among those who smoked control cigarettes. Cigarettes with lower nicotine content, as compared with control cigarettes, reduced exposure to and dependence on nicotine, as well as craving during abstinence from smoking, without significantly increasing the expired carbon monoxide level or total puff volume, suggesting minimal compensation. Adverse events were generally mild and similar among groups. In this 6-week study, reduced-nicotine cigarettes versus standard-nicotine cigarettes reduced nicotine exposure and dependence and the number of cigarettes smoked. (Funded by the National Institute on Drug Abuse and the Food and Drug Administration Center for Tobacco Products; ClinicalTrials.gov number, NCT01681875.).

Safety and Preliminary Efficacy Of the Acetylcholinesterase Inhibitor Huperzine A As A Treatment For Cocaine Use Disorder De La Garza 2nd, R,Verrico CD, Newton TF, Mahoney 3rd, JJ, Thompson-Lake DG Y. Int J Neuropsychopharmacol. 2015.

Cholinergic transmission is altered by drugs of abuse and contributes to psychostimulant reinforcement. In particular, acetylcholinesterase inhibitors, like huperzine A, may be effective as treatments for cocaine use disorder. The current report describes results from a double-blind, placebo-controlled study in which participants (n=14-17/group) were randomized to huperzine A

(0.4 or 0.8mg) or placebo. Participants received randomized infusions of cocaine (0 and 40mg, IV) on days 1 and 9. On day 10, participants received noncontingent, randomized infusions of cocaine (0 and 20mg, IV) before making 5 choices to receive additional infusions.Huperzine A was safe and well-tolerated and compared with placebo, treatment with huperzine A did not cause significant changes in any cocaine pharmacokinetic parameters (all P>.05). Time-course and peak effects analyses show that treatment with 0.4mg of huperzine A significantly attenuated cocaine-induced increases of "Any Drug Effect," "High," "Stimulated," "Willing to Pay," and "Bad Effects" (all P>.05).The current study represents a significant contribution to the addiction field since it serves as the first published report on the safety and potential efficacy of huperzine A as a treatment for cocaine use disorder.

Response To Transdermal Selegiline Smoking Cessation Therapy and Markers In the 15q24 Chromosomal Region Sarginson JE, Killen JD, Lazzeroni LC, Fortmann SP, Ryan HS, Amel N, Schatzberg AF, Murphy Jr, GM. Nicotine Tob Res. 2015; 17(9): 1126-1133.
Current treatments for smoking cessation have limited efficacy. A potential pharmaceutical treatment for smoking cessation is selegiline, a selective and irreversible monoamine oxidase B inhibitor. A few clinical trials have been carried out using selegiline but the results have been mixed. The authors sought to determine if genetic markers in cholinergic loci in the 15q24 chromosomal region predict response to smoking cessation therapy with selegiline.They performed an 8-week double-blind, placebo-controlled clinical trial of the selegiline transdermal system in heavy smokers, with follow-up at weeks 25 and 52. Eight single nucleotide polymorphisms (SNPs) in the 15q24 region, which contains the genes for the nicotinic acetylcholine receptor subunits CHRNA5, CHRNA3, and CHRNB4, were investigated for association with treatment response.The CHRNB4 promoter SNP rs3813567 was associated with both point prevalence abstinence and post-quit craving. Carriers of the minor C allele treated with selegiline showed lower rates of abstinence and higher levels of craving than selegiline-treated non-carriers, indicating that the rs3813567 C allele adversely affects abstinence in selegiline-treated smokers. This effect was not present among placebo-treated smokers. Selegiline-treated smokers with the CHRNA5 rs680244 GG genotype had lower post-quit craving, and unlike placebo-treated GG-carrying smokers, did not experience a post-quit increase in depressive symptoms.Variants in genes encoding cholinergic receptors affect abstinence, craving and mood in selegiline-treated smokers. Selegiline primarily affects dopamine levels in the brain, but cholinergic input affects nicotine-induced dopaminergic activity. These markers may have value in identifying those likely to respond to selegiline for smoking cessation.

Cocaine Choice Procedures In Animals, Humans, and Treatment-seekers: Can We Bridge The Divide? Moeller SJ, Stoops WW. Pharmacol Biochem Behav. 2015; 138: 133-141.
Individuals with cocaine use disorder chronically self-administer cocaine to the detriment of other rewarding activities, a phenomenon best modeled in laboratory drug-choice procedures. These procedures can evaluate the reinforcing effects of drugs versus comparably valuable alternatives under multiple behavioral arrangements and schedules of reinforcement. However, assessing drug-choice in treatment-seeking or abstaining humans poses unique challenges: for ethical reasons, these populations typically cannot receive active drugs during research studies. Researchers have thus needed to rely on alternative approaches that approximate drug-choice behavior or assess more general forms of decision-making, but whether these alternatives have relevance to real-world drug-taking that can inform clinical trials is not well-understood. In this mini-review, the authors (a) summarize several important modulatory variables that influence cocaine choice in nonhuman animals and non-treatment seeking humans; (b) discuss some of the ethical considerations that

could arise if treatment-seekers are enrolled in drug-choice studies; (c) consider the efficacy of alternative procedures, including non-drug-related decision-making and simulated; drug-choice (a choice is made, but no drug is administered) to approximate drug choice; and (d) suggest opportunities for new translational work to bridge the current divide between preclinical and clinical research.

Zonisamide Reduces Withdrawal Symptoms But Does Not Enhance Varenicline-Induced Smoking Cessation Dunn KE, Marcus TF, Kim C, Schroeder JR, Vandrey R, Umbricht A. Nicotine Tob Res. 2015.
Varenicline (Chantix) is a first-line treatment for smoking cessation but does not produce cessation in many individuals. It may be possible to improve abstinence by co-administering varenicline with other medications. Zonisamide (Zonegran) has a similar pharmacologic profile to topiramate, which has been shown to reduce smoking, but is better tolerated. This study evaluated whether combined zonisamide and varenicline reduced tobacco withdrawal and increased abstinence among smokers trying to quit, relative to varenicline and placebo.This was a double-blind, randomized, placebo-controlled pilot trial of zonisamide + varenicline versus placebo + varenicline for smoking cessation. Smokers received brief counseling and study medications, and completed weekly assessments for 10 consecutive weeks. The primary outcome was continuous abstinence rates (biochemically verified) during the final 4 weeks of treatment. Results are presented as intent-to-treat and completer analyses. Seventy-four individuals were enrolled; 45 completed the study. Overall, 14.9% (intent-to-treat) and 25.0% (completer) of participants maintained sustained abstinence during the final 4 weeks of treatment. There were no differences between groups for biochemically-verified smoking, but zonisamide + varenicline reduced self-reported smoking, nicotine withdrawal, and craving compared to placebo + varenicline. Zonisamide decreased nicotine withdrawal and craving, though not of sufficient magnitude to modify smoking behavior. The sample size was small and low rates of abstinence across groups suggest the study population was difficult to treat. Additional evaluation of zonisamide or other medications that increase GABA or decrease glutamate in larger or more diverse populations may yield positive clinical benefit for nicotine/tobacco cessation. This study provides support for layering novel medications with varenicline for smoking cessation, for investigating medications that target the GABA and glutamate system, and for assessing the contribution that reductions in nicotine withdrawal have on ultimate cessation outcomes.

Surveying Lactation Professionals Regarding Marijuana Use and Breastfeeding Bergeria CL, Heil SH. Breastfeed Med. 2015; 10(7): 377-380.
Breastfeeding is associated with substantial benefits for both the child and mother. Most guidelines state that women who use illicit drugs should not breastfeed. Although this recommendation has traditionally included marijuana, this drug's changing legal status and the limited scientific research regarding marijuana's effect on breastfeeding and the nursing child may lead to varying recommendations made by lactation professionals to clients who use marijuana. Additionally, to the authors' knowledge, there are no data estimating the prevalence of marijuana use among breastfeeding women, making it unclear how common it is. This study assessed recommendations around breastfeeding and marijuana use and estimated the prevalence of marijuana use among breastfeeding women. A convenience sample of lactation professionals who practice throughout New England and were attending the 2014 Vermont Lactation Consultant Association conference was offered the opportunity to complete a five-item survey. Of 120 conference attendees, 74 completed the survey. Forty-four percent reported their recommendations around breastfeeding and

marijuana use depended on factors like the severity of maternal use. Another 41% reported recommending continued breastfeeding because the benefits outweigh the harms. The remaining 15% reported recommending that a woman should stop breastfeeding if she cannot stop using marijuana. Survey completers estimated that 15% (1,203/7,843) of their breastfeeding clients in the past year used marijuana. Lactation professionals vary widely in their recommendations to breastfeeding clients who use marijuana. The estimate of prevalence also suggests this is a relatively common issue. More research is needed to assess the generalizability of these findings.

Breakdowns Of Eye Movement Control Toward Smoking Cues In Young Adult Light Smokers DiGirolamo GJ; Sophis EJ, Daffron JL, Gonzalez G, Romero-Gonzalez M, Gillespie SA. Addict Behav. 2016; 52: 98-102.
Many studies suggest that dependent smokers have a preference or attentional bias toward smoking cues. The purpose of this study was to test the ability of infrequent non-dependent light smokers to control their eye movements by look away from smoking cues. Poor control in the lightest of smokers would suggest nicotine cue-elicited behavior occurring even prior to nicotine dependency as measured by daily smoking.17 infrequent non-dependent light smokers and 17 lifetime non-smokers performed an antisaccade task (look away from suddenly appearing cue) on smoking, alcohol, neutral, and dot cues.The light smokers, who were confirmed light smokers and non-dependent (MFaegerström Dependency Score=0.35), were significantly worse at controlling their eye movements to smoking cues relative to both neutral cues ($p<.04$) and alcohol cues ($p<.02$). Light smokers made significantly more errors to smoking cues than non-smokers ($p<.004$).These data suggest that prior to developing clinical symptoms of severe dependence or progressing to heavier smoking (e.g., daily smoking), the lightest of smokers are showing a specific deficit in control of nicotine cue-elicited behavior.

Memantine Improves Buprenorphine/Naloxone Treatment For Opioid Dependent Young Adults Gonzalez G, DiGirolamo G, Romero-Gonzalez M, Smelson D, Ziedonis D, Kolodziej M. Drug Alcohol Depend. 2015; 156: 243-253.
Opioid use disorders are considered a serious public health problem among young adults. Current treatment is limited to long-term opioid substitution therapy, with high relapse rates after discontinuation. This study evaluated the co-administration of memantine to brief buprenorphine pharmacotherapy as a treatment alternative. This was a 13-week double-blind placebo-controlled trial evaluating 80 young adult opioid dependent participants treated with buprenorphine/naloxone 16-4mg/day and randomized to memantine (15mg or 30mg) or placebo. Primary outcomes were a change in the weekly mean proportion of opioid use, and cumulative abstinence rates after rapid buprenorphine discontinuation on week 9. Treatment retention was not significantly different between groups. The memantine 30mg group was significantly less likely to relapse and to use opioids after buprenorphine discontinuation. Among participants abstinent on week 8, those in the memantine 30mg group (81.9%) were significantly less likely to relapse after buprenorphine was discontinued compared to the placebo group (30%) ($p<0.025$). Also, the memantine 30mg group had significantly reduced opioid use (mean=0, SEM±0.00) compared to the placebo group (mean=0.33, SEM±0.35; $p<0.004$) during the last 2 weeks of study participation. Memantine 30mg significantly improved short-term treatment with buprenorphine/naloxone for opioid dependent young adults by reducing relapse and opioid use after buprenorphine discontinuation. Combined short-term treatment with buprenorphine/naloxone may be an effective alternative treatment to long-term methadone or buprenorphine maintenance in young adults.

Effect Of Cocaine Dependence On Brain Connections: Clinical Implications Ma L, Steinberg JL, Moeller FG,Johns SE, Narayana PA. Expert Rev Neurother. 2015; 15(11): 1307-1319.
Cocaine dependence (CD) is associated with several cognitive deficits. Accumulating evidence, based on human and animal studies, has led to models for interpreting the neural basis of cognitive functions as interactions between functionally related brain regions. In this review, the authors focus on magnetic resonance imaging (MRI) studies using brain connectivity techniques as related to CD. The majority of these brain connectivity studies indicated that cocaine use is associated with altered brain connectivity between different structures, including cortical-striatal regions and default mode network. In cocaine users some of the altered brain connectivity measures are associated with behavioral performance, history of drug use, and treatment outcome. The implications of these brain connectivity findings to the treatment of CD and the pros and cons of the major brain connectivity techniques are discussed. Finally potential future directions in cocaine use disorder research using brain connectivity techniques are briefly described.

Safety Of Oral Dronabinol During Opioid Withdrawal In Humans Jicha CJ, Lofwall MR, Nuzzo PA, Babalonis S, Elayi SC,Walsh SL. Drug Alcohol Depend. 2015; 157: 179-183.
Opioid dependence remains a significant public health problem worldwide with only three FDA-approved treatments, all targeting the mu-opioid receptor. Dronabinol, a cannabinoid (CB) 1 receptor agonist, is currently under investigation as a novel opioid withdrawal treatment. This study reports on safety outcomes of dronabinol among adults in opioid withdrawal. Twelve adults physically dependent on short-acting opioids participated in this 5-week within-subject, randomized, double blind, placebo-controlled inpatient study. Volunteers were maintained on oral oxycodone 30mgqid. Double-blind placebo substitutions occurred for 21h before each of 7 experimental sessions in order to produce opioid withdrawal. A single oral test dose was administered each session (placebo, oxycodone 30 and 60mg, dronabinol 5, 10, 20, and 30mg [decreased from 40mg]). Heart rate, blood pressure, respiratory outcomes and pupil diameter were assessed repeatedly. Dronabinol 40mg produced sustained sinus tachycardia accompanied by anxiety and panic necessitating dose reduction to 30mg. Sinus tachycardia and anxiety also occurred in one volunteer after dronabinol 20mg. Compared to placebo, dronabinol 20 and 30mg produced significant increases in heart rate beginning 1h after drug administration that lasted approximately 2h ($p<0.05$). Dronabinol 5 and 10mg produced placebo-like effects. Oxycodone produced prototypic mu-opioid agonist effects (e.g., miosis).Dronabinol 20mg and higher increased heart rate among healthy adults at rest who were in a state of opioid withdrawal, raising concern about its safety. These results have important implications for future dosing strategies and may limit the utility of dronabinol as a treatment for opioid withdrawal.

Opioids In Pregnancy and Neonatal Abstinence Syndrome Stover MW, Davis JM. Semin Perinatol. 2015; 39(7): 561-565.
Opiate use in pregnancy has increased dramatically over the past decade and now represents a major public health problem. More women are using prescription opioids, illegal opioids, and opioid-substitution therapy. These drugs have been associated with numerous obstetrical complications including intrauterine growth restriction, placental abruption, preterm delivery, oligohydramnios, stillbirth, and maternal death. Neonatal complications are also significant, such as an increased risk of mortality as well as neonatal abstinence syndrome (NAS). NAS is a serious and highly variable condition characterized by central nervous system hyperirritability and autonomic nervous system dysfunction. The present review seeks to define current practices regarding the management of opiate dependence in pregnancy and care of the neonate with prenatal opiate exposure. Since

genetic factors appear to be associated with the incidence and severity of NAS, opportunities for "personalized genomic medicine" and unique therapeutic interventions could be developed in the future.

Characterizing Pain and Associated Coping Strategies In Methadone and Buprenorphine-maintained Patients Dunn KE, Finan PH, Tompkins DA, Fingerhood M, Strain EC. Drug Alcohol Depend. 2015; 157: 143-149.
Chronic pain is common among patients receiving opioid maintenance treatment (OMT) for opioid use disorder. To aid development of treatment recommendations for coexisting pain and opioid use disorder, it is necessary to characterize pain treatment needs and assess whether needs differ as a function of OMT medication. A point-prevalence survey assessing pain and engagement in coping strategies was administered to 179 methadone and buprenorphine-maintained patients. Forty-two percent of participants were categorized as having chronic pain. Methadone patients had greater severity of pain relative to buprenorphine patients, though both groups reported high levels of interference with daily activities, and participants with pain attended the emergency room more frequently relative to participants without pain. Only 2 coping strategies were being utilized by more than 50% of participants (over-the-counter medication, prayer). Results indicate that pain among OMT patients is common, severe, and of significant impairment. Methadone patients reported greater severity pain, particularly worse pain in the past 24h, though interference from pain in daily activities did not vary as a function of OMT. Most participants with pain were utilizing few evidenced-based pain coping strategies. Increasing OMT patient access to additional pain treatment strategies is an opportunity for immediate intervention, and similarities across OMT type suggest interventions do not need to be customized to methadone vs. buprenorphine patients.

Decreased Nicotinic Receptor Availability In Smokers With Slow Rates Of Nicotine Metabolism Dubroff JG, Doot RK, Falcone M, Schnoll RA, Ray R, Tyndale RF, Brody AL, Hou C, Schmitz A, Lerman C. J Nucl Med. 2015; 56(11): 1724-1729.
The nicotine metabolite ratio (NMR), a stable measure of hepatic nicotine metabolism via the CYP2A6 pathway and total nicotine clearance, is a predictive biomarker of response to nicotine replacement therapy, with increased quit rates in slower metabolizers. Nicotine binds directly to nicotinic acetylcholine receptors (nAChRs) to exert its psychoactive effects. This study examined the relationship between NMR and nAChR (α4β2* subtype) availability using PET imaging of the radiotracer 2-(18)F-fluoro-3-(2(S)-azetidinylmethoxy)pyridine (2-(18)F-FA-85380, or 2-(18)F-FA).Twenty-four smokers-12 slow metabolizers (NMR < 0.26) and 12 normal metabolizers (NMR ≥ 0.26)-underwent 2-(18)F-FA-PET brain imaging after overnight nicotine abstinence (18 h before scanning), using a validated bolus-plus-infusion protocol. Availability of nAChRs was compared between NMR groups in a priori volumes of interest, with total distribution volume (VT/fP) being the measure of nAChR availability. Cravings to smoke were assessed before and after the scans. Thalamic nAChR α4β2* availability was significantly reduced in slow nicotine metabolizers (P = 0.04). Slow metabolizers exhibited greater reductions in cravings after scanning than normal metabolizers; however, craving was unrelated to nAChR availability.The rate of nicotine metabolism is associated with thalamic nAChR availability. Additional studies could examine whether altered nAChR availability underlies the differences in treatment response between slow and normal metabolizers of nicotine.

Pharmacological Options For Smoking Cessation In Heavy-Drinking Smokers Yardley MM, Mirbaba MM, Ray LA. CNS Drugs. 2015; 29(10): 833-845.
There is a high prevalence of comorbid tobacco use and alcohol use disorder (AUD), affecting more than 6 million people in the US. Globally, tobacco and alcohol use rank fourth and fifth, respectively, for disability-adjusted life-years lost. Levels of alcohol use are higher in smokers than nonsmokers, and the prevalence of smoking is higher in heavy drinkers compared with nondrinkers. This relationship is driven by many different factors, including genetics, neurobiological mechanisms, conditioning processes, and psychosocial influences. Although this unique population tends to experience more negative health consequences, more severe AUD, and poorer response to treatment than those with either AUD or tobacco use disorder alone, there are currently no available treatment protocols tailored to this comorbid condition. In this review, the authors provide a comprehensive review of ongoing clinical research into smoking cessation options for heavy-drinking smokers (HDS) through an evaluation of the effect of promising novel pharmacotherapies as well as combination therapies, including varenicline, naltrexone, the combination of varenicline and naltrexone, and the combination of naltrexone and nicotine replacement therapy (NRT). These treatments are considered in light of the standard of care for smoking cessation, and seek to improve upon the available guidelines for this sizeable subgroup of smokers, namely those smokers who drink heavily.

Cue-reactivity In Experienced Electronic Cigarette Users: Novel Stimulus Videos and A Pilot fMRI Study Nichols TT, Foulds J, Yingst JM, Veldheer S, Hrabovsky S,Richie J,Eissenberg T, Wilson SJ. Brain Res Bull. 2015.
Some individuals who try electronic cigarettes (e-cigarettes) continue to use long-term. Previous research has investigated the safety of e-cigarettes and their potential for use in smoking cessation, but comparatively little research has explored chronic or habitual e-cigarette use. In particular, the relationship between e-cigarette cues and craving is unknown. The authors sought to bridge this gap by developing a novel set of e-cigarette (salient) and electronic toothbrush (neutral) videos for use in cue-reactivity paradigms. Additionally, they demonstrate the utility of this approach in a pilot fMRI study of 7 experienced e-cigarette users. Participants were scanned while viewing the cue videos before and after 10min use of their own e-cigarettes (producing an 11.7ng/ml increase in plasma nicotine concentration). A significant session (pre- and post-use) by video type (salient and neutral) interaction was exhibited in many sensorimotor areas commonly activated in other cue-reactivity paradigms. The authors did not detect significant cue-related activity in other brain regions notable in the craving literature. Possible reasons for this discrepancy are discussed, including the importance of matching cue stimuli to participants's experiences.

Longitudinal Care Improves Cessation In Smokers Who Do Not Initially Respond To Treatment By Increasing Cessation Self-Efficacy, Satisfaction, and Readiness To Quit: A Mediated Moderation Analysis Burns RJ, Rothman AJ, Fu SS, Lindgren B, Vock DM, Joseph AM. Ann Behav Med. 2015.
The Tobacco Longitudinal Care study was a randomized controlled trial for smoking cessation. It demonstrated that longitudinal care for smoking cessation, in which telephone-based counseling and nicotine replacement therapy were offered for 12 months, was more effective than the standard 8-week treatment. This study aims to identify for whom and how longitudinal care increased the likelihood of abstinence. Mediated moderation analyses were utilized across three time points. There was a trend towards smokers who did not respond to treatment (i.e., were still smoking) by 21 days being more likely to be abstinent at 6 months if they received longitudinal care rather than

usual care. Similarly, those who did not respond to treatment by 3 months were more likely to be abstinent at 12 months if they received longitudinal care. At both time points, the likelihood of abstinence did not differ across treatment conditions among participants who responded to treatment (i.e., quit smoking). The effect on 6-month outcomes was mediated by satisfaction and readiness to quit. Cessation self-efficacy, satisfaction, and readiness to quit mediated the effect on 12-month outcomes. The effect of treatment condition on the likelihood of abstinence at 18 months was not moderated by response to treatment at 6 months. Smokers who did not respond to initial treatment benefited from longitudinal care. Differential effects of treatment condition were not observed among those who responded to early treatment. Conditional assignment to longitudinal care may be useful. Determining for whom and how interventions work over time will advance theory and practice.

Pain Volatility and Prescription Opioid Addiction Treatment Outcomes In Patients With Chronic Pain Worley MJ, Heinzerling KG, Shoptaw S, Ling W. Exp Clin Psychopharmacol. 2015; 23(6): 428-435.
The combination of prescription opioid dependence and chronic pain is increasingly prevalent and hazardous to public health. Variability in pain may explain poor prescription opioid addiction treatment outcomes in persons with chronic pain. This study examined pain trajectories and pain volatility in patients with chronic pain receiving treatment for prescription opioid addiction. The authors conducted secondary analyses of adults with chronic pain (n = 149) who received buprenorphine/naloxone (BUP/NLX) and counseling for 12 weeks in an outpatient, multisite clinical trial. Good treatment outcome was defined as urine-verified abstinence from opioids at treatment endpoint (Week 12) and during at least 2 of the previous 3 weeks. Pain severity significantly declined over time during treatment ($b = -0.36$, $p < .001$). Patients with greater pain volatility were less likely to have a good treatment outcome (odds ratio = 0.55, $p < .05$), controlling for baseline pain severity and rate of change in pain over time. A 1 standard deviation increase in pain volatility was associated with a 44% reduction in the probability of endpoint abstinence. The significant reduction in subjective pain during treatment provides observational support for the analgesic effects of BUP/NLX in patients with chronic pain and opioid dependence. Patients with greater volatility in subjective pain during treatment have increased risk of returning to opioid use by the conclusion of an intensive treatment with BUP/NLX and counseling. Future research should examine underlying mechanisms of pain volatility and identify related therapeutic targets to optimize interventions for prescription opioid addiction and co-occurring chronic pain.

Determining Menstrual Phase In Human Biobehavioral Research: A Review With Recommendations Allen AM, McRae-Clark AL, Carlson S, Saladin ME, Gray KM,; Wetherington CL, McKee SA, Allen SS. Exp Clin Psychopharmacol. 2015.
Given the volume and importance of research focusing on menstrual phase, a review of the strategies being used to identify menstrual phase and recommendations that will promote methodological uniformity in the field is needed. The authors conducted a literature review via Ovid Medline and PsycINFO. Their goal was to review methods used to identify menstrual phase and subphases in biobehavioral research studies with women who had physiologically natural menstrual cycles. Therefore, they excluded articles that focused on any of the following: use of exogenous hormones, the postpartum period, menstrual-related problems (e.g., polycystic ovarian syndrome, endometriosis), and infertility/anovulation. The authors also excluded articles on either younger (<18 years old) or older (>45 years old) study samples. They initially identified a total of 1,809 articles. After their exclusionary criteria were applied, 146 articles remained, within which our

review identified 6 different methods used to identify menstrual phase and subphases. The most common method used was self-report of onset of menses (145/146 articles) followed by urine luteinizing hormone testing (50/146 articles) and measurement of hormones (estradiol and/or progesterone) in blood samples (49/146 articles). Overall, the authors found a lack of consistency in the methodology used to determine menstrual phase and subphases. They provide several options to improve accuracy of phase identification, as well as to minimize costs and burden. Adoption of these recommendations will decrease misclassification within individual studies, facilitate cross-study comparisons, and enhance the reproducibility of results.

Heroin Delay Discounting: Modulation By Pharmacological State, Drug-use Impulsivity, and Intelligence Stoltman JK, Woodcock EA, Lister JJ, Lundahl LH, Greenwald MK. Exp Clin Psychopharmacol. 2015; 23(6): 455-463.
Delay discounting (DD) refers to how rapidly an individual devalues goods based on delays to receipt. DD usually is considered a trait variable but can be state dependent, yet few studies have assessed commodity valuation at short, naturalistically relevant time intervals that might enable state-dependent analysis. This study aimed to determine whether drug-use impulsivity and intelligence influence heroin DD at short (ecologically relevant) delays during two pharmacological states (heroin satiation and withdrawal). Out-of-treatment, intensive heroin users (n = 170; 53.5% African American; 66.7% male) provided complete DD data during imagined heroin satiation and withdrawal. Delays were 3, 6, 12, 24, 48, 72, and 96 hours; maximum delayed heroin amount was thirty $10 bags. Indifference points were used to calculate area under the curve (AUC). We also assessed drug-use impulsivity (subscales from the Impulsive Relapse Questionnaire [IRQ]) and estimated intelligence (Shipley IQ) as predictors of DD. Heroin discounting was greater (smaller AUC) during withdrawal than satiation. In regression analyses, lower intelligence and IRQ Capacity for Delay as well as higher IRQ Speed (to return to drug use) predicted greater heroin discounting in the satiation condition. Lower intelligence and higher IRQ Speed predicted greater discounting in the withdrawal condition. Sex, race, substance use variables, and other IRQ subscales were not significantly related to the withdrawal or satiation DD behavior. In summary, heroin discounting was temporally rapid, pharmacologically state dependent, and predicted by drug-use impulsivity and estimated intelligence. These findings highlight a novel and sensitive measure of acute DD that is easy to administer.

Efficacy and Acceptability Of Pharmacotherapy For Smoking Cessation In Adults With Serious Mental Illness: A Systematic Review and Network Meta-analysis Roberts E, Evins AE, McNeill A, Robson D. Addiction. 2015.
The aim of this study was to assess the efficacy and tolerability of adjunctive pharmacotherapy for smoking cessation in adults with serious mental illness (SMI) by means of a systematic review and network meta-analysis.The authors searched Embase, Medline, PsychINFO and the Cochrane Central Register of Controlled Trials, from database inception to 1 December 2014 for randomised controlled trials (RCTs) published in English. They included all studies of smokers with SMI (including schizophrenia, schizoaffective disorder, bipolar disorder, delusional disorder and depressive psychoses) who were motivated to quit smoking. Pharmacotherapies included nicotine replacement therapy (NRT), bupropion and varenicline delivered as monotherapy or in combination compared with each other or placebo. The efficacy outcome was self-reported sustained smoking cessation, biochemically verified at the longest reported time point. The tolerability outcome was number of patients discontinuing the trial due to any adverse event. Seventeen study reports were included which represented fourteen individual RCTs. No trials were found in patients with

depressive psychoses, delusional disorder or which compared NRT monotherapy with placebo. A total of 356 and 423 participants were included in the efficacy and tolerability analyses respectively. From the network meta-analysis both bupropion and varenicline were more effective than placebo (OR 4.51 95% Credible Interval (CrI) 1.45 to 14.04 and OR 5.17 95% CrI 1.78 to 15.06 respectively). Data were insensitive to an assessment of varenicline versus bupropion (OR 1.15 95% CrI 0.24 to 5.45). There were no significant differences in tolerability. All outcomes were rated by GRADE criteria as very low quality. The limited evidence available to date suggests that bupropion and varenicline are effective and acceptable for smoking cessation in adults with serious mental illnesses.

Combined Analysis Of N'-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol In The Urine Of Cigarette Smokers and E-cigarette Users Kotandeniya D, Carmella SG, Pillsbury ME, Hecht SS. J Chromatogr B Analyt Technol Biomed Life Sci. 2015; 1007: 121-126.
A liquid chromatography-electrospray ionization-tandem mass spectrometry (HPLC-ESI(+)-MS/MS) method for the analysis of the tobacco-specific carcinogens N';-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and their glucuronides (total NNN and total NNAL) in human urine was developed. The method has excellent accuracy and intra-day and inter-day precision, and limits of quantitation of 0.015 and 0.075pmol/mL urine, respectively, for total NNN and total NNAL. A unique aspect of this method is internal assessment of possible artifactual formation of NNN by inclusion of the monitor amine [pyridine-D4] nornicotine. The authors found that artifactual formation of NNN comprised only 2.5% of the measured amounts of total NNN in urine of cigarette smokers, under our conditions using ammonium sulfamate as an inhibitor of nitrosation. The method was applied to urine samples from cigarette smokers and e-cigarette users. Levels of total NNN and total NNAL in the urine of cigarette smokers averaged 0.060±0.035pmol/mL and 2.41±1.41pmol/mL urine, (N=38), respectively, which were both significantly greater than in the urine of 27 e-cigarette users.

Plasma Cannabinoid Pharmacokinetics After Controlled Smoking and Ad Libitum Cannabis Smoking In Chronic Frequent Users Lee D, Bergamaschi MM, Milman G, Barnes AJ, Queiroz RHC, Vandrey R, Huestis MA. J Anal Toxicol. 2015; 39(8): 580-587.
More Americans are dependent on cannabis than any other illicit drug. The main analytes for cannabis testing include the primary psychoactive constituent, Δ(9)-tetrahydrocannabinol (THC), equipotent 11-hydroxy-THC (11-OH-THC) and inactive 11-nor-9-carboxy-THC (THCCOOH). Eleven adult chronic frequent cannabis smokers resided on a closed research unit with unlimited access to 5.9% THC cannabis cigarettes from 12:00 to 23:00 during two ad libitum smoking phases, followed by a 5-day abstinence period in seven participants. A single cigarette was smoked under controlled topography on the last day of the smoking and abstinence phases. Plasma cannabinoids were quantified by two-dimensional gas chromatography-mass spectrometry. Median plasma maximum concentrations (Cmax) were 28.3 (THC), 3.9 (11-OH-THC) and 47.0 μg/L (THCCOOH) 0.5 h after controlled single cannabis smoking. Median Cmax 0.2-0.5 h after ad libitum smoking was higher for all analytes: 83.5 (THC), 14.2 (11-OH-THC) and 155 μg/L (THCCOOH). All 11 participants; plasma samples were THC and THCCOOH-positive, 58.3% had THC ≥5 μg/L and 79.2% were 11-OH-THC-positive 8.1-14 h after last cannabis smoking. Cannabinoid detection rates in seven participants 106-112 h (4-5 days) after last smoking were 92.9 (THC), 35.7 (11-OH-THC) and 100% (THCCOOH), with limits of quantification of 0.5 μg/L for THC and THCCOOH, and 1.0 μg/L for 11-OH-THC. These data greatly expand prior research findings on cannabinoid excretion

profiles in chronic frequent cannabis smokers during ad libitum smoking. Smoking multiple cannabis cigarettes led to higher Cmax and AUC compared with smoking a single cigarette. The chronic frequent cannabis smokers exhibited extended detection windows for plasma cannabinoids, reflecting a large cannabinoid body burden.

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

Blood-Derived CD4 T Cells Naturally Resist Pyroptosis During Abortive HIV-1 Infection
Muñoz-Arias I, Doitsh G, Yang Z, Sowinski S, Ruelas D, Greene WC. Cell Host Microbe. 2015 Oct 14; 18(4): 463-470. doi: 10.1016/j.chom.2015.09.010.
Progression to AIDS is driven by CD4 T cell depletion, mostly involving pyroptosis elicited by abortive HIV infection of CD4 T cells in lymphoid tissues. Inefficient reverse transcription in these cells leads to cytoplasmic accumulation of viral DNAs that are detected by the DNA sensor IFI16, resulting in inflammasome assembly, caspase-1 activation, and pyroptosis. Unexpectedly, the authors found that peripheral blood-derived CD4 T cells naturally resist pyroptosis. This resistance is partly due to their deeper resting state, resulting in fewer HIV-1 reverse transcripts and lower IFI16 expression. However, when co-cultured with lymphoid-derived cells, blood-derived CD4 T cells become sensitized to pyroptosis, likely recapitulating interactions occurring within lymphoid tissues. Sensitization correlates with higher levels of activated NF-κB, IFI16 expression, and reverse transcription. Blood-derived lymphocytes purified from co-cultures lose sensitivity to pyroptosis. These differences highlight how the lymphoid tissue microenvironment encountered by trafficking CD4 T lymphocytes dynamically shapes their biological response to HIV.

Cell-to-Cell Transmission of HIV-1 Is Required to Trigger Pyroptotic Death of Lymphoid-Tissue-Derived CD4 T Cells Galloway NL, Doitsh G, Monroe KM, Yang Z, Muñoz-Arias I, Levy DN, Greene WC.Cell Rep. 2015 Sep 8; 12(10): 1555-1563. doi: 10.1016/j.celrep.2015.08.011. Epub 2015 Aug 28.
The progressive depletion of CD4 T cells underlies clinical progression to AIDS in untreated HIV-infected subjects. Most dying CD4 T cells correspond to resting nonpermissive cells residing in lymphoid tissues. Death is due to an innate immune response against the incomplete cytosolic viral DNA intermediates accumulating in these cells. The viral DNA is detected by the IFI16 sensor, leading to inflammasome assembly, caspase-1 activation, and the induction of pyroptosis, a highly inflammatory form of programmed cell death. The authors now show that cell-to-cell transmission of HIV is obligatorily required for activation of this death pathway. Cell-free HIV-1 virions, even when added in large quantities, fail to activate pyroptosis. These findings underscore the infected CD4 T cells as the major killing units promoting progression to AIDS and highlight a previously unappreciated role for the virological synapse in HIV pathogenesis.

SERINC3 and SERINC5 Restrict HIV-1 Infectivity and are Counteracted By Nef
Usami Y, Wu Y, Göttlinger HG. Nature. 2015 Oct 8;526(7572):218-23. doi: 10.1038/nature15400. Epub 2015 Sep 30.
HIV-1 Nef and the unrelated mouse leukaemia virus glycosylated Gag (glycoGag) strongly enhance the infectivity of HIV-1 virions produced in certain cell types in a clathrin-dependent manner. Here the authors show that Nef and glycoGag prevent the incorporation of the multipass transmembrane proteins serine incorporator 3 (SERINC3) and SERINC5 into HIV-1 virions to an extent that correlates with infectivity enhancement. Silencing of both SERINC3 and SERINC5 precisely phenocopied the effects of Nef and glycoGag on HIV-1 infectivity. The infectivity of nef-deficient virions increased more than 100-fold when produced in double-knockout human CD4(+) T cells that lack both SERINC3 and SERINC5, and re-expression experiments confirmed that the absence of SERINC3 and SERINC5 accounted for the infectivity enhancement. Furthermore, SERINC3 and SERINC5 together restricted HIV-1 replication, and this restriction was evaded by Nef. SERINC3

and SERINC5 are highly expressed in primary human HIV-1 target cells, and inhibiting their down regulation by Nef is a potential strategy to combat HIV/AIDS.

HIV Transmission Networks in the San Diego-Tijuana Border Region Mehta SR, Wertheim JO, Brouwer KC, Wagner KD, Chaillon A, Strathdee S, Patterson TL, Rangel MG, Vargas M, Murrell B, Garfein R, Little SJ, Smith DM. EBioMedicine. 2015 Jul 18; 2(10): 1456-1463. doi: 10.1016/j.ebiom.2015.07.024. eCollection 2015.
HIV sequence data can be used to reconstruct local transmission networks. Along international borders, like the San Diego-Tijuana region, understanding the dynamics of HIV transmission across reported risks, racial/ethnic groups, and geography can help direct effective prevention efforts on both sides of the border. The authors gathered sociodemographic, geographic, clinical, and viral sequence data from HIV infected individuals participating in ten studies in the San Diego-Tijuana border region. Phylogenetic and network analysis was performed to infer putative relationships between HIV sequences. Correlates of identified clusters were evaluated and spatiotemporal relationships were explored using Bayesian phylogeographic analysis. After quality filtering, 843 HIV sequences with associated demographic data and 263 background sequences from the region were analyzed, and 138 clusters were inferred (2-23 individuals). Overall, the rate of clustering did not differ by ethnicity, residence, or sex, but bisexuals were less likely to cluster than heterosexuals or men who have sex with men ($p = 0.043$), and individuals identifying as white ($p \leq 0.01$) were more likely to cluster than other races. Clustering individuals were also 3.5 years younger than non-clustering individuals ($p < 0.001$). Although the sampled San Diego and Tijuana epidemics were phylogenetically compartmentalized, five clusters contained individuals residing on both sides of the border. This study sampled ~ 7% of HIV infected individuals in the border region, and although the sampled networks on each side of the border were largely separate, there was evidence of persistent bidirectional cross-border transmissions that linked risk groups, thus highlighting the importance of the border region as a "melting pot" of risk groups.

Marijuana Use as a Sex-Drug is Associated with HIV Risk Among Black MSM and Their Network Morgan E, Skaathun B, Michaels S, Young L, Khanna A, Friedman SR, Davis B, Pitrak D, Schneider J, UConnect Study Team. AIDS Behav. 2015 Sep 23. [Epub ahead of print].
Black men who have sex with men (BMSM) are at highest risk for HIV seroconversion in the United States. Little attention has been paid to marijuana use among BMSM and potential for HIV risk. A sample of 202 BMSM was generated through respondent driven sampling. The relationship between differential marijuana use and both HIV risk behavior and social network factors were examined using weighted logistic regression. Of the BMSM in this sample 60.4 % use marijuana in general and 20.8 % use marijuana as a sex-drug. General marijuana use was significantly associated with participation in group sex (AOR 3.50; 95 % CI 1.10-11.10) while marijuana use as a sex drug was significantly associated with both participation in condomless sex (AOR 2.86; 95% CI 1.07-7.67) and group sex (AOR 3.39; 95% CI 1.03-11.22). Respondents with a moderate or high perception of network members who use marijuana were more likely to use marijuana both in general and as a sex-drug. Network member marijuana use, while not associated with risk behaviors, is associated with individual marijuana use and individual marijuana use in the context of sex is associated with risk practices. Targeting interventions towards individuals and their respective networks that use marijuana as a sex drug may reduce HIV risk.

A Genomic and Clinical Prognostic Index For Hepatitis C-related Early-stage Cirrhosis That Predicts Clinical Deterioration King LY, Canasto-Chibuque C, Johnson KB, Yip S, Chen X, Kojima K, Deshmukh M, Venkatesh A,Tan PS,Sun X,Villanueva A, Sangiovanni A, Nair V, Mahajan M, Kobayashi M, Kumada H, Iavarone M, Colombo M, Fiel MI, Friedman SL, Llovet JM, Chung RT,Hoshida Y. Gut. 2015; 64(8): 1296-1302.
The number of patients with HCV-related cirrhosis is increasing, leading to a rising risk of complications and death. Prognostic stratification in patients with early-stage cirrhosis is still challenging. The authors aimed to develop and validate a clinically useful prognostic index based on genomic and clinical variables to identify patients at high risk of disease progression. They developed a prognostic index, comprised of a 186-gene signature validated in their previous genome-wide profiling study, bilirubin (>1 mg/dL) and platelet count (<100,000/mm(3)), in an Italian HCV cirrhosis cohort (training cohort, n=216, median follow-up 10 years). The gene signature test was implemented using a digital transcript counting (nCounter) assay specifically developed for clinical use and the prognostic index was evaluated using archived specimens from an independent cohort of HCV-related cirrhosis in the USA (validation cohort, n=145, median follow-up 8 years). In the training cohort, the prognostic index was associated with hepatic decompensation (HR=2.71, p=0.003), overall death (HR=6.00, p<0.001), hepatocellular carcinoma (HR=3.31, p=0.001) and progression of Child-Turcotte-Pugh class (HR=6.70, p<0.001). The patients in the validation cohort were stratified into high-risk (16%), intermediate-risk (42%) or low-risk (42%) groups by the prognostic index. The high-risk group had a significantly increased risk of hepatic decompensation (HR=7.36, p<0.001), overall death (HR=3.57, p=0.002), liver-related death (HR=6.49, p<0.001) and all liver-related adverse events (HR=4.98, p<0.001). A genomic and clinical prognostic index readily available for clinical use was successfully validated, warranting further clinical evaluation for prognostic prediction and clinical trial stratification and enrichment for preventive interventions.

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; 19(12): 2177-2183.
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.

Preventing HIV Transmission Among Partners Of HIV-Positive Male Sex Workers In Mexico City: A Modeling Study Monteiro JFG, Marshall BDL, Escudero D, Sosa-Rubí SG, González A, Flanigan T, Operario D, Mayer KH, Lurie MN, Galárraga O. AIDS Behav. 2015; 19(9): 1579-1588.
Mexico has a concentrated HIV epidemic, with male sex workers constituting a key affected population. The authors estimated annual HIV cumulative incidence among male sex workers; partners, and then compared incidence under three hypothetical intervention scenarios: improving condom use; and scaling up HIV treatment as prevention, considering current viral suppression rates (CVS, 60.7 %) or full viral suppression among those treated (FVS, 100 %). Clinical and behavioral data to inform model parameterization were derived from a sample (n = 79) of male sex

workers recruited from street locations and Clínica Condesa, an HIV clinic in Mexico City. The authors estimated annual HIV incidence among male sex workers; partners to be 8.0 % (95 % CI: 7.3-8.7). Simulation models demonstrated that increasing condom use by 10 %, and scaling up HIV treatment initiation by 50 % (from baseline values) would decrease the male sex workers-attributable annual incidence to 5.2, 4.4 % (CVS) and 3.2 % (FVS), respectively. Scaling up the number of male sex workers on ART and implementing interventions to ensure adherence is urgently required to decrease HIV incidence among male sex workers; partners in Mexico City.

CD4+ T-Cell-Dependent Reduction In Hepatitis C Virus-Specific Neutralizing Antibody Responses After 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; 212(6): 914-923.
Human immunodeficiency virus (HIV) infection leads to lower rates of hepatitis C virus (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 binding antibody titers, neutralizing antibody (nAb) titers, and nAb 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 nAb titers was detected in subjects with CD4(+) T-cell counts <350/mm(3) after HIV infection, and subjects with CD4(+) T-cell counts <200/mm(3) also showed a reduction in nAb breadth. Subjects who maintained CD4(+) T-cell counts ≥350/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, nAb titers, and nAb breadth.

Virologic Response and Haematologic Toxicity Of Boceprevir- and Telaprevir-containing Regimens In Actual Clinical Settings Butt AA, Yan P, Shaikh OS, Freiberg MS, Lo Re 3rd V, Justice AC, Sherman KE, ERCHIVES (Electronically Retrieved Cohort of HCV Infected Veterans) Study Team. J Viral Hepat. 2015; 22(9): 691-700.
Effectiveness, safety and tolerability of boceprevir (BOC) and telaprevir (TPV) in actual clinical settings remain unknown. The authors determined rates of sustained virologic response (SVR) and haematologic adverse effects among persons treated with BOC- or TPV-containing regimens, compared with pegylated interferon/ribavirin (PEG/RBV). Using an established cohort of hepatitis C virus (HCV)-infected persons, Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES), the authors identified those treated with a BOC- or TPV-containing regimen and HCV genotype 1-infected controls treated with PEG/RBV. They excluded those with HIV coinfection and missing HCV RNA values to determine SVR. Primary endpoints were SVR (undetectable HCV RNA ≥12 weeks after treatment completion) and haematologic toxicity (grade 3/4 anaemia, neutropenia and thrombocytopenia). The authors evaluated 2288 persons on BOC-, 409 on TPV-containing regimen and 6308 on PEG/RBV. Among these groups, respectively, 31%, 43% and 9% were treatment-experienced; 17%, 37% and 14% had baseline cirrhosis; 63%, 54% and 48% were genotype 1a. SVR rates among noncirrhotics were as follows: treatment naïve: 65% (BOC), 67% (TPV) and 31% (PEG/RBV); treatment experienced: 57% (BOC), 54% (TPV) and 13% (PEG/RBV); (P-value not significant for BOC vs TPV; P < 0.0001 for BOC or TPV vs PEG/RBV). Haematologic toxicities among BOC-, TPV- and PEG/RBV-treated groups were as follows: grade 3/4 anaemia 7%, 11% and 3%; grade 4 thrombocytopenia 2.2%, 5.4% and 1.7%;

grade 4 neutropenia 8.2%, 5.6% and 3.4%. SVR rates are higher and closer to those reported in pivotal clinical trials among BOC- and TPV-treated persons compared with PEG/RBV-treated persons. Haematologic adverse events are frequent, but severe toxicity is uncommon.

Adherence and HIV RNA Suppression In The Current Era Of Highly Active Antiretroviral Therapy Viswanathan S, Justice AC, Alexander GC, Brown TT, Gandhi NR, McNicholl IR, Rimland D, Rodriguez-Barradas MC, Jacobson LP. J Acquir Immune Defic Syndr. 2015; 69(4): 493-498.
The authors examined trends in adherence to highly active antiretroviral therapy (HAART) and HIV RNA suppression and estimated the minimum cutoff of adherence to newer HAART formulations needed for HIV RNA suppression by regimen type. They used Veterans Affairs pharmacy dispensing data from the Veterans Aging Cohort Study Virtual Cohort between October 2000 and September 2010 and defined adherence as the duration of time the patient had the medications available, relative to the total number of days between refills for all antiretrovirals in a year. Temporal trends in adherence and viral load suppression were examined by the patient's most frequently used HAART regimen in the year. The minimum needed adherence was defined as the level at which the odds of suppression was not significantly different than that observed with ≥ 95% adherence using repeated-measures logistic regression. A total of 21,865 HAART users contributed 82,217 person-years of follow-up. There was a significant increase (P(trend) < 0.001) in the proportion virally suppressed even among those with <95% adherence (2001: 38% to 2010: 84%), and the trend was similar when restricting to their first HAART regimen. For nonnucleoside reverse transcriptase inhibitor multi-pill users, the odds of suppression did not differ for 85%-89% adherence compared to those with ≥ 95% adherence [odds ratios: 0.82 (0.64-1.04)], but for protease inhibitor users, the odds of suppression significantly differed if adherence levels were <95% compared to ≥ 95% adherence. Although all HIV-infected persons should be instructed to achieve perfect adherence, concerns of slightly lower adherence should not hinder prescribing new HAART regimens early in HIV infection.

Racial Differences In Bone Loss and Relation To Menopause Among HIV-infected and Uninfected Women Sharma A, Flom PL, Rosen CJ, Schoenbaum EE. Bone. 2015; 77: 24-30.
The aims of this study were to characterize changes in bone mineral density (BMD) according to race among HIV-infected and uninfected women, and to evaluate the relationship between race and menopause-related bone loss. Dual X-ray absorptiometry measured BMD on study entry and a minimum of 18 months later in 246 HIV-infected and 219 HIV-uninfected women in the Menopause Study. Linear regression analyses determined percent annual BMD change at the total hip (TH), femoral neck (FN), and lumbar spine (LS) after adjusting for potential confounders. Race-stratified and HIV-infected subgroup analyses were performed. At baseline, mean age was 45 years, 19% of women were postmenopausal. HIV-infected women were more likely to be black (58% vs. 38%), and had lower BMI and less cigarette exposure when compared to HIV-uninfected women. Women who were perimenopausal at baseline and postmenopausal at follow-up had the greatest TH bone loss (-1.68%/yr, p < .0001) followed by those postmenopausal throughout (-1.02%/yr, p = .007). The authors found a significant interaction between HIV status and race in multivariate analyses of BMD change at the FN and TH. In race-stratified analyses, HIV infection was associated with TH BMD loss in non-black women. Black women experienced greater menopause-associated decline in TH BMD compared with non-black women. The association of HIV and BMD differs strikingly by race, as do the effects of the menopausal transition on bone. Determining the

extent to which the effect of HIV on fracture risk varies by race will be crucial to identify HIV-infected women at greatest risk for osteoporotic fracture, particularly as they enter menopause.

Clinical Characteristics Of Human Immunodeficiency Virus Patients Being Referred For Liver Transplant Evaluation: A Descriptive Cohort Study Martel-Laferrière V, Michel A, Schaefer S, Bindal S, Bichoupan K, Branch AD, Huprikar S, Schiano TD, Perumalswami PV. Transpl Infect Dis. 2015; 17(4): 527-535.
Liver transplantation (LT) is a treatment option for select human immunodeficiency virus (HIV)-infected patients with advanced liver disease. The aim of this study was to describe LT evaluation outcomes in HIV-infected patients.All HIV-infected patients referred for their first LT evaluation at the Mount Sinai Medical Center were included in this retrospective, descriptive cohort study. Multivariable logistic regression was used to identify factors independently associated with listing.Between February 2000 and April 2012, 366 patients were evaluated for LT, with 66 (18.0%) listed for LT and 300 (82.0%) not listed. Fifty-one patients (13.9%) died before completing evaluation and 85 (23.2%) were too early for listing. Reasons patients were declined for listing were psychosocial (15.8%), HIV-related (10.4%), loss to follow-up (9.6%), surgical/medical (6.0%), liver-related (4.4%), patient choice (3.4%), and financial (1.6%). Listed patients were more likely to have hepatocellular carcinoma (HCC) (43.1% vs. 17.1%; $P < 0.0001$) and less likely to have hepatitis B (6.2% vs. 15.7%; $P = 0.04$) or a psychiatric history (19.7% vs. 35.2%; $P = 0.02$) than those not listed. In multivariable analysis, HCC (odds ratio [OR] 5.79; 95% confidence interval [95% CI]: 2.97-11.28), model for end-stage liver disease (MELD) score at referral (OR 1.06; 95% CI 1.01-1.11), and hepatitis B (OR 0.26; 95% CI 0.08-0.79) were associated with listing.MELD score and HCC were positive predictors of listing in HIV-infected patients referred for LT evaluation and, therefore, timely referrals are vital in these patients. As MELD is a predictor for death while undergoing evaluation, rapid evaluation should be performed in HIV-infected patients with a higher MELD score.

An Electronic Daily Diary Study Of Anal Intercourse In Drug-Using Women Reynolds GL, Fisher DG, Laurenceau J-P, Fortenberry JD. AIDS Behav. 2015; 19(12): 2325-1232.
Women (N = 138) with histories of illicit drug use were recruited into an electronic diary study that used Android smartphones for data collection. The diary was to be completed each day for 12 weeks using an "app" created in HTML5 and accessed over the Internet via smartphone. Data collection included information on sexual behaviors with up to 10 partners per day and contextual factors surrounding sexual behavior such as drug use before/after, type of sexual behavior (oral, vaginal, anal), and other activities such as using condoms for vaginal and anal intercourse and use of sexual lubricants. The sample was predominantly African American (58 %); 20 % Latina, 20 % White and 2 % reported as Other. Most women reported either less than a high school education (33 %) or having a high school diploma (33 %). The mean age was 39 years (SD = 11.78). Anal intercourse occurred on days when women also reported using illicit drugs, specifically methamphetamine and cocaine. Anal intercourse was not an isolated sexual activity, but took place on days when vaginal intercourse and giving and receiving oral sex also occurred along with illicit drug use. Anal intercourse also occurred on days when women reported they wanted sex. HIV prevention interventions must address the risks of anal intercourse for women, taking into account concurrent drug use and sexual pleasure that may reduce individual harm-reduction behaviors.

A Longitudinal Study Of Hepatitis C Virus Testing and Infection Status Notification On Behaviour Change In People Who Inject Drugs Spelman T, Morris MD, Zang G, Rice T, Page K, Maher L, Lloyd A, Grebely J, Dore GJ, Kim AY, Shoukry NH, Hellard M, Bruneau J, International Collaborative of Incident HIV and Hepatitis C in Injecting Cohorts (InC3 Study). J Epidemiol Community Health. 2015; 69(8): 745-752.
Hepatitis C virus (HCV) testing and counselling have the potential to impact individual behaviour and transmission dynamics at the population level. Evidence of the impact of an HCV-positive status notification on injection risk reduction is limited. The objectives of this study were to (1) assess drug and alcohol use and injection risk behaviours following notification; (2) to compare behaviour change in people who inject drugs (PWID) who received a positive test result and those who remained negative; and (3) to assess the effect of age on risk behaviour. Data from the International Collaboration of Incident HIV and HCV Infection in Injecting Cohorts (InC3 Study) were analysed. Participants who were initially HCV seronegative were followed prospectively with periodic HCV blood testing and post-test disclosure and interview-administered questionnaires assessing drug use and injection behaviours. Multivariable generalised estimating equations were used to assess behavioural changes over time.Notification of an HCV-positive test was independently associated with a small increase in alcohol use relative to notification of a negative test. No significant differences in postnotification injection drug use, receptive sharing of ancillary injecting equipment and syringe borrowing postnotification were observed between diagnosis groups. Younger PWID receiving a positive HCV test notification demonstrated a significant increase in subsequent alcohol use compared with younger HCV negative. The proportion of PWID reporting alcohol use increased among those receiving an HCV-positive notification, increased the frequency of alcohol use postnotification, while no reduction in injection drug use behaviours was observed between notification groups. These findings underscore the need to develop novel communication strategies during post-test notification to improve their impact on subsequent alcohol use and risk behaviours.

A Thymine-adenine Dinucleotide Repeat Polymorphism Near IL28B Is Associated With Spontaneous Clearance Of Hepatitis C Virus Hiramine S, Sugiyama M, Furusyo N, Uto H, Ido A, Tsubouchi H, Watanabe H, Ueno Y, Korenaga M, Murata K, Masaki N, Hayashi J, Thomas DL, Mizokami M. J Gastroenterol. 2015; 50(10): 1069-1077.
Genome-wide association studies have revealed several single-nucleotide polymorphisms around interleukin 28B (IL28B) that are strongly associated with hepatitis C virus (HCV) clearance. However, their predictive value is not perfect, which suggests that other genetic factors may also be involved in HCV clearance. The authors previously reported a wide variation in the length of a thymine-adenine (TA) dinucleotide repeat in the promoter region of IL28B and that the transcriptional activity of the promoter increased gradually in a TA repeat length-dependent manner. The authors determined the length of the TA repeats of 1,060 Japanese and 201 African-American samples to investigate the relation to spontaneous HCV clearance.The distribution of the TA repeats greatly differed between the two ethnicities. The variation ranged from 10 to 18 repeats, and the most frequent allele, 12, accounted for over 80 % for Japanese. The African-American data showed a gently sloping distribution, and the allele with six repeats was detected only in the African-American sample. The TA repeats 11 or greater were correlated with spontaneous clearance. Multiple logistic regression analysis extracted the genotype of the TA repeats as an independent factor in both the Japanese [p = 0.0004, odds ratio (OR) = 13.02 95 % confidence interval (CI) = 2.59-237.0] and African-American (p = 0.027, OR = 3.70 95 % CI = 1.16-11.8) populations.A long TA repeat in the promoter region of IL28B was associated with spontaneous

HCV clearance. Although its efficacy may be limited in Japanese population because of its allele distribution, this novel genetic factor will be useful for predicting HCV clearance especially for the African Americans.

Adenovirus-Vectored Broadly Neutralizing Antibodies Directed Against Gp120 Prevent Human Immunodeficiency Virus Type 1 Acquisition In Humanized Mice Liu S, Jackson A, Beloor J, Kumar P, Sutton RE. Hum Gene Ther. 2015; 26(9): 622-634.
Despite nearly three decades of research, a safe and effective vaccine against human immunodeficiency virus type 1 (HIV-1) has yet to be achieved. More recently, the discovery of highly potent anti-gp160 broadly neutralizing antibodies (bNAbs) has garnered renewed interest in using antibody-based prophylactic and therapeutic approaches. Here, the authors encoded bNAbs in first-generation adenoviral (ADV) vectors, which have the distinctive features of a large coding capacity and ease of propagation. A single intramuscular injection of ADV-vectorized bNAbs in humanized mice generated high serum levels of bNAbs that provided protection against multiple repeated challenges with a high dose of HIV-1, prevented depletion of peripheral CD4(+) T cells, and reduced plasma viral loads to below detection limits. Their results suggest that ADV vectors may be a viable option for the prophylactic and perhaps therapeutic use of bNAbs in humans.

Risk Factors For Stimulant Use Among Homeless and Unstably Housed Adult Women Riley ED, Shumway M, Knight KR, Guzman D, Cohen J, Weiser SD. Drug Alcohol Depend. 2015; 153: 173-179.
One of the most common causes of death among homeless and unstably housed women is acute intoxication where cocaine is present. While correlates of stimulant use have been determined in prior research, few studies have assessed risk factors of use specifically in this high-risk population.The authors sampled biological women with a history of housing instability from community-based venues to participate in a cohort study. Baseline and 6-month follow-up data were used to determine the relative risk of stimulant use (crack cocaine, powder cocaine or methamphetamine) among individuals who did not use at baseline. Among 260 study participants, the median age was 47 years, 70% were women of color; 47% reported having unmet subsistence needs and 53% reported abstinence from stimulants at baseline. In analyses adjusting for baseline sociodemographics and drug treatment, the risk of using stimulants within 6 months was significantly higher among women who reported recent sexual violence (Adjusted Relative Risk [ARR]=4.31; 95% CI:1.97-9.45), sleeping in a shelter or public place (ARR=2.75; 95% CI:1.15-6.57), and using unprescribed opioid analgesics (ARR=2.54; 95% CI:1.01-6.38). The authors found that almost half of homeless and unstably housed women used stimulants at baseline and 14% of those who did not use began within 6 months. Addressing homelessness and sexual violence is critical to reduce stimulant use among impoverished women.

Hepatitis C Virus Infection and Pain Sensitivity In Patients On Methadone Or Buprenorphine Maintenance Therapy For Opioid Use Disorders Tsui JI, Lira MC, Cheng DM, Winter MR, Alford DP, Liebschutz JM, Mao J, Edwards RR, Samet JH. Drug Alcohol Depend. 2015; 153: 286-292.
Patients with opioid use disorders on opioid agonist therapy (OAT) have lower pain tolerance compared to controls. While chronic viral infections such as HCV and HIV have been associated with chronic pain in this population, no studies have examined their impact on pain sensitivity. The authors recruited 106 adults (41 uninfected controls; 40 HCV mono-infected; and 25 HCV/HIV co-infected) on buprenorphine or methadone to assess whether HCV infection (with or without HIV)

was associated with increased experimental pain sensitivity and self-reported pain. The primary outcome was cold pain tolerance assessed by cold-pressor test. Secondary outcomes were cold pain thresholds, wind-up ratios to repetitive mechanical stimulation (i.e., temporal summation) and acute and chronic pain. Multivariable regression models evaluated associations between viral infection status and outcomes, adjusting for other factors.No significant differences were detected across groups for primary or secondary outcomes. Adjusted mean cold pain tolerance was 25.7 (uninfected controls) vs. 26.8 (HCV mono-infection) vs. 25.3 (HCV/HIV co-infection) seconds (global p-value=0.93). Current pain appeared more prevalent among HCV mono-infected (93%) compared to HCV/HIV co-infected participants (76%) and uninfected controls (80%), as did chronic pain (77% vs. 64% vs. 61%, respectively). However, differences were not statistically significant in multivariable models.This study did not detect an association between HCV infection and increased sensitivity to pain among adults with and without HIV who were treated with buprenorphine or methadone for opioid use disorders. Results reinforce that pain and hyperalgesia are common problems in this population.

Response To Treatment Following Recently Acquired Hepatitis C Virus Infection In A Multicentre Collaborative Cohort Doyle JS, Deterding K, Grebely J, Wedemeyer H, Sacks-Davis R, Spelman T, Matthews G, Rice TM, Morris MD, McGovern BH, Kim AY, Bruneau J, Lloyd AR, Page K, Manns MP, Hellard ME, Dore GJ, InC3 Study Group. J Viral Hepat. 2015; 22(12): 1020-1032.

Pegylated interferon therapy is highly effective in recently acquired HCV. The optimal timing of treatment, regimen and influence of host factors remains unclear. The authors aimed to measure sustained virological response (SVR) during recent HCV infection and identify predictors of response. Data were from five prospective cohorts of high-risk individuals in Australia, Canada, Germany and the United States. Individuals with acute or early chronic HCV who commenced pegylated interferon therapy were included. The main outcome was SVR, and predictors were assessed using logistic regression. Among 516 with documented recent HCV infection, 237 were treated (pegylated interferon n = 161; pegylated interferon/ribavirin n = 76) (30% female, median age 35 years, 56% ever injected drugs, median duration of infection 6.2 months). Sixteen per cent (n = 38) were HIV/HCV co-infected. SVR among those with HCV mono-infection was 64% by intention to treat; SVR was 68% among HCV/HIV co-infection. Independent predictors of SVR in HCV mono-infection were duration of HCV infection (the odds of SVR declined by 8% per month of infection, aOR 0.92, 95% CI 0.85-0.99, P = 0.033), IFNL4 genotype (adjusted OR 2.27, 95% CI 1.13-4.56, P = 0.021), baseline HCV RNA <400 000 IU/mL (aOR 2.06, 95% CI 1.03-4.12, P = 0.041) and age ≥40 years (vs <30: aOR 2.92, 95% CI 1.31-6.49, P = 0.009), with no difference by drug regimen, HCV genotype, symptomatic infection or gender. The effect of infection duration on odds of SVR was greater among genotype-1 infection. Interferon-based HCV treatment is highly effective in recent HCV infection. Duration of infection, IFNL4 genotype and baseline HCV RNA levels can predict virological response and may inform clinical decision-making.

Injecting Risk Behaviours Following Treatment For Hepatitis C Virus Infection Among People Who Inject Drugs: The Australian Trial In Acute Hepatitis C Alavi M, Spelman T, Matthews GV, Haber PS, Day C, van Beek I, Walsh N, Yeung B, Bruneau J, Petoumenos K, Dolan K, Kaldor JM, Dore GJ, Hellard M, Grebely J, ATAHC Study Group. Int J Drug Policy. 2015; 26(10): 976-983.

A barrier to hepatitis C virus (HCV) treatment among people who inject drugs (PWID) has been a concern that interferon-based HCV treatment may increase injecting risk behaviours. This study

evaluated recent (past month) injecting risk behaviours during follow-up among PWID that did and did not receive HCV treatment. The Australian Trial in Acute Hepatitis C (ATAHC) was a prospective study of natural history and treatment of recent HCV infection. Analyses were performed using generalized estimating equations.Among 124 participants with a history of injecting drug use (median age 32 years), 69% were male, and 68% were treated for HCV infection. HCV treatment was not associated with an increase in recent injecting drug use (adjusted odds ratio (aOR) 1.06, 95% CI 0.93, 1.21) or recent used needle and syringe borrowing during follow-up (aOR 0.99, 95% CI 0.89, 1.08). HCV treatment was associated with a decrease in recent ancillary injecting equipment sharing during follow-up (aOR 0.85, 95% CI 0.74, 0.99). Further, among treated participants who remained in follow-up (n=24), ancillary injecting equipment sharing significantly decreased from 54% at enrolment to 17% during follow-up (P=0.012). HCV treatment was not associated with drug use or used needle and syringe borrowing during follow-up, but was associated with decreased ancillary injecting equipment sharing during follow-up. Programs to enhance HCV assessment and treatment among PWID should be expanded, given that HCV treatment does not lead to increases in injecting risk behaviours and has previously been demonstrated to be safe and effective among PWID.

"Hepatitis C Treatment Turned Me Around:" Psychological And Behavioral Transformation Related To Hepatitis C Treatment Batchelder AW, Peyser D, Nahvi S, Arnsten JH, Litwin AH. Drug Alcohol Depend. 2015; 153: 66-71.
Hepatitis C (HCV) is a significant public health problem that primarily affects current and former substance users. However, individuals with a history of substance use are less likely to have access to or engage in HCV care. Psychological and behavioral barriers prevent many HCV-infected individuals from initiating or engaging in HCV treatment. This study aimed to investigate the psychological and behavioral experiences of current and former substance users receiving HCV treatment within a combined methadone and primary care clinic in the United States. The authors conducted 31 semi-structured qualitative interviews with opioid-dependent adults enrolled in an integrated HCV treatment program within a methadone maintenance clinic in the Bronx, NY. The authors used thematic analysis, informed by grounded theory, and inquired about perceptions of HCV before and after initiating HCV treatment, reasons for initiating HCV treatment, and the decision to participate in individual versus group HCV treatment. Participants described psychological and behavioral transformation over the course of HCV treatment. These included reductions in internalized stigma and shame related to HCV and addiction, increases in HCV disclosure and self-care, reductions in substance use, and new desire to help others who are living with HCV.Integrating HCV treatment with methadone maintenance has the potential to create psychological and behavioral transformations among substance using adults, including reductions in HCV- and addiction-related shame and improvements in overall self-care.

Pre-cART Elevation Of CRP and CD4+ T-Cell Immune Activation Associated With HIV Clinical Progression In A Multinational Case-Cohort Study Balagopal A, Asmuth DM, Yang W-T, Campbell TB, Gupte N, Smeaton L, Kanyama C, Grinsztejn B, Santos B, Supparatpinyo K, Badal-Faesen S, Lama JR, Lalloo UG, Zulu F, Pawar JS, Riviere C, Kumarasamy N, Hakim J, Li X-D, Pollard RB, Semba RD, Thomas DL, Bollinger RC, Gupta A, ACTG PEARLS and NWCS 319 Study team. J Acquir Immune Defic Syndr. 2015; 70(2): 163-171.
Despite the success of combination antiretroviral therapy (cART), a subset of HIV-infected patients who initiate cART develop early clinical progression to AIDS; therefore, some cART initiators are not fully benefitted by cART. Immune activation pre-cART may predict clinical progression in

cART initiators.A case-cohort study (n = 470) within the multinational Prospective Evaluation of Antiretrovirals in Resource-Limited Settings clinical trial (1571 HIV treatment-naive adults who initiated cART; CD4 T-cell count <300 cells/mm; 9 countries) was conducted. A subcohort of 30 participants per country was randomly selected; additional cases were added from the main cohort. Cases [n = 236 (random subcohort 36; main cohort 200)] had clinical progression (incident WHO stage 3/4 event or death) within 96 weeks after cART initiation. Immune activation biomarkers were quantified pre-cART. Associations between biomarkers and clinical progression were examined using weighted multivariable Cox-proportional hazards models.Median age was 35 years, 45% were women, 49% black, 31% Asian, and 9% white. Median CD4 T-cell count was 167 cells per cubic millimeter. In multivariate analysis, highest quartile C-reactive protein concentration [adjusted hazard ratio (aHR), 2.53; 95% confidence interval (CI): 1.02 to 6.28] and CD4 T-cell activation (aHR, 5.18; 95% CI: 1.09 to 24.47) were associated with primary outcomes, compared with lowest quartiles. sCD14 had a trend toward association with clinical failure (aHR, 2.24; 95% CI: 0.96 to 5.21).Measuring C-reactive protein and CD4 T-cell activation may identify patients with CD4 T-cell counts <300 cells per cubic millimeter at risk for early clinical progression when initiating cART. Additional vigilance and symptom-based screening may be required in this subset of patients even after beginning cART.

Brief Report: Gonorrhea and Chlamydia Testing Increasing But Still Lagging In HIV Clinics In The United States Berry SA, Ghanem KG, Mathews WC, Korthuis PT, Yehia BR, Agwu AL, Lehmann CU, Moore RD, Allen SL, Gebo KA, HIV Research Network. J Acquir Immune Defic Syndr. 2015; 70(3): 275-279.
Screening persons living with HIV for gonorrhea and chlamydia has been recommended since 2003. The authors compared annual gonorrhea/chlamydia testing to syphilis and lipid testing among 19,368 adults (41% men who have sex with men, 30% heterosexual men, and 29% women) engaged in HIV care. In 2004, 22%, 62%, and 70% of all patients were tested for gonorrhea/ chlamydia, syphilis, and lipid levels, respectively. Despite increasing steadily [odds ratio per year (95% confidence interval): 1.14 (1.13 to 1.15)], gonorrhea/chlamydia testing in 2010 remained lower than syphilis and lipid testing (39%, 77%, 76%, respectively). Interventions to improve gonorrhea/chlamydia screening are needed. A more targeted screening approach may be warranted.

A Cell Culture System For Distinguishing Hepatitis C Viruses With and Without Liver Cancer-related Mutations In the Viral Core Gene El-Shamy A, Eng FJ, Doyle EH, Klepper AL, Sun X, Sangiovanni A, Iavarone M, Colombo M, Schwartz RE, Hoshida Y, Branch AD. J Hepatol. 2015; 63(6): 1323-1333.
Although patients infected by genotype 1b hepatitis C virus (HCV) with Q(70) and/or M(91) core gene mutations have an almost five-fold increased risk of developing hepatocellular carcinoma (HCC) and increased insulin resistance, the absence of a suitable experimental system has precluded direct experimentation on the effects of these mutations on cellular gene expression.HuH7 cells were treated long-term with human serum to induce differentiation and to produce a model system for testing high-risk and control HCV. For clinical validation, profiles of infected cells were compared to each other and to those of liver biopsies of patients with early-stage HCV-related cirrhosis followed prospectively for up to 23 years (n=216). Long-term culture in human serum produced growth-arrested, hepatocyte-like cells whose gene profile overlapped significantly with that of primary human hepatocytes. High-risk (Q(70)/M(91)) and control (R(70)/L(91)) viruses had dramatically different effects on gene expression of these cells. The high-risk virus enhanced expression of pathways associated with cancer and type II diabetes, while the control virus

enhanced pathways associated with oxidative phosphorylation. Of special clinical relevance, the transcriptome of cells replicating the high-risk virus correlated significantly with an HCC high-risk profile in patients (Bonferroni-corrected p=0.03), whereas no such association was observed for non-HCC-related clinical outcomes. The cell-based system allowed direct head-to-head comparison of HCV variants, and provided experimental support for previous clinical data indicating an oncogenic effect of core gene mutations. This simple experimental system distinguished HCV variants and will enable future mechanistic analysis and exploration of interventional approaches.

Effect Of Legal Status Of Pharmacy Syringe Sales On Syringe Purchases By Persons Who Inject Drugs In San Francisco and San Diego, CA Siddiqui SS, Armenta RF, Evans JL, Yu M, Cuevas-Mota J, Page K, Davidson P, Garfein RS. Int J Drug Policy. 2015; 26(11): 1150-1157.
Sharing blood-contaminated syringes is the main risk factor for acquiring and transmitting blood-borne infections among persons who inject drugs (PWID). To reduce this risk, in 2005, California enacted legislation allowing local health jurisdictions to legalize non-prescription syringe sales after approving a disease prevention demonstration project (DPDP). With San Francisco approving a DPDP immediately and San Diego never approving one, the authors compared PWID across cities for their use of pharmacies PWID to obtain syringes. PWID age 18-30 years old were recruited into separate studies in San Francisco (n=243) and San Diego (n=338) between 2008 and 2011. They used multivariable logistic regression to compare the proportions of PWID who obtained syringes from pharmacies by city while controlling for sociodemographics, injection practices and other risk behaviors. Overall, most PWID were White (71%), male (63%), and between the ages of 18-25 years (55%). Compared to San Francisco, a smaller proportion of PWID in San Diego had bought syringes from pharmacies in the prior three months (16.9% vs. 49.8%; p<0.001), which remained statistically significant after adjusting for sociodemographic and behavioral factors (adjusted odds ratio=4.45, 95% confidence interval: 2.98, 6.65).Use of pharmacies to obtain syringes was greater where it was legal to do so. Public health policy can influence HIV and hepatitis C associated risk among PWID; however, implementation of these policies is crucial for the benefits to be realized.

Hepatitis C Virus Infection and Spontaneous Clearance In HTLV-1 And HIV Co-infected Patients In Salvador, Bahia, Brazil Le Marchand C, Bahia F, Page K, Brites C. Braz J Infect Dis. 2015; 19(5): 486-491.
While 20-40% of patients with hepatitis C virus (HCV) monoinfection will spontaneously clear the virus, less is known regarding clearance with coinfections. HCV, human immunodeficiency virus (HIV), and human T-cell lymphotrophic virus 1 and 2 (HTLV-1/2) coinfection occurs due to shared routes of transmission and is prevalent in Brazil.The aim of this study was to compare the proportion of patients who have spontaneously cleared HCV in patients with HCV monoinfection to patients coinfected by HCV/HIV, or HCV/HIV/HTLV-1. Using medical records from two clinics in Salvador, Brazil, including demographic data and serological markers of HCV, HIV and HTLV-I/II, cross-sectional data was obtained from 197 patients. Patients who were anti-HCV positive and HCV RNA negative, and who did not receive HCV treatment were defined as having cleared infection. Nineteen patients (9.5%) showed evidence of spontaneous HCV clearance; with clearance in 9 of 108 (8.3%) patients in the HCV monoinfected group, 5 of 68 (7.4%) patients with HCV/HIV, and 5 of 21 (23.8%) patients with HCV/HIV/HTLV. Demographic data were not associated with HCV clearance status. Patients coinfected with both HIV and HTLV-1 had increased odds (5.50; 95% CI 1.00, 30.17) of spontaneous clearance of HCV compared with patients who were HIV negative or of unknown HIV status. This study found that patients coinfected with HIV and HTLV-1 were more likely to spontaneously clear hepatitis C virus than patients with HIV/HCV or HCV alone. The

effects of HTLV coinfection on the immune response of such patients may be associated with these findings.

Barriers Along the Care Cascade Of HIV-infected Men In A Large Urban Center Of Brazil Hoffmann M, MacCarthy S, Batson A, Crawford-Roberts A, Rasanathan J, Nunn A, Silva LA, Dourado I. AIDS Care. 2015: 1-6.
Global and national HIV/AIDS policies utilize the care cascade to emphasize the importance of continued engagement in HIV services from diagnosis to viral suppression. Several studies have documented barriers that men experience in accessing services at specific stages of care, but few have analyzed how these barriers operate along the care cascade. Brazil offers a unique setting for analyzing barriers to HIV care because it is a middle-income country with a large HIV epidemic and free, universal access to HIV/AIDS services. Semi-structured interviews were conducted in 2011 with HIV-infected men (n = 25) receiving care at the only HIV/AIDS state reference center in Salvador, Brazil, the third largest city in the country. Interviews were transcribed and coded for analysis. Researchers identified barriers to services along the care cascade: health service-related obstacles (poor-quality care, lengthy wait times, and drug supply problems); psychosocial and emotional challenges (fear of disclosure and difficulty accepting HIV diagnosis); indirect costs (transportation and absenteeism at work or school); low perceived risk of HIV; and toxicity and complexity of antiretroviral drug (ARV) regimens. The stages of the care cascade interrupted by each barrier were also identified. Most barriers affected multiple, and often all, stages of care, while toxicity and complexity of ARV regimens was only present at a single care stage. Efforts to eliminate more prevalent barriers have the potential to improve care continuity at multiple stages. Going forward, assessing the relative impact of barriers along one's entire care trajectory can help tailor improvements in service provision, facilitate achievement of viral suppression, and improve access to life-saving testing, treatment, and care.

SEC14L2 Enables Pan-genotype HCV Replication In Cell Culture Saeed M, Andreo U, Chung H-Y, Espiritu C, Branch AD, Silva JM, Rice CM. Nature. 2015; 524(7566): 471-475.
Since its discovery in 1989, efforts to grow clinical isolates of the hepatitis C virus (HCV) in cell culture have met with limited success. Only the JFH-1 isolate has the capacity to replicate efficiently in cultured hepatoma cells without cell culture-adaptive mutations. The authors hypothesized that cultured cells lack one or more factors required for the replication of clinical isolates. To identify the missing factors, they transduced Huh-7.5 human hepatoma cells with a pooled lentivirus-based human complementary DNA (cDNA) library, transfected the cells with HCV subgenomic replicons lacking adaptive mutations, and selected for stable replicon colonies. This led to the identification of a single cDNA, SEC14L2, that enabled RNA replication of diverse HCV genotypes in several hepatoma cell lines. This effect was dose-dependent, and required the continuous presence of SEC14L2. Full-length HCV genomes also replicated and produced low levels of infectious virus. Remarkably, SEC14L2-expressing Huh-7.5 cells also supported HCV replication following inoculation with patient sera. Mechanistic studies suggest that SEC14L2 promotes HCV infection by enhancing vitamin E-mediated protection against lipid peroxidation. This provides a foundation for development of in vitro replication systems for all HCV isolates, creating a useful platform to dissect the mechanisms by which cell culture-adaptive mutations act.

Increased Fracture Incidence In Middle-Aged HIV-Infected and HIV-Uninfected Women: Updated Results From The Women's Interagency HIV Study Sharma A, Shi Q, Hoover DR, Anastos K, Tien PC, Young MA, Cohen MH, Golub ET, Gustafson D,Yin MT. J Acquir Immune Defic Syndr. 2015; 70(1): 54-61.
The authors previously reported that fracture incidence rates did not differ by HIV status among predominantly premenopausal Women's Interagency HIV Study participants. They now conduct a follow-up study with 5 additional observation years to further characterize fracture risk associated with HIV infection in women as they age. The authors measured time to first new fracture at any site in 2375 (1713 HIV-infected and 662 HIV-uninfected) Women's Interagency HIV Study participants, with median 10-year follow-up. Fractures were self-reported semiannually. Proportional hazards models assessed predictors of incident fracture. At index visit, HIV-infected women were older [median age of 40 years (IQR: 34-46) vs. 35 (27-43), $P < 0.0001$] and more likely to be postmenopausal, hepatitis C virus infected, and weigh less than HIV-uninfected women. Among HIV-infected women, mean CD4 count was 480 cells per microliter and 63% were taking highly active antiretroviral therapy. Unadjusted incidence rates of any fracture were higher in HIV-infected than in HIV-uninfected women [2.19/100 person-years (py) vs. 1.54/100 py, $P = 0.002$]. In multivariate models, HIV status, older age, white (vs. black) race, prior fracture, history of cocaine use, and history of injection drug use were significant predictors of incident fracture. Among HIV-infected women, age, white race, prior fracture, smoking, and prior AIDS were predictors of new fracture.Middle-aged HIV-infected women had a higher adjusted fracture rate than HIV-uninfected women. Cocaine use and injection drug use were also associated with a greater risk of incident fracture. Further research is needed to understand whether the risk of fracture associated with cocaine use relates to increased rate of falls or direct effects on bone metabolism.

Successful Treatment Of Chronic Hepatitis C With Triple Therapy In An Opioid Agonist Treatment Program Litwin AH, Soloway IJ, Cockerham-Colas L, Reynoso S, Heo M, Tenore C, Roose RJ. Int J Drug Policy. 2015; 26(10): 1014-1019.
People who inject drugs (PWID) constitute 10 million people globally with hepatitis C virus, including many opioid agonist treatment patients. Little data exist describing clinical outcomes for patients receiving HCV treatment with direct-acting antiviral agents (DAAs) in opioid agonist treatment settings. In this retrospective observational study, the authors describe clinical outcomes for 50 genotype-1 patients receiving HCV treatment with triple therapy: telaprevir (n=42) or boceprevir (n=8) in combination with pegylated interferon and ribavirin on-site in an opioid agonist treatment program. Overall, 70% achieved an end of treatment response (ETR) and 62% achieved a sustained virological response (SVR). These treatment outcomes are nearly equivalent to previously published HCV outcomes shown in registration trials, despite high percentages of recent drug use prior to treatment (52%), ongoing drug use during treatment (45%) and psychiatric comorbidity (86%). Only 12% (n=6) discontinued antiviral treatment early for non-virological reasons. Four patients received a blood transfusion, and one discontinued telaprevir due to severe rash. These data demonstrate that on-site HCV treatment with direct-acting antiviral agents is effective in opioid agonist treatment patients including patients who are actively using drugs. Future interferon-free regimens will likely be even more effective. Opioid agonist treatment programs represent an opportunity to safely and effectively treat chronic hepatitis C, and PWID should have unrestricted access to DAAs.

"Sexual Behavior Patterns and PrEP Dosing Preferences In A Large Sample Of North American Men Who Have Sex With Men" Stack C, Oldenburg C, Mimiaga M, Elsesser SA, Krakower D, Novak DS, Egan J, Stall R, Safren S, Mayer KH. J Acquir Immune Defic Syndr. 2015.
Pre-exposure prophylaxis (PrEP), taken as a single daily co-formulated pill containing tenofovir-emtricitabine, is a promising intervention to reduce the likelihood of HIV acquisition in at-risk individuals, including men who have sex with men (MSM). Little is known about the acceptability of less than daily, intermittent PrEP (iPrEP) regimens. The authors conducted an online survey of North American MSM to characterize their sexual frequency and planning behaviors and correlate these with PrEP dosing preferences. Of the 3,217 respondents who completed the survey, 46% reported engaging in unplanned condomless anal intercourse (CAI) at least once in the prior 3 months and 8% reported engaging in CAI more than once per week. In multivariable analysis, reporting unplanned CAI was associated with lower educational level, identifying as homosexual/gay as compared to bisexual, being in a monogamous relationship, having a higher self-perceived risk of HIV acquisition, higher income, engaging in CAI more than five times in the last 3 months, and not having visited a healthcare provider in the previous year. Frequent CAI (>1x/week) was associated with being younger, identifying as homosexual/gay as compared to bisexual, being in a monogamous relationship, and having a higher self-perceived risk of HIV. Having had only planned sex over the last 3 months was associated with a preference for event-based PrEP, while having frequent or unplanned CAI was associated with a preference for daily or time-driven PrEP regimens, respectively. These findings suggest that preferences for different PrEP regimens are associated with the sexual frequency and planning behaviors of potential users.

Cocaine Use May Be Associated With Increased Depression In Persons Infected With HIV
Hammond ER, Lai S, Wright CM, Treisman GJ. AIDS Behav. 2015.
HIV infection, depression, and cocaine use are independently associated with increased inflammatory signal production. There is increasing evidence about the role of inflammation in depression. In HIV disease, cocaine use may increase disease progression as well as alter T cell functioning resulting in cytokine activation and thereby increasing susceptibility to depression. The authors examined the association between cocaine use and depression among 447 African American persons infected with HIV who were frequent cocaine users or non-users, enrolled in an observational study in Baltimore, Maryland, between August 2003 and December 2012. The overall prevalence of depression was 40.9 % (183 of 447) participants. Among persons who were depressed, the prevalence of cocaine use was 81.4 % (149 of 183), compared to 69.3 % among persons who were not depressed (183 of 264), P = 0.004. Cocaine use was associated with nearly twofold increased odds of depression, unadjusted odds ratio (OR) 1.94, (95 % CI 1.23, 3.06); P = 0.004, compared to never using cocaine, and OR 1.02, (95 % CI 1.10, 1.05); P = 0.04 in adjusted analysis. A dose-response relationship between increasing duration of cocaine use and depression was observed. Frequency and duration of cocaine use may be associated with depression. The authors speculate that depression among cocaine users with HIV may involve an inflammatory component that needs further examination.

Prevalence Of Sexually Transmitted Infections Including HIV In Street-connected Adolescents In Western Kenya Winston SE, Chirchir AK, Muthoni LN, Ayuku D, Koech J, Nyandiko W, Carter EJ, Braitstein P. Sex Transm Infect. 2015; 91(5): 353-359.
The objectives of this study were to characterise the sexual health of street-connected adolescents in Eldoret, Kenya, analyse gender disparity of risks, estimate the prevalence of sexually transmitted infections (STIs), and identify factors associated with STIs.A cross-sectional study of street-

connected adolescents ages 12-21 years was conducted in Eldoret, Kenya. Participants were interviewed and screened for Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis, herpes simplex virus-2, syphilis and HIV. Descriptive statistics and logistic regression were used to identify factors associated with having any STI.Of the 200 participants, 81 (41%) were female. 70.4% of females and 60.5% of males reported sexual activity. Of those that participated in at least one STI test, 28% (55/194) had ≥1 positive test, including 56% of females; 14% (28/194) had >1 positive test. Twelve females and zero males (6% overall, 14.8% of females) were HIV positive. Among females, those with HIV infection more frequently reported transactional sex (66.7% vs. 26.1%, p=0.01), drug use (91.7% vs. 56.5%, p=0.02), and reported a prior STI (50.0% vs. 14.7%, p<0.01). Having an adult caregiver was less likely among those with HIV infection (33.3% vs. 71.0%, p=0.04). Transactional sex (AOR 3.02, 95% CI (1.05 to 8.73)), a previous STI (AOR 3.46 95% CI (1.05 to 11.46)) and ≥2 sexual partners (AOR 5.62 95% (1.67 to 18.87)) were associated with having any STI.Street-connected adolescents in Eldoret, Kenya are engaged in high-risk sexual behaviours and females in particular have a substantial burden of STIs and HIV. There is a need for STI interventions targeted to street-connected youth.

Methamphetamine Induces Trace Amine-associated Receptor 1 (TAAR1) Expression In Human T Lymphocytes: Role In Immunomodulation Sriram U, Cenna JM, Haldar B, Fernandes NC, Razmpour R, Fan S, Ramirez SH, Potula R. J Leukoc Biol. 2015.
The novel transmembrane G protein-coupled receptor, trace amine-associated receptor 1 (TAAR1), represents a potential, direct target for drugs of abuse and monoaminergic compounds, including amphetamines. For the first time, the authors' studies have illustrated that there is an induction of TAAR1 mRNA expression in resting T lymphocytes in response to methamphetamine. Methamphetamine treatment for 6 h significantly increased TAAR1 mRNA expression ($P < 0.001$) and protein expression ($P < 0.01$) at 24 h. With the use of TAAR1 gene silencing, the authors demonstrate that methamphetamine-induced cAMP, a classic response to methamphetamine stimulation, is regulated via TAAR1. They also show by TAAR1 knockdown that the down-regulation of IL-2 in T cells by methamphetamine, which they reported earlier, is indeed regulated by TAAR1. These results also show the presence of TAAR1 in human lymph nodes from HIV-1-infected patients, with or without a history of methamphetamine abuse. TAAR1 expression on lymphocytes was largely in the paracortical lymphoid area of the lymph nodes with enhanced expression in lymph nodes of HIV-1-infected methamphetamine abusers rather than infected-only subjects. In vitro analysis of HIV-1 infection of human PBMCs revealed increased TAAR1 expression in the presence of methamphetamine. In summary, the ability of methamphetamine to activate trace TAAR1 in vitro and to regulate important T cell functions, such as cAMP activation and IL-2 production; the expression of TAAR1 in T lymphocytes in peripheral lymphoid organs, such as lymph nodes; and our in vitro HIV-1 infection model in PBMCs suggests that TAAR1 may play an important role in methamphetamine -mediated immune-modulatory responses.

Pain and Mortality Risk In A Cohort Of HIV-Infected Persons With Alcohol Use Disorders Tsui JI, Cheng DM, Quinn E, Bridden C, Merlin JS, Saitz R, Samet JH. AIDS Behav. 2015.
Pain has been associated with increased risk for mortality in some studies. The authors analyzed data from a cohort study [HIV-longitudinal interrelationships of viruses and ethanol (HIV-LIVE)] of HIV-infected persons with alcohol use disorders enrolled 2001-2003 to explore whether reporting moderate or greater pain interference was associated with mortality. The main independent variable was pain that at least moderately interfered with work based on a single question from the SF-12. Primary analyses dichotomized at "moderately" or above. Cox

proportional hazards models assessed the association between pain interference and death adjusting for demographics, substance use, CD4 count, HIV viral load and co-morbidities. Although significant in unadjusted models (HR = 1.58 (95 % CI 1.03-2.41; p value = 0.04)), after adjusting for confounders, ≥moderate pain interference was not associated with an increased risk of death [aHR = 1.30 (95 % CI 0.81-2.11, p value = 0.28)]. Among HIV-infected persons with alcohol use disorders, we did not detect a statistically significant independent association between pain interference and risk of death after adjustment for potential confounders.

Differences In Attitudes About HIV Pre-Exposure Prophylaxis Use Among Stimulant Versus Alcohol Using Men Who Have Sex With Men Oldenburg CE, Mitty JA, Biello KB, Closson EF, Safren SA, Mayer KH, Mimiaga MJ. AIDS Behav. 2015.
Alcohol and stimulant use are independently associated with increased HIV acquisition among men who have sex with men (MSM). The authors assessed differences in acceptability and perceived barriers to uptake of pre-exposure prophylaxis (PrEP) among stimulant and alcohol-using MSM in Boston. From September 2012-2013, a quantitative assessment was conducted with 254 MSM respondents who reported recent condomless sex in the context of concurrent stimulant (crack/cocaine and crystal methamphetamine; n = 132) or alcohol use (n = 122). Thirteen (5.1%) reported previous PrEP use. In multivariable models, stimulant users were more likely to be concerned that substance use would affect PrEP adherence (aRR = 2.79, 95% CI 1.63-4.77), and were less concerned about HIV stigma as a barrier to PrEP uptake (aRR = 0.52, 95% CI 0.30-0.90) compared to alcohol users. Barriers to PrEP uptake and adherence differ by type of substance used. Different strategies may be required for PrEP implementation among MSM who use stimulants and alcohol.

Underascertainment Of Acute Hepatitis C Virus Infections In the U.S. Surveillance System: A Case Series and Chart Review Onofrey S, Aneja J, Haney GA, Nagami EH, DeMaria Jr, A, Lauer GM, Hills-Evans K, Barton K, Kulaga S, Bowen MJ, Cocoros N, McGovern BH, Church DR, Kim AY. Ann Intern Med. 2015; 163(4): 254-261.
In 2010, the incidence of hepatitis C virus (HCV) infection in the United States was estimated to be 17 000 cases annually, based on 850 acute HCV cases reported to the Centers for Disease Control and Prevention by local public health authorities. Absence of symptomatic disease and lack of a specific laboratory test for acute infection complicates diagnosis and surveillance. To validate estimates of the incidence of acute HCV infection by determining the reporting rate of clinical diagnoses of acute infection to the Massachusetts Department of Public Health (MDPH) and Centers for Disease Control and Prevention. Case series and chart review. Two hospitals and the state correctional health care system in Massachusetts.183 patients clinically diagnosed with acute HCV infection from 2001 to 2011 and participating in a research study. Rate of electronic case reporting of acute HCV infection to the MDPH and rate of subsequent confirmation according to national case definitions.149 of 183 (81.4%) clinical cases of acute HCV infection were reported to the MDPH for surveillance classification. The MDPH investigated 43 of these reports as potential acute cases of HCV infection based on their surveillance requirements; ultimately, only 1 met the national case definition and was counted in nationwide statistics published by the Centers for Disease Control and Prevention. Discordance in clinical and surveillance classification was often related to missing clinical or laboratory data at the MDPH as well as restrictive definitions, including requirements for negative hepatitis A and B laboratory results. Findings may not apply to other jurisdictions because of differences in resources for surveillance. Clinical diagnoses of acute HCV infection were grossly underascertained by formal surveillance reporting. Incomplete clinician

reporting, problematic case definitions, limitations of diagnostic testing, and imperfect data capture remain major limitations to accurate case ascertainment despite automated electronic laboratory reporting. These findings may have implications for national estimates of the incidence of HCV infection.

Therapeutical Neurotargeting Via Magnetic Nanocarrier: Implications To Opiate-Induced Neuropathogenesis and NeuroAIDS Sagar V, Pilakka-Kanthikeel S, Atluri VSR, Ding H, Arias AY, Jayant RD, Kaushik A, Nair M. J Biomed Nanotechnol. 2015; 11(10): 1722-1733.
Magnetite (Fe3O4) is the most commonly and extensively explored magnetic nanoparticles (MNPs) for drug-targeting and imaging in the field of biomedicine. Nevertheless, its potential application as safe and effective drug-carrier for CNS (Central Nervous System) anomalies is very limited. Previous studies have shown an entangled epidemic of opioid use and HIV infection and increased neuropathogenesis. Opiate such as morphine, heroine, etc. are used frequently as recreational drugs. Existing treatments to alleviate the action of opioid are less effective at CNS level due to impermeability of therapeutic molecules across brain barriers. Thus, development of an advanced nanomedicine based approach may pave the way for better treatment strategies. The authors herein report magnetic nanoformulation of a highly selective and potent morphine antagonist, CTOP (D-Pen-Cys-Tyr-DTrp-Orn-Thr-Pen-Thr-NH2), which is impenetrable to the brain. MNPs, synthesized in size range from 25 to 40 nm, were characterized by Transmission electron microscopy and assembly of MNPs-CTOP nanoformulations were confirmed by FTIR spectroscopy and fluorescent detection. Flow-cytometry analysis showed that biological efficacy of this nanoformulation in prevention of morphine induced apoptosis in peripheral blood mononuclear cells remains equivalent to that of free CTOP. Similarly, confocal microscopy reveals comparable efficacy of free and MNPs bound CTOP in protecting modulation of neuronal dendrite and spine morphology during morphine exposure and morphine-treated HIV infection. Further, typical transmigration assay showed increased translocation of MNPs across in vitro blood-brain barrier upon exposure of external magnetic force where barrier integrity remains unaltered. Thus, the developed nanoformulation could be effective in targeting brain by application of external magnetic force to treat morphine addiction in HIV patients.

Acute Hepatitis C Virus Infection Induces Consistent Changes In Circulating MicroRNAs That Are Associated With Nonlytic Hepatocyte Release El-Diwany R, Wasilewski LN, Witwer KW, Bailey JR, Page K, Ray SC, Cox AL, Thomas DL, Balagopal A. J Virol. 2015; 89(18): 9454-9464.
Plasma microRNAs (miRNAs) change in abundance in response to disease and have been associated with liver fibrosis severity in chronic hepatitis C virus (HCV) infection. However, the early dynamics of miRNA release during acute HCV infection are poorly understood. In addition, circulating miRNA signatures have been difficult to reproduce among separate populations. The authors studied plasma miRNA abundance during acute HCV infection to identify an miRNA signature of early infection. They measured 754 plasma miRNAs by quantitative PCR array in a discovery cohort of 22 individuals before and during acute HCV infection and after spontaneous resolution (n = 11) or persistence (n = 11) to identify a plasma miRNA signature. The discovery cohort derived from the Baltimore Before and After Acute Study of Hepatitis. During acute HCV infection, increases in miR-122 ($P < 0.01$) and miR-885-5p ($P_{corrected} < 0.05$) and a decrease in miR-494 ($P_{corrected} < 0.05$) were observed at the earliest time points after virus detection. Changes in miR-122 and miR-885-5p were sustained in persistent ($P < 0.001$) but not resolved HCV infection. The circulating miRNA signature of acute HCV infection was confirmed in a separate

validation cohort that was derived from the San Francisco-based You Find Out (UFO) Study (n = 28). As further confirmation, cellular changes of signature miRNAs were examined in a tissue culture model of HCV in hepatoma cells: HCV infection induced extracellular release of miR-122 and miR-885-5p despite unperturbed intracellular levels. In contrast, miR-494 accumulated intracellularly ($P < 0.05$). Collectively, these data are inconsistent with necrolytic release of hepatocyte miRNAs into the plasma during acute HCV infection of humans. MicroRNAs are small noncoding RNA molecules that emerging research shows can transmit regulatory signals between cells in health and disease. HCV infects 2% of humans worldwide, and chronic HCV infection is a major cause of severe liver disease. The authors profiled plasma miRNAs in injection drug users before, during, and (in the people with resolution) after HCV infection. They discovered miRNA signatures of acute and persistent viremia and confirmed these findings two ways: (i) in a separate cohort of people with newly acquired HCV infection and (ii) in an HCV cell culture system. These results demonstrate that acute HCV infection induces early changes in the abundance of specific plasma miRNAs that may affect the host response to HCV infection.

Effectiveness Of Simeprevir Plus Sofosbuvir, With Or Without Ribavirin, In Real-World Patients With HCV Genotype 1 Infection Sulkowski MS, Vargas HE, Di Bisceglie AM, Kuo PA, Reddy KR, Lim JK, Morelli G, Darling JM, Feld JJ, Brown RS, Frazier LM, Stewart TG, Fried MW, Nelson DR, Jacobson IM, HCV-TARGET Study Group. Gastroenterology. 2015.
The interferon-free regimen of simeprevir plus sofosbuvir was recommended by professional guidelines for certain patients with hepatitis C virus (HCV) genotype 1 infection based on the findings of a phase 2 trial. The authors aimed to evaluate the safety and efficacy of this regimen in clinical practice settings in North America. They collected demographic, clinical, and virologic data, as well as reports of adverse outcomes, from sequential participants in HCV-TARGET-a prospective, observational cohort study of patients undergoing HCV treatment in routine clinical care settings. From January through October 2014, 836 patients with HCV genotype 1 infection began 12 weeks of treatment with simeprevir plus sofosbuvir (treatment duration of up to 16 weeks); 169 of these patients received ribavirin. Most patients were male (61%), Caucasian (76%), or black (13%); 59% had cirrhosis. Most had failed prior treatment with peginterferon and ribavirin without (46%) or with telaprevir or boceprevir (12%). The primary outcome was sustained virologic response (SVR), defined as level of HCV RNA below quantification at least 64 days after the end of treatment (beginning of week 12 after treatment-a 2 week window). Logistic regression models with inverse probability weights were constructed to adjust for baseline covariates and potential selection bias. The overall rate of SVR rate was 84% (675/802 patients, 95% CI: 81-87%). Model-adjusted estimates indicate patients with cirrhosis, prior decompensation, and previous protease inhibitor treatments were less likely to achieve an SVR. The addition of ribavirin had no detectable effects on SVR. The most common adverse events were fatigue, headache, nausea, rash, and insomnia. Serious adverse events and treatment discontinuation occurred in only 5% and 3% of participants, respectively. In a large, prospective observational cohort study, a 12 week regimen of simeprevir plus sofosbuvir was associated with high rates of SVR and infrequent treatment discontinuation. ClinicalTrials.gov: NCT01474811.

Methadone Pharmacogenetics: CYP2B6 Polymorphisms Determine Plasma Concentrations, Clearance,and Metabolism Kharasch ED, Regina KJ, Blood J, Friedel C. Anesthesiology. 2015; 123(5): 1142-1153.
Interindividual variability in methadone disposition remains unexplained, and methadone accidental overdose in pain therapy is a significant public health problem. Cytochrome P4502B6 (CYP2B6) is

the principle determinant of clinical methadone elimination. The CYP2B6 gene is highly polymorphic, with several variant alleles. CYP2B6.6, the protein encoded by the CYP2B6*6 polymorphism, deficiently catalyzes methadone metabolism in vitro. This investigation determined the influence of CYP2B6*6, and other allelic variants encountered, on methadone concentrations, clearance, and metabolism. Healthy volunteers in genotype cohorts CYP2B6*1/*1 (n = 21), CYP2B6*1/*6 (n = 20), and CYP2B6*6/*6 (n = 17), and also CYP2B6*1/*4 (n = 1), CYP2B6*4/*6 (n = 3), and CYP2B6*5/*5 (n = 2) subjects, received single doses of IV and oral methadone. Plasma and urine methadone and metabolite concentrations were determined by tandem mass spectrometry. Average S-methadone apparent oral clearance was 35 and 45% lower in CYP2B6*1/*6 and CYP2B6*6/*6 genotypes, respectively, compared with CYP2B6*1/*1. R-methadone apparent oral clearance was 25 and 35% lower in CYP2B6*1/*6 and CYP2B6*6/*6 genotypes, respectively, compared with CYP2B6*1/*1. R- and S-methadone apparent oral clearance was threefold and fourfold greater in CYP2B6*4 carriers. IV and oral R- and S-methadone metabolism was significantly lower in CYP2B6*6 carriers compared with that of CYP2B6*1 homozygotes and greater in CYP2B6*4 carriers. Methadone metabolism and clearance were lower in African Americans in part because of the CYP2B6*6 genetic polymorphism.CYP2B6 polymorphisms influence methadone plasma concentrations, because of altered methadone metabolism and thus clearance. Genetic influence is greater for oral than IV methadone and S- than R-methadone. CYP2B6 pharmacogenetics explains, in part, interindividual variability in methadone elimination. CYP2B6 genetic effects on methadone metabolism and clearance may identify subjects at risk for methadone toxicity and drug interactions.

Metabolic Syndrome Among Marijuana Users In The United States: An Analysis Of National Health and Nutrition Examination Survey Data Vidot DC, Prado G, Hlaing WWM, Florez HJ, Arheart KL, Messiah SE. Am J Med. 2015.
Research on the health effects of marijuana use in light of its increased medical use and the current obesity epidemic is needed. The authors' objective was to explore the relationship between marijuana use and metabolic syndrome across stages of adulthood. An analysis of 20- to 59-year-olds (n = 8478) who completed the 2005-2010 National Health and Nutrition Examination Surveys was conducted. Marijuana use was categorized as: never used, past use (used previously but not within the last 30 days), and current use (≥1 day in the last 30 days). Metabolic syndrome was defined as ≥3 of the following: elevated fasting glucose, high triglycerides, low high-density-lipoprotein cholesterol, elevated systolic/diastolic blood pressure, and increased waist circumference. An age-stratified analysis was conducted to examine the relationship between marijuana use and metabolic syndrome among emerging adults (20-30 years), adults (31-44 years), and middle-aged adults (45-59 years). Fourteen percent (13.8%) of current marijuana users and 17.5% of past marijuana users presented with metabolic syndrome, compared with 19.5% of never users (P = .0003 and P = .03, respectively). Current marijuana users had lower odds of presenting with metabolic syndrome than never users (adjusted odds ratio [AOR] 0.69; 95% confidence interval [CI], 0.47-1.00; P = .05). Among emerging adults, current marijuana users were 54% less likely than never users to present with metabolic syndrome. Current (AOR 0.49; 95% CI, 0.25-0.97) and past (AOR 0.61; 95% CI, 0.40-0.91) middle-aged adult marijuana users were less likely to have metabolic syndrome than never users. Current marijuana use is associated with lower odds of metabolic syndrome across emerging and middle-aged US adults. Future studies should examine the biological pathways of this relationship.

Factors Associated With Iohexol-based Glomerular Filtration Rate Slope Over 36 Months In HIV-negative and HIV-positive Individuals Lucas GM, Atta MG, Zook K, McFall AM, Mehta SH, Fine DM, Stein JH, Schwartz GJ. AIDS. 2015.
Monitoring kidney function is important in HIV-positive persons, but creatinine-based estimates of glomerular filtration rate (GFR) have limitations. There are little to no data available assessing GFR trends in HIV-positive persons using a gold-standard measure of GFR. The authors measured GFR based on iohexol plasma disappearance (iGFR) annually for 3 years in nondiabetic, HIV-negative and HIV-positive volunteers with normal estimated kidney function. They used mixed linear models to evaluate factors associated with baseline iGFR and iGFR slope. Hundred HIV-negative and 191 HIV-positive, predominantly black individuals (median age 49 years) participated in the study and completed a total of 960 iGFR assessments over a median of 36 months. Despite similar estimated GFR at baseline, average iGFR values were lower in HIV-positive compared with HIV-negative participants (103.2 vs. 110.8, ml/min/1.73 m, P=0.004). However, subsequent iGFR slope was not significantly different in HIV-positive and HIV-negative patients. In the HIV-positive group, the presence of carotid plaque and hepatitis C virus coinfection were associated with significantly lower iGFR values at baseline. A nonsuppressed HIV RNA level at baseline was associated with a significantly more rapid iGFR decline compared with individuals with HIV RNA less than 400 copies/ml (-4.69 vs. -1.31 ml/min/1.73 m per year, P=0.005). Other factors significantly associated with iGFR slope included albuminuria and glycosylated hemoglobin. Compared with HIV-negative persons, HIV-positive participants had significantly lower baseline iGFR, despite similar estimated GFR in the two groups. Nonsuppressed HIV RNA at baseline was associated with a more rapid iGFR decline over 3 years.

Investigation Of Neuropathogenesis In HIV-1 Clade B and C Infection Associated With IL-33 and ST2 Regulation Yndart A, Kaushik A, Agudelo M, Raymond A, Atluri VS, Saxena SK, Nair M. ACS Chem Neurosci. 2015; 6(9): 1600-1612.
In the present research, for the first time, the authors demonstrate that neuropathogenesis in HIV-1 clade B and C infection is associated with IL-33 and ST2 dysregulation, that is, implication toward neuropathogenesis. It is known that neuropathogenesis of HIV infected individuals is clade dependent. Proinflammatory cytokines and related receptors play a significant role in the complex regulatory mechanisms of neuropathogenesis in HIV-1 infection. Among them, IL-33 is an inflammatory cytokine expressed in the central nervous system (CNS) and activates microglia cells and may affect neuroimmune inflammatory processes involved in HIV neuropathogenesis. Beside this, IL-33 receptor (ST2) plays a role in neuroinflammatory processes through the modulation of the biological action of IL-33. quantitative real time PCR (qRT-PCR), ELISA, Western blot (WB), and flow cytometry experiments were performed to elucidate the role of IL-33/ST2 in HIV neuropathogenesis in CNS cells. Apoptosis and mechanisms of IL-33 in neuronal cells were studied using caspase-3 assay and RT-PCR. Results of these studies suggest that the infection in CNS cells with HIV-1 clade B resulted in higher levels of IL-33/ST2L expression compared to HIV-1 clade C infection. Furthermore, higher concentrations of IL-33 were associated with a decrease in myocyte enhancer factor 2C (MEF2C) expression, a transcription factor that regulates synaptic function, and an increase in apoptosis, NOD2, and SLC11A1 in clade B infection. This led to neuroinflammation which dysregulates synaptic function and apoptosis. These parameters are common in neuroAIDS provoked by HIV infection.

Relationship Between Current Substance Use and Unhealthy Weight Loss Practices Among Adolescents Vidot DC, Messiah SE, Prado G, Hlaing WWM. Matern Child Health J. 2015.
The objective of this study was to determine the relationship between current substance use and unhealthy weight loss practices (UWLP) among 12-to-18 year olds. Participants were 12-to-18 year olds who completed the 2013 Youth Risk Behavior Survey in Florida (N = 5620). Current alcohol, tobacco, and marijuana use was self-reported based on last 30-day use. UWLP was defined based on self-report of at least one of three methods to lose weight in last 30-days: (1) ≥24 h of fasting, (2) diet pill use, and (3) laxative use/purging. The reference group included those with no reported UWLP. Logistic regression models adjusted for age, gender, race/ethnicity, academic performance, age-sex-specific body mass index percentiles, and perceived weight status were fitted to assess relationships between UWLP and current substance use. About 15 and 41 % of adolescents reported ≥1 UWLP and use of ≥1 substance in the last 30-days, respectively. Over half (60.1 %) of adolescents who reported substance use engaged in UWLP ($p < 0.0001$). The prevalence of current alcohol use (50.6 %) was the highest among those who reported UWLP, followed by marijuana (31.9 %), tobacco (19.7 %), and cocaine (10.5 %) use. Adolescents who reported current tobacco [adjusted odds ratio (AOR) 2.7, 95 % confidence interval (CI) 2.1-3.6], alcohol (AOR 2.2, 95 % CI 1.9-2.6), or marijuana (AOR 2.1, 95 % CI 1.7-2.5) use had significantly higher odds of UWLP compared to their non-user counterparts. This cross-sectional study shows that substance use and UWLP behaviors are likely to co-exist in adolescents. Further studies are necessary to determine the temporal relationship between substance use and UWLP. It is recommended that intervention programs for youth consider targeting these multiple health risk behaviors.

SERVICES RESEARCH

States' Implementation of the Affordable Care Act and the Supply of Physicians Waivered to Prescribe Buprenorphine for Opioid Dependence Knudsen HK, Lofwall MR, Havens JR, Walsh SL. Drug and Alcohol Dependence. Accepted Manuscript, downloaded October 22, 2015.
Although the Affordable Care Act (ACA) is anticipated to affect substance use disorder (SUD) treatment, its impact on the supply of physicians waivered to treat opioid dependence with buprenorphine has not been considered. This study examined whether states more supportive of ACA, meaning those that had opted to expand Medicaid and establish a state based health insurance exchange, experienced greater growth in physician supply than less supportive states. Buprenorphine physician supply, including total physician supply, supply of 30-patient physicians, and supply of 100-patient physicians per 100,000 state residents, was measured from June 2013 to May 2015. State characteristics were drawn from multiple secondary sources, with states categorized as ACA-supportive, ACA-hybrid (where states either expanded Medicaid or established a state-based exchange), or ACA-resistant (where states took neither action). Mixed effects regression was used to estimate state-level growth curves to test whether rates of growth varied by states' approaches to implementing ACA. The supply of waivered physicians grew significantly over the two-year period. Rates of growth were significantly lower in ACA-hybrid and ACA-resistant states relative to growth in ACA supportive states. Average buprenorphine physician supply at baseline varied by region, the percentage of residents covered by Medicaid, and the supply of specialty SUD treatment programs. This study found a positive impact of the ACA on growth in the supply of buprenorphine-waivered physicians in US states. Future research should address whether the ACA affects the number of patients receiving buprenorphine, Medicaid spending, and the quality of treatment services delivered.

Messaging to Increase Public Support for Naloxone Distribution Policies in the United States: Results from a Randomized Survey Experiment Bachhuber MA, McGinty EE,; Kennedy-Hendricks A, Niederdeppe J, Barry CL. PLOS One. 2015; July 1.
Barriers to public support for naloxone distribution include lack of knowledge, concerns about potential unintended consequences, and lack of sympathy for people at risk of overdose. A randomized survey experiment was conducted with a nationally-representative web-based survey research panel (GfK KnowledgePanel). Participants were randomly assigned to read different messages alone or in combination: 1) factual information about naloxone; 2) pre-emptive refutation of potential concerns about naloxone distribution; and 3) a sympathetic narrative about a mother whose daughter died of an opioid overdose. Participants were then asked if they support or oppose policies related to naloxone distribution. For each policy item, logistic regression models were used to test the effect of each message exposure compared with the no-exposure control group. The final sample consisted of 1,598 participants (completion rate: 72.6%). Factual information and the sympathetic narrative alone each led to higher support for training first responders to use naloxone, providing naloxone to friends and family members of people using opioids, and passing laws to protect people who administer naloxone. Participants receiving the combination of the sympathetic narrative and factual information, compared to factual information alone, were more likely to support all policies: providing naloxone to friends and family members (OR: 2.0 [95% CI: 1.4 to 2.9]), training first responders to use naloxone (OR: 2.0 [95% CI: 1.2 to 3.4]), passing laws to protect people if they administer naloxone (OR: 1.5 [95% CI: 1.04 to 2.2]), and passing laws to protect people if they call for medical help for an overdose (OR: 1.7 [95% CI: 1.2 to 2.5]).All messages increased public support, but combining factual information and the sympathetic narrative

was most effective. Public support for naloxone distribution can be improved through education and sympathetic portrayals of the population who stands to benefit from these policies.

Racialized Risk Environments In A Large Sample Of People Who Inject Drugs In The United States Cooper HLF, Linton S, Kelley ME, Ross Z, Wolfe ME, Chen Y-T, Zlotorzynsk M, Hunter-Jones J, Friedman SR, Des Jarlais D, Semaan S, Tempalski B, DiNenno E, Broz D, Wejnert C, Paz-Bailey G, National HIV Behavioral Surveillance Study Group. Int J Drug Policy. 2015.
Substantial racial/ethnic disparities exist in HIV infection among people who inject drugs (PWID) in many countries. To strengthen efforts to understand the causes of disparities in HIV-related outcomes and eliminate them, the authors expand the "Risk Environment Model" to encompass the construct "racialized risk environments," and investigate whether PWID risk environments in the United States are racialized. Specifically, we investigate whether black and Latino PWID are more likely than white PWID to live in places that create vulnerability to adverse HIV-related outcomes. As part of the Centers for Disease Control and Prevention's National HIV Behavioral Surveillance, 9170 PWID were sampled from 19 metropolitan statistical areas (MSAs) in 2009. Self-reported data were used to ascertain PWID race/ethnicity. Using Census data and other administrative sources, the authors characterized features of PWID risk environments at four geographic scales (i.e., ZIP codes, counties, MSAs, and states). Means for each feature of the risk environment were computed for each racial/ethnic group of PWID, and were compared across racial/ethnic groups.
Almost universally across measures, black PWID were more likely than white PWID to live in environments associated with vulnerability to adverse HIV-related outcomes. Compared to white PWID, black PWID lived in ZIP codes with higher poverty rates and worse spatial access to substance abuse treatment and in counties with higher violent crime rates. Black PWID were less likely to live in states with laws facilitating sterile syringe access (e.g., laws permitting over-the-counter syringe sales). Latino/white differences in risk environments emerged at the MSA level (e.g., Latino PWID lived in MSAs with higher drug-related arrest rates).PWID risk environments in the US are racialized. Future research should explore the implications of this racialization for racial/ethnic disparities in HIV-related outcomes, using appropriate methods.

"Sub Is A Weird Drug:" A Web-based Study Of Lay Attitudes About Use Of Buprenorphine To Self-treat Opioid Withdrawal Symptoms Daniulaityte R, Carlson R, Brigham G, Cameron D, Sheth A. Am J Addict. 2015; 24(5): 403-409.
Illicit use of buprenorphine has increased in the U.S., but our understanding of its use remains limited. This study aims to explore Web-forum discussions about the use of buprenorphine to self-treat opioid withdrawal symptoms. PREDOSE, a novel Semantic Web platform, was used to extract relevant posts from a Web-forum that allows free discussions on illicit drugs. First, the authors extract information about the total number of buprenorphine-related posts per year between 2005 and 2013. Second, PREDOSE was used to identify all posts that potentially contained discussions about buprenorphine and opioid withdrawal. A total number of 1,217 posts that contained these terms were extracted and entered into NVivo data base. A random sample of 404 (33%) posts was selected and content analyzed. Buprenorphine-related posts increased over time, peaking in 2011. The posts were about equally divided between those that expressed positive and negative views about the effectiveness of buprenorphine in relieving withdrawal symptoms. Web-forum participants emphasized that buprenorphine's effectiveness may become compromised because of the "size of a person habit," and/or when users repeatedly switch back and forth between buprenorphine and other illicit opioids. Most posts reported use of significantly lower amounts of buprenorphine (≤2 mg) than doses used in standard treatment. Concomitant use of other

psychoactive substances was also commonly reported, which may present significant health risks. These findings highlight the usefulness of Web-based data in drug abuse research and add new information about lay beliefs about buprenorphine that may help inform prevention and policy measures.

High Uptake Of Naloxone-Based Overdose Prevention Training Among Previously Incarcerated Syringe-Exchange Program Participants Barocas JA, Baker L, Hull SJ, Stokes S, Westergaard RP. Drug Alcohol Depend. 2015; 154: 283-286.
Incarceration is common among people who inject drugs. Prior research has shown that incarceration is a marker of elevated risk for opioid overdose, suggesting that the criminal justice system may be an important, under-utilized venue for implementing overdose prevention strategies. To better understand the feasibility and acceptability of such strategies, the authors evaluated the utilization of naloxone-based overdose prevention training among people who inject drugs with and without a history of incarceration. They surveyed clients who utilize a multi-site syringe exchange program (SEP) in 2 cities in the Midwestern United States. Participants completed an 88-item, computerized survey assessing history of incarceration, consequences associated with injection, injecting practices, and uptake of harm reduction strategies. Among 543 respondents who injected drugs in the prior 30 days, 243 (43%) reported prior incarceration. Comparing those with and without a history of incarceration, there were no significant differences with respect to age, gender, or race. Those who observed an overdose, experienced overdose, and received training to administer or have administered naloxone were more likely to report incarceration. Overall, 69% of previously incarcerated clients had been trained to administer naloxone. People who inject drugs with a history of incarceration appear to have a higher risk of opioid overdose than those never incarcerated, and are more willing to utilize naloxone as an overdose prevention strategy. Naloxone training and distribution is an important component of comprehensive prevention services for persons with opioid use disorders. Expansion of services for persons leaving correctional facilities should be considered.

Federal Parity Law Associated with Increased Probability of Using Out-of-Network Substance Use Disorder Treatment Services McGinty EE, Busch SH, Stuart EA, Huskamp HA, Gibson TB, Goldman HH, Barry C. Health Affairs. 2015; 34(8):1331-1339.
The Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act of 2008 requires commercial insurers providing group coverage for substance use disorder services to offer benefits for those services at a level equal to those for medical or surgical benefits. Unlike previous parity policies instituted for federal employees and in individual states, the law extends parity to out-of-network services. The authors conducted an interrupted time-series analysis using insurance claims from large self-insured employers to evaluate whether federal parity was associated with changes in out-of-network treatment for 525,620 users of substance use disorder services. Federal parity was associated with an increased probability of using out-of-network services, an increased average number of out-of-network outpatient visits, and increased average total spending on out-of-network services among users of those services. The findings were broadly consistent with the contention of federal parity proponents that extending parity to out-of-network services would broaden access to substance use disorder care obtained outside of plan networks.

HIV Testing, Care, and Treatment Among Women Who Use Drugs From A Global Perspective: Progress and Challenges Metsch L, Philbin MM, Parish C, Shiu K, Frimpong JA, Giang Le M. J Acquir Immune Defic Syndr. 2015; 69 Suppl 2: S162-168.
The article reviews data on HIV testing, treatment, and care outcomes for women who use drugs in 5 countries across 5 continents. The authors chose countries in which the HIV epidemic has, either currently or historically, been fueled by injection and non-injection drug use and that have considerable variation in social structural and drug policies: Argentina, Vietnam, Australia, Ukraine, and the United States. There is a dearth of available HIV care continuum outcome data [i.e., testing, linkage, retention, antiretroviral therapy (ART) provision, viral suppression] among women drug users, particularly among non-injectors. Although some progress has been made in increasing HIV testing in this population, HIV-positive women drug users in 4 of the 5 countries have not fully benefitted from ART nor are they regularly engaged in HIV care. Issues such as the criminalization of drug users, HIV-specific criminal laws, and the lack of integration between substance use treatment and HIV primary care play a major role. Strategies that effectively address the pervasive factors that prevent women drug users from engaging in HIV care and benefitting from ART and other prevention services are critical. Future success in enhancing the HIV continuum for women drug users should consider structural and contextual level barriers and promote social, economic, and legal policies that overhaul the many years of discrimination and stigmatization faced by women drug users worldwide. Such efforts must emphasis the translation of policies into practice and approaches to implementation that can help HIV-infected women who use drugs engage at all points of the HIV care continuum.

Item Banks For Substance Use From The Patient-Reported Outcomes Measurement Information System (PROMIS(®)): Severity Of Use and Positive Appeal Of Use Pilkonis PA, Yu L, Dodds NE, Johnston KL, Lawrence SM, Hilton TF, Daley DC, Patkar AA, McCarty D. Drug Alcohol Depend. 2015.
Two item banks for substance use were developed as part of the Patient-Reported Outcomes Measurement Information System (PROMIS(®)): severity of substance use and positive appeal of substance use. Qualitative item analysis (including focus groups, cognitive interviewing, expert review, and item revision) reduced an initial pool of more than 5300 items for substance use to 119 items included in field testing. Items were written in a first-person, past-tense format, with 5 response options reflecting frequency or severity. Both 30-day and 3-month time frames were tested. The calibration sample of 1336 respondents included 875 individuals from the general population (ascertained through an internet panel) and 461 patients from addiction treatment centers participating in the National Drug Abuse Treatment Clinical Trials Network. Final banks of 37 and 18 items were calibrated for severity of substance use and positive appeal of substance use, respectively, using the two-parameter graded response model from item response theory (IRT). Initial calibrations were similar for the 30-day and 3-month time frames, and final calibrations used data combined across the time frames, making the items applicable with either interval. Seven-item static short forms were also developed from each item bank. Test information curves showed that the PROMIS item banks provided substantial information in a broad range of severity, making them suitable for treatment, observational, and epidemiological research in both clinical and community settings.

Childhood Maltreatment and Risk Of Suicide Attempt: A Nationally Representative Study
Hoertel N, Franco S, Wall MM, Oquendo MA, Wang S, Limosin F, Blanco C. J Clin Psychiatry. 2015; 76(7): 916-923.
Previous research suggests that various types of childhood maltreatment frequently co-occur and confer risk for attempting suicide. However, it is unknown whether the effect of childhood maltreatment on this risk occurs through diverse, specific mechanisms or through a generalized liability, independently of psychopathology. Although these competing explanations have different implications for intervention, they have never been evaluated empirically. Structural equation modeling was used to examine the effect of different types of childhood maltreatment (i.e., sexual abuse, physical and emotional abuse and neglect) on suicide attempt risk, and on age at first suicide attempt and repeated suicide attempts among attempters. Analyses controlled for demographic characteristics and DSM-IV Axis I and Axis II disorders. Data were drawn from a nationally representative survey of US adults, the 2004-2005 National Epidemiologic Survey on Alcohol and Related Conditions (N = 34,653). Childhood maltreatment was associated with an increased risk for attempting suicide and an earlier age at first suicide attempt among attempters, independently of psychopathology (P < .005). These associations operated mainly through the latent variable representing effects shared by the different types of childhood maltreatment, although sexual abuse had an additional, direct effect on the risk of suicide attempt. Childhood maltreatment types were not significantly associated with a history of multiple suicide attempts (all P values > .05).The association between childhood maltreatment and suicide attempt operates mainly through a single broad liability, suggesting that the mechanisms underlying this dimension should be considered as an important therapeutic target for suicide prevention.

Treatment Readiness, Attitudes Toward, and Experiences With Methadone and Buprenorphine Maintenance Therapy Among People Who Inject Drugs In Malaysia
Vijay A, Bazazi AR, Yee I, Kamarulzaman A, Altice FL. J Subst Abuse Treat. 2015; 54: 29-36.
Little is known about attitudes toward and experiences with opioid maintenance therapy (OMT) among people who inject drugs in Malaysia, a country where people who inject drugs comprise 1.3% of the adult population. In 2010, 460 people who inject drugs in Greater Kuala Lumpur, Malaysia were surveyed to evaluate attitudes toward and experiences with OMT and treatment readiness. Attitudes towards OMT with both methadone and buprenorphine were assessed using an opinions scale. Multivariable linear regression was used to assess correlates of treatment readiness, measured with the 19-item Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES).All 460 participants used opioids and nearly all (99.1%) met criteria for opioid dependence. Few had had previous experience with methadone (9.3%) or buprenorphine (12.6%) maintenance therapy, yet many had used methadone (55.2%) or buprenorphine (51.7%) outside of treatment settings. Fifteen percent had injected buprenorphine in the past month, and of the few that were currently receiving buprenorphine maintenance therapy, almost all were injecting it. The majority of subjects exhibited a moderate level of treatment readiness and a preference for methadone over buprenorphine. Those with low treatment readiness scores were more likely to have previous experience with compulsory drug detention centers ($p<0.01$), needle/syringe exchange programs ($p<0.005$), or be of Indian ethnicity ($p<0.001$). Past use of methadone ($p<0.01$), older age ($p<0.001$), higher stress symptom severity ($p<0.001$), and sharing of needles or syringes ($p<0.05$) were associated with higher treatment readiness scores. There are suboptimal levels of OMT experience among people who inject drugs that may be improved by addressing factors that influence patient attitudes. Those individuals with moderate treatment readiness may be targeted by

brief motivational and cognitive interventions in primary care, prisons or OMT clinics aimed at improving entry into and retention in treatment.

Correlates Of Opioid Use In Adults With Self-Reported Drug Use Recruited From Public Safety-Net Primary Care Clinics Ries R, Krupski A, West II, Maynard C, Bumgardner K, Donovan D, Dunn C, Roy-Byrne P. J Addict Med. 2015; 9(5): 417-426.
The purpose of this study was to compare demographic, clinical, and survival characteristics of drug-using safety-net primary care patients who used or did not use opioids, and to examine treatment implications of our findings. The sample consisted of 868 adults who reported illicit drug use in the 90 days before study enrollment, 396 (45.6%) of whom were opioid users. Multiple measures indicated that, as a group, opioid users were less physically and psychiatrically healthy than drug users who did not endorse using opioids, and were heavy users of medical services (e.g., emergency departments, inpatient hospitals, and outpatient medical) at considerable public expense. After adjusting for age, they were 2.61 (confidence interval, 1.48-4.61) times more likely to die in the 1 to 5 years after study enrollment and more likely to die from accidental poisoning than non-opioid users. Subgroup analyses suggested patients using any non-prescribed opioids had more serious drug problems including more intravenous drug use and greater HIV risk than patients using opioids only as prescribed. Use of opioids adds a dimension of severity over and above illicit drug use as it presents in the primary care setting. Opioid users may benefit from psychiatric and addiction care integrated into their primary care setting, naloxone overdose prevention kits, and prevention efforts such as clean needle exchanges. Addiction or primary care providers are in a key position to facilitate change among such patients, especially the third or more opioid users having a goal of abstinence from drugs.

The Effects Of Opioid Substitution Treatment and Highly Active Antiretroviral Therapy On The Cause-Specific Risk Of Mortality Among HIV-Positive People Who Inject Drugs Nosyk B, Min JE, Evans E, Li L, Liu L, Lima VD, Wood E, Montaner JSG. Clin Infect Dis. 2015; 61(7): 1157-1165.
Prior studies indicated opioid substitution treatment (OST) reduces mortality risk and improves the odds of accessing highly active antiretroviral therapy (HAART); however, the relative effects of these treatments for human immunodeficiency virus (HIV)-positive people who inject drugs (PWID) are unclear. The authors determine the independent and joint effects of OST and HAART on mortality, by cause, within a population of HIV-positive PWID initiating HAART. Using a linked population-level database for British Columbia, Canada, they used time-to-event analytic methods, including competing risks models, proportional hazards models with time-varying covariates, and marginal structural models, to identify the independent and joint effects of OST and HAART on all-cause as well as drug- and HIV-related mortality, controlling for covariates. Among 1727 HIV-positive PWID, 493 (28.5%) died during a median 5.1 years (interquartile range, 2.1-9.1) of follow-up: 18.7% due to drug-related causes, 55.8% due to HIV-related causes, and 25.6% due to other causes. Standardized mortality ratios were 12.2 (95% confidence interval [CI], 9.8, 15.0) during OST and 30.0 (27.1, 33.1) during periods out of OST. Both OST (adjusted hazard, 0.34; 95% CI, .23, .49) and HAART (0.39 [0.31, 0.48]) decreased the hazard of all-cause mortality; however, individuals were at lowest risk of death when these medications were used jointly (0.16 [0.10, 0.26]). Both OST and HAART independently protected against HIV-related death, drug-related death and death due to other causes. While both OST and HAART are life-saving treatments, joint administration is urgently needed to protect against both drug- and HIV-related mortality.

Use Of Prescription Pain Medications Among Medical Cannabis Patients: Comparisons Of Pain Levels, Functioning, and Patterns Of Alcohol and Other Drug Use Perron BE, Bohnert K, Perone AK, Bonn-Miller MO, Ilgen M. J Stud Alcohol Drugs. 2015; 76(3): 406-413.
Management of chronic pain is one of the most common reasons given by individuals seeking medical cannabis. However, very little information exists about the concurrent use of cannabis and prescription pain medication (PPM). This study fills this gap in knowledge by systematically comparing medical cannabis users who use or do not use PPM, with an emphasis on understanding whether concurrent use of cannabis and PPM is associated with more serious forms of alcohol and other drug involvement. Data from this study were collected from a medical cannabis clinic in southwestern Michigan (N = 273). Systematic comparisons were made on measures of socio-demographics, reasons for substance use, pain, functioning, and perceptions of PPM and medical cannabis efficacy. PPM users tended to be older and reported higher levels of pain and lower levels of functioning. The overall sample exhibited higher lifetime and past-3-month rates of alcohol and other non-cannabis drug use than did the general population. Approximately 40% of subjects reported combining cannabis with alcohol, but no significant difference was observed between PPM users and nonusers. PPM users and nonusers did not exhibit any difference in either lifetime or past-3-month use of other drugs, including cocaine, sedatives, street opioids, and amphetamines. PPM users rated the efficacy of cannabis higher than PPM for pain management and indicated a strong desire to reduce PPM usage. Use of PPM among medical cannabis users was not identified as a correlate for more serious forms of alcohol and other drug involvement. However, longitudinal study designs are needed to better understand the trajectories of alcohol and other drug involvement over time among medical cannabis users.

The Impact Of Implementing A Test, Treat and Retain HIV Prevention Strategy In Atlanta Among Black Men Who Have Sex With Men With A History Of Incarceration: A Mathematical Model Lima VD, Graf I, Beckwith CG, Springer S, Altice FL, Coombs D, Kim B, Messina L, Montaner JSG, Spaulding A. PLoS One. 2015; 10(4): e0123482.
Annually, 10 million adults transition through prisons or jails in the United States (US) and the prevalence of HIV among entrants is three times higher than that for the country as a whole. The authors assessed the potential impact of increasing HIV Testing/Treatment/Retention (HIV-TTR) in the community and within the criminal justice system (CJS) facilities, coupled with sexual risk behavior change, focusing on black men-who-have-sex-with-men, 15-54 years, in Atlanta, USA. The authors modeled the effect of a HIV-TTR strategy on the estimated cumulative number of new (acquired) infections and mortality, and on the HIV prevalence at the end of ten years. They additionally assessed the effect of increasing condom use in all settings. In the Status Quo scenario, at the end of 10 years, the cumulative number of new infections in the community, jail and prison was, respectively, 9246, 77 and 154 cases; HIV prevalence was 10815, 69 and 152 cases, respectively; and the cumulative number of deaths was 2585, 18 and 34 cases, respectively. By increasing HIV-TTR coverage, the cumulative number of new infections could decrease by 15% in the community, 19% in jail, and 8% in prison; HIV prevalence could decrease by 8%, 9% and 7%, respectively; mortality could decrease by 20%, 39% and 18%, respectively. Based on the model results, the authors have shown that limited use and access to condoms have contributed to the HIV incidence and prevalence in all settings. Aggressive implementation of a CJS-focused HIV-TTR strategy has the potential to interrupt HIV transmission and reduce mortality, with benefit to the community at large. To maximize the impact of these interventions, retention in treatment, including during the period after jail and prison release, and increased condom use was vital for decreasing the burden of the HIV epidemic in all settings.

Burden Of Substance Use Disorders, Mental Illness, and Correlates Of Infectious Diseases Among Soon-to-be Released Prisoners In Azerbaijan Azbel L, Wickersham JA, Wegman MP, Polonsky M, Suleymanov M, Ismayilov R, Dvoryak S, Rotberga S, Altice FL. Drug Alcohol Depend. 2015; 151: 68-75.
Despite low HIV prevalence in the South Caucasus region, transmission is volatile. Little data are available from this region about addiction and infectious diseases among prisoners who transition back to communities. A nation-wide randomly sampled biobehavioral health survey was conducted in 13 non-specialty Azerbaijani prisons among soon-to-be-released prisoners. After informed consent, participants underwent standardized health assessment surveys and testing for HIV, hepatitis B and C, and syphilis. Of the 510 participants (mean age = 38.2 years), 11.4% were female, and 31.9% reported pre-incarceration drug injection, primarily of heroin. Prevalence of HCV (38.2%), HIV (3.7%), syphilis (3.7%), and HBV (2.7%) was high. Among the 19 HIV-infected inmates, 14 (73.7%) were aware of their HIV status, 12 (63.2%) were receiving antiretroviral therapy (ART), and 5 (26.3%) had CD4 < 350 cells/mL (4 of these were on ART). While drug injection was the most significant independent correlate of HCV (AOR = 12.9; p = 0.001) and a significant correlate of HIV (AOR = 8.2; p = 0.001), both unprotected sex (AOR = 3.31; p = 0.049) and working in Russia/Ukraine (AOR = 4.58; p = 0.008) were also correlated with HIV.HIV and HCV epidemics are concentrated among people who inject drugs (PWIDs) in Azerbaijan, and magnified among prisoners. A transitioning HIV epidemic is emerging from migration from high endemic countries and heterosexual risk. The high diagnostic rate and ART coverage among Azerbaijani prisoners provides new evidence that HIV treatment as prevention in former Soviet Union (FSU) countries is attainable, and provides new insights for HCV diagnosis and treatment as new medications become available. Within prison evidence-based addiction treatments with linkage to community care are urgently needed.

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. 2015; 26(7): 675-681.
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. Sociodemographic, 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 polysubstance use, and working with police to improve the risk environment.

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. 2015; 53: 33-38.
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.

HIV Stigma In Prisons and Jails: Results From A Staff Survey Belenko S, Dembo R, Copenhaver M, Hiller M, Swan H, Albizu Garcia C, O'Connell D, Oser C, Pearson F, Pankow J. AIDS Behav. 2015.
With numerous HIV service gaps in prisons and jails, there has been little research on HIV stigma attitudes among correctional staff. Such attitudes may undermine HIV services for inmates at risk of or infected with HIV. This HIV stigma attitudes survey among 218 correctional staff in 32 US facilities (1) provides an overview of staff's stigma attitudes, (2) reports psychometric analyses of domains in Earnshaw and Chaudoir's HIV Stigma Framework (HSF), and (3) explores differences in stigma attitudes among different staff types. Overall, correctional and medical staff expressed non stigmatizing attitudes toward people living with HIV/AIDS, but perceived that stigma and discrimination exist in others. Factor analyses revealed a three factor structure capturing two mechanisms of the HSF (prejudice, discrimination). Few factor score differences were found by staff type or setting. Implications for correctional HIV services and future research on HIV stigma attitudes are discussed.

HIV-infected Men Who Have Sex With Men, Before and After Release From Jail: The Impact Of Age and Race, Results From A Multi-site Study Vagenas P, Zelenev A, Altice FL, Di Paola A, Jordan AO, Teixeira PA, Frew PM, Spaulding AC, Springer SA. AIDS Care. 2015; 1-10.
The US HIV/AIDS epidemic is concentrated among men who have sex with men (MSM). Black men are disproportionately affected by incarceration and Black MSM experience higher infection rates and worse HIV-related health outcomes compared to non-Black MSM. The authors compared HIV treatment outcomes for Black MSM to other HIV-infected men from one of the largest cohorts of HIV-infected jail detainees (N = 1270) transitioning to the community. Of the 574 HIV-infected

men released, 113 (19.7%) self-identified as being MSM. Compared to other male subgroups, young Black MSM (<30 years old, N = 18) were significantly less likely: (1) before incarceration, to have insurance, access to an HIV healthcare provider, and use cocaine; (2) during incarceration, to receive a disease management intervention; and (3) in the 6 months post-release, to link to HIV care. Interventions that effectively link and retain young HIV-infected Black MSM in care in communities before incarceration and post-release from jail are urgently needed.

Rate Of Nicotine Metabolism and Smoking Cessation Outcomes In A Community-based Sample Of Treatment-Seeking Smokers Kaufmann A, Hitsman B, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, Gariti P, Tyndale RF, Schnoll RA. Addict Behav. 2015; 51: 93-99.

In samples from controlled randomized clinical trials, a smoker's rate of nicotine metabolism, measured by the 3-hydroxycotinine to cotinine ratio (NMR), predicts response to transdermal nicotine. Replication of this relationship in community-based samples of treatment-seeking smokers may help guide the implementation of the NMR for personalized treatment for nicotine dependence. Data from a community-based sample of treatment seeking smokers (N=499) who received 8 weeks of transdermal nicotine and 4 behavioral counseling sessions were used to evaluate associations between the NMR and smoking cessation. Secondary outcomes included withdrawal and craving, depression and anxiety, side effects, and treatment adherence. The NMR was a significant predictor of abstinence (OR=.56, 95% CI: 0.33-0.95, p=.03), with faster metabolizers showing lower quit rates than slower metabolizers (24% vs. 33%). Faster nicotine metabolizers exhibited significantly higher levels of anxiety symptoms over time during treatment, vs. slower metabolizers (NMR x Time interaction: F[3,357]=3.29, p=.02). NMR was not associated with changes in withdrawal, craving, depression, side effects, and treatment adherence (p>.05). In a community-based sample of treatment-seeking smokers, faster nicotine metabolizers were significantly less likely to quit smoking and showed higher rates of anxiety symptoms during a smoking cessation treatment program, vs. slower nicotine metabolizers. These results provide further evidence that transdermal nicotine is less effective for faster nicotine metabolizers and suggest the need to address cessation-induced anxiety symptoms among these smokers to increase the chances for successful smoking cessation.

Sex-Related Disparities In Criminal Justice and HIV Treatment Outcomes: A Retrospective Cohort Study Of HIV-Infected Inmates Meyer JP, Cepeda J, Taxman FS, Altice FL. Am J Public Health. 2015; 105(9): 1901-1910.

The authors evaluated sex-related differences in HIV and criminal justice (CJ) outcomes. They quantified sex-related differences in criminal offenses, incarcerations, and HIV outcomes among all HIV-infected inmates on antiretroviral therapy (ART) in Connecticut (2005-2012). Computed criminogenic risk scores estimated future CJ involvement. Stacked logistic regression models with random effects identified significant correlates of HIV viral suppression on CJ entry, reflecting preceding community-based treatment. Compared with 866 HIV-infected men on ART (1619 incarcerations), 223 women (461 incarcerations) were more likely to be younger, White, and medically insured, with shorter incarceration periods (mean = 196.8 vs 368.1 days), mostly for public disorder offenses. One third of both women and men had viral suppression on CJ entry, correlating positively with older age and having treated comorbidities. Entry viral suppression inversely correlated with incarceration duration for women and with criminogenic risk score for men. In the largest contemporary cohort of HIV-infected inmates on ART, women's higher prevalence of nonviolent offenses and treatable comorbidities supports alternatives to incarceration

strategies. Sex-specific interventions for CJ populations with HIV effectively align public health and safety goals.

Recreational Drug Use Among Primary Care Patients: Implications Of A Positive Self-report Bernstein J, Cheng DM, Wang N, Trilla C, Samet J, Saitz R. Ann Fam Med. 2015; 13(3): 257-260.
Should recreational drug use raise clinical concern? The authors examined the association between weekend-only recreational drug use at baseline (yes vs no) and any increase in recreational drug use frequency or severity over 6 months among primary care patients who screen positive for drug use. In the weekend-only recreational drug use group (52/483 [10.8%]), 54% (28/52) started using drugs on weekdays. Compared with use not limited to weekends, weekend-only use was associated with lower odds of increasing drug use frequency (AOR 0.48, P = 0.03) and lower odds (non-significant) of increasing severity (AOR 0.56, P = 0.07). Although weekend-only recreational drug use appears prognostically less severe, the findings nonetheless suggest that continued episodic monitoring may be clinically wise.

Laboratory-induced Stress and Craving Among Individuals With Prescription Opioid Dependence Back SE, Gros DF, Price M, LaRowe S, Flanagan J, Brady KT, Davis C, Jaconis M, McCauley JL. Drug Alcohol Depend. 2015; 155: 60-67.
Stress and conditioned drug cues have been implicated in the initiation, maintenance and relapse to substances of abuse. Although stress and drug cues are often encountered together, little research exists on whether stress potentiates the response to drug cues. Participants (N=75) were 39 community recruited individuals with current prescription opioid (PO) dependence and 36 healthy controls. Participants stayed overnight in the hospital for one night and then completed laboratory testing the following morning. During laboratory testing, participants were randomly assigned to a stress task (Trier Social Stress Task; TSST) or a no-stress condition. Following the stress manipulation, all participants completed a PO cue paradigm. Immediately before and after the stress and cue tasks, the following were assessed: subjective (stress, craving, anger, sadness, happiness), physiological (heart rate, blood pressure, galvanic skin response), and neuroendocrine responses (cortisol and dehydroepiandrosterone). Internal validity of the stress task was demonstrated, as evidenced by significantly higher subjective stress, as well as cortisol, heart rate and blood pressure in the TSST compared to the no-stress group. Individuals with PO dependence evidenced significantly greater reactivity to the stress task than controls. Craving increased significantly in response to the drug cue task among PO participants. No stress—cue interaction was observed. In this study, heightened stress reactivity was observed among individuals with PO dependence. Exposure to acute stress, however, did not potentiate craving in response to conditioned drug cues.

Heroin Use, HIV-Risk, and Criminal Behavior In Baltimore: Findings From Clinical Research Schwartz RP, Kelly SM, Gryczynski J, Mitchell SG, O'Grady KE, Jaffe JH. J Addict Dis. 2015; 34(2-3): 151-161.
This article reviews research conducted in Baltimore over the past 15 years, examining the following: (1) What factors differentiate heroin-addicted individuals who enter methadone treatment from those who do not? (2) How difficult is gaining access to methadone treatment? (3) What are effective ways to overcome barriers to treatment entry? (4) Why do so many methadone patients drop out of treatment prematurely? (5) What are the added benefits of counseling when coupled with methadone or buprenorphine treatment? (6) Does increasing access to treatment have an impact on overdose deaths? Specific recommendations are made for

policymakers concerned with addressing heroin addiction.

Successful Treatment Of Chronic Hepatitis C With Triple Therapy In An Opioid Agonist Treatment Program Litwin AH, Soloway IJ, Cockerham-Colas L, Reynoso S, Heo M, Tenore C, Roose RJ. Int J Drug Policy. 2015; 26(10): 1014-1019.
People who inject drugs (PWID) constitute 10 million people globally with hepatitis C virus, including many opioid agonist treatment patients. Little data exist describing clinical outcomes for patients receiving HCV treatment with direct-acting antiviral agents (DAAs) in opioid agonist treatment settings. In this retrospective observational study, the authors describe clinical outcomes for 50 genotype-1 patients receiving HCV treatment with triple therapy: telaprevir (n=42) or boceprevir (n=8) in combination with pegylated interferon and ribavirin on-site in an opioid agonist treatment program. Overall, 70% achieved an end of treatment response (ETR) and 62% achieved a sustained virological response (SVR). These treatment outcomes are nearly equivalent to previously published HCV outcomes shown in registration trials, despite high percentages of recent drug use prior to treatment (52%), ongoing drug use during treatment (45%) and psychiatric comorbidity (86%). Only 12% (n=6) discontinued antiviral treatment early for non-virological reasons. Four patients received a blood transfusion, and one discontinued telaprevir due to severe rash. These data demonstrate that on-site HCV treatment with direct-acting antiviral agents is effective in opioid agonist treatment patients including patients who are actively using drugs. Future interferon-free regimens will likely be even more effective. Opioid agonist treatment programs represent an opportunity to safely and effectively treat chronic hepatitis C, and PWID should have unrestricted access to DAAs.

Engagement In The HIV Care Continuum Among Key Populations In Tijuana, Mexico Smith LR, Patterson TL, Magis-Rodriguez C, Ojeda VD, Burgos JL, Rojas SA, Zuniga ML, Strathdee SA. AIDS Behav. 2015.
In Tijuana, Mexico, HIV is concentrated in sub-epidemics of key populations: persons who inject drugs (PWID), sex workers (SW), and men who have sex with men (MSM). To date, data on engagement in the HIV care continuum among these key populations, particularly in resource-constrained settings, are sparse. The authors pooled available epidemiological data from six studies (N = 3368) to examine HIV testing and treatment uptake in these key populations; finding an overall HIV prevalence of 5.7 %. Of the 191 identified HIV-positive persons, only 11.5 % knew their HIV-positive status and 3.7 % were on ART. Observed differences between these HIV-positive key populations suggest PWID (vs. non-PWID) were least likely to have previously tested or initiate HIV care. MSM (vs. non-MSM) were more likely to have previously tested but not more likely to know their HIV-positive status. Of persons aware of their HIV-positive status, SW (vs. non-SW) were more likely to initiate HIV care. Findings suggest engagement of key populations in HIV treatment is far below estimates observed for similarly resource-constrained generalized epidemics in sub-Saharan Africa. These data provide one of the first empirical-snapshots highlighting the extent of HIV treatment disparities in key populations.

Latent Class Analysis Of Substance Use Among Men Who Have Sex With Men In Malaysia: Findings From The Asian Internet MSM Sex Survey Lim SH, Cheung DH, Guadamuz TE, Wei C, Koe S, Altice FL. Drug Alcohol Depend. 2015; 151: 31-37.
High prevalence of substance use among men who have sex with men (MSM) may drive the HIV epidemic in Malaysia but patterns of substance use among Malaysian MSM have not been examined. This study investigated specific Malaysian MSM risk groups to determine the association

between their substance use and sexual risk behaviors. Data from Malaysian respondents (n=1235) in a large, multinational online survey of Asian MSM in 2010 were used to identify latent classes of substance use. Subsequent covariates were included in a joint model to predict class membership. The 3-class model was identified as the best fitting model, which included: (1) 'negligible substance use' for those reporting none or using any substance sparingly; (2) 'soft substance use' for those using poppers, ecstasy and drinking before sex; and (3) 'amphetamine-type stimulant (ATS) use' for those using stimulants (methamphetamine, ecstasy), erectile dysfunction drugs and recreational drug use before sex. Men in the 'ATS use' category were significantly less likely to not know their HIV status (AOR: 0.30, 95% CI: 0.14,0.66), more likely to have had more than 6 male sex partners (AOR: 4.83, 95% CI: 1.92-12.2), to have group sex (AOR:4.07, 95% CI: 2.31-7.15), to report inconsistent condom use (AOR:2.01, 95% CI: 1.12-3.60), to be HIV-infected (AOR:3.92, 95% CI: 1.63-8.42) and to have had any sexually transmitted infections (AOR:3.92, 95% CI:1.70, 9.08), compared to men in the 'negligible substance use' category. Our study identified subgroups of Malaysian MSM with distinct substance use patterns and HIV-related risk profiles, which provides implication for targeting HIV prevention in this subpopulation.

Efficacy Of A Process Improvement Intervention On Inmate Awareness Of HIV Services: A Multi-Site Trial Swan H, Hiller ML, Albizu-Garcia CE, Pich M, Patterson Y, O'Connell DJ. Health Justice. 2015; 3: 11.

The prevalence of HIV among U.S. inmates is much greater than in the general population, creating public health concerns and cost issues for the criminal justice system. The HIV Services and Treatment Implementation in Corrections protocol of the NIDA funded Criminal Justice Drug Abuse Treatment Studies cooperative tested the efficacy of an organizational process improvement strategy on improving HIV services in correctional facilities. For this paper, the authors analyzed efficacy of this strategy on improving inmate awareness and perceptions of HIV services. The study used a multi-site (n=28) clustered randomized trial approach. Facilities randomized to the experimental condition used a coach-driven local change team approach to improve HIV services at their facility. Facilities in the control condition were given a directive to improve HIV services on their own. Surveys about awareness and perceptions of HIV services were administered anonymously to inmates who were incarcerated in study facilities at baseline (n=1253) and follow-up (n=1048). A series of one-way ANOVAs were run to test whether there were differences between inmates in the experimental and control facilities at baseline and follow-up. Differences were observed at baseline, with the experimental group having significantly lower scores than the control group on key variables. But, at post-test, following the intervention, these differences were no longer significant. Taken in context of the findings from the main study, these results suggest that the change team approach to improving HIV services in correctional facilities is efficacious for improving inmates' awareness and perceptions of HIV services.

Motivational Tools To Improve Probationer Treatment Outcomes Taxman FS, Walters ST, Sloas LB, Lerch J, Rodriguez M. Contemp Clin Trials. 2015; 43: 120-128.

Motivational interviewing (MI) is a promising practice to increase motivation, treatment retention, and reducing recidivism among offender populations. Computer-delivered interventions have grown in popularity as a way to change behaviors associated with drug and alcohol use.
Motivational Assistance Program to Initiate Treatment (MAPIT) is a three arm, multisite, randomized controlled trial, which examines the impact of Motivational interviewing (MI), a motivational computer program (MC), and supervision as usual (SAU) on addiction treatment initiation, engagement, and retention. Secondary outcomes include drug/alcohol use, probation

progress, recidivism (i.e., criminal behavior) and HIV/AIDS testing and treatment among probationers. Participant characteristics are measured at baseline, 2, and 6 months after assignment. The entire study will include 600 offenders, with each site recruiting 300 offenders (Baltimore City, Maryland and Dallas, Texas). All participants will go through standard intake procedures for probation and participate in probation requirements as usual. After standard intake, participants will be recruited and screened for eligibility. The results of this clinical trial will fill a gap in knowledge about ways to motivate probationers to participate in addiction treatment and HIV care. This randomized clinical trial is innovative in the way it examines the use of in-person vs. technological approaches to improve probationer success.

Maximizing Effectiveness Trials In PTSD and SUD Through Secondary Analysis: Benefits and Limitations Using the National Institute On Drug Abuse Clinical Trials Network "Women and Trauma" Study As A Case Example Hien DA, Campbell ANC, Ruglass LM, Saavedra L, Mathews AG, Kiriakos G, Morgan-Lopez A. J Subst Abuse Treat. 2015; 56: 23-33.
Recent federal legislation and a renewed focus on integrative care models underscore the need for economical, effective, and science-based behavioral health care treatment. As such, maximizing the impact and reach of treatment research is of great concern. Behavioral health issues, including the frequent co-occurrence of substance use disorders (SUD) and posttraumatic stress disorder (PTSD), are often complex, with a myriad of factors contributing to the success of interventions. Although treatment guides for comorbid SUD/PTSD exist, most patients continue to suffer symptoms following the prescribed treatment course. Further, the study of efficacious treatments has been hampered by methodological challenges (e.g., overreliance on "superiority" designs (i.e., designs structured to test whether or not one treatment statistically surpasses another in terms of effect sizes) and short term interventions). Secondary analyses of randomized controlled clinical trials offer potential benefits to enhance understanding of findings and increase the personalization of treatment. This paper offers a description of the limits of randomized controlled trials as related to SUD/PTSD populations, highlights the benefits and potential pitfalls of secondary analytic techniques, and uses a case example of one of the largest effectiveness trials of behavioral treatment for co-occurring SUD/PTSD conducted within the National Drug Abuse Treatment Clinical Trials Network (NIDA CTN) and producing 19 publications. The paper concludes with implications of this secondary analytic approach to improve addiction researchers' ability to identify best practices for community-based treatment of these disorders. Innovative methods are needed to maximize the benefits of clinical studies and better support SUD/PTSD treatment options for both specialty and non-specialty healthcare settings. Moving forward, planning for and description of secondary analyses in randomized trials should be given equal consideration and care to the primary outcome analysis.

Improving Adherence To Antiretroviral Therapy With Triggered Real-time Text Message Reminders: The China Adherence Through Technology Study Sabin LL, Bachman DeSilva M, Gill CJ, Zhong L, Vian T, Xie W, Cheng F, Xu K, Lan G, Haberer JE, Bangsberg DR, Li Y, Lu H, Gifford AL. J Acquir Immune Defic Syndr. 2015; 69(5): 551-559.
Real-time adherence monitoring is now possible through medication storage devices equipped with cellular technology. The authors assessed the effect of triggered cell phone reminders and counseling using objective adherence data on antiretroviral therapy (ART) adherence among Chinese HIV-infected patients. They provided ART patients in Nanning, China, with a medication device (Wisepill) to monitor their ART adherence electronically. After 3 months, they randomized subjects within optimal (≥95%) and suboptimal (<95%) adherence strata to intervention vs. control

arms. In months 4-9, intervention subjects received individualized reminders triggered by late dose taking (no device opening by 30 minutes past dose time) and counseling using device-generated data. Controls received no reminders or data-informed counseling. The authors compared post-intervention proportions achieving optimal adherence, mean adherence, and clinical outcomes. Of 120 subjects enrolled, 116 (96.7%) completed the trial. Pre-intervention optimal adherence was similar in intervention vs. control arms (63.5% vs. 58.9%, respectively; P = 0.60). In the last intervention month, 87.3% vs. 51.8% achieved optimal adherence [risk ratio (RR): 1.7, 95% confidence interval (CI): 1.3 to 2.2] and mean adherence was 96.2% vs. 89.1% (P = 0.003). Among pre-intervention suboptimal adherers, 78.3% vs. 33.3% (RR: 2.4, CI: 1.2 to 4.5) achieved optimal adherence and mean adherence was 93.3% vs. 84.7% (P = 0.039). Proportions were 92.5% and 62.9% among optimal adherers, respectively (RR: 1.5, CI: 1.1 to 1.9) and mean adherence was 97.8% vs. 91.7% (P = 0.028). Post-intervention clinical outcomes were not significant. Real-time reminders significantly improved ART adherence in this population. This approach seems promising for managing HIV and other chronic diseases and warrants further investigation and adaptation in other settings.

Longitudinal Examination Of Medical Staff Utilization In Substance Use Disorder Treatment Organizations Fields D, Roman P. J Subst Abuse Treat. 2015.
This study examined changes in utilization of medical staff within organizations specializing in treatment of patients with substance use disorder (SUD) at two points in time (2007 and 2010). Utilization was calculated as the number of hours paid weekly for psychiatrists, physicians, nurses, and other medical staff working as employees or on contract. Study data come from a longitudinal national sample of 274 substance use disorder treatment centers. Average utilization of medical staff by these SUD treatment organizations increased by 26% from 2007 to 2010. The results showed that growing SUD treatment centers that obtained more referrals from health care providers, used case managers to coordinate comprehensive approaches to patient care, provided medication assisted treatment (MAT), and that were connected more closely with hospitals made increased use of medical staff over the 2007-2010 period. In 2010, these organizations seem to have been moving in directions consistent with trends forecasted for the SUD treatment environment after implementation of the Affordable Care Act.

Gender Abuse and Incident HIV/STI Among Transgender Women In New York City: Buffering Effect Of Involvement In A Transgender Community Nuttbrock L, Bockting W, Rosenblum A, Hwahng S, Mason M, Macri M, Becker J. AIDS Behav. 2015; 19(8): 1446-1453.
In a 3 year prospective study of 230 transgender women from the New York City Area, the authors further examined associations of gender-related abuse with HIV sexual risk behavior and incident HIV/STI, focusing here and the extent to which these associations are buffered by involvement in a transgender community. Largely consistent with the prior study, gender abuse was longitudinally associated with unprotected receptive anal intercourse (URAI) with casual and commercial sex partners, and the presumed biological outcome of this behavioral risk, new cases of HIV/STI. Both of these associations, gender abuse with URAI and HIV/STI, were significantly buffered by transgender community involvement (interaction effects). However, independent of these interaction effects, transgender community involvement was also positively associated with URAI and HIV/STI (direct effects). HIV prevention in this population should emphasize the benefits of interactions with transgender peers while also emphasizing the importance of resisting normative permission for HIV risk behavior from these same peers.

Clinical Impact Of Treatment Timing For Chronic Hepatitis C Infection: A Decision Model
Pho MT, Jensen DM, Meltzer DO, Kim AY, Linas BP. J Viral Hepat. 2015; 22(8): 630-638.
Recent advances in the treatment of hepatitis C virus (HCV) infection have led to the availability of both highly efficacious interferon-containing and interferon-sparing regimens. However, the use of such therapies faces restrictions due to high costs. For patients who are medically eligible to receive interferon, the choice between the two will likely be impacted by preferences surrounding interferon, severity of disease, coverage policies and out-of-pocket costs. The authors developed a decision model to quantify the trade-offs between immediate, interferon-containing therapy and delayed, interferon-free therapy for patients with chronic, genotype 1 HCV infection. They projected the quality-adjusted life expectancy stratified by the presence or absence of cirrhosis for four strategies: (i) no treatment; (ii) immediate, one-time treatment with an interferon-containing regimen; (iii) immediate treatment as above with the opportunity for retreatment in patients who fail to achieve sustained virologic response with interferon-free therapy in 1 year; and (iv) delayed therapy with interferon-free therapy in 1 year. When compared to one-time immediate treatment with the interferon-containing regimen, delayed treatment with the interferon-free regimen in 1 year resulted in longer life expectancy, with a 0.2 quality-adjusted life year (QALY) increase in non-cirrhotic patients, and a 1.1 QALY increase in patients with cirrhosis. This superiority in health benefits was lost when wait time for interferon-free therapy was greater than 3-3.2 years. In this modelling analysis, interferon-free therapy resulted in superior health benefits compared to immediate therapy with interferon until wait time exceeded 3-3.2 years. Such data can inform decision-making regarding treatment initiation for HCV as healthcare financing evolves.

"HIV Prevalence, Estimated Incidence, and Risk Behaviors Among People Who Inject Drugs In Kenya" Kurt AE, Cleland CM, Des Jarlais DC, Musyoki H, Lizcano JA, Chhun N, Cherutich P. J Acquir Immune Defic Syndr. 2015.
HIV infection in sub-Saharan Africa increasingly occurs among people who inject drugs (PWID). Kenya is one of the first to implement a national needle and syringe program (NSP). This study undertook a baseline assessment as part of evaluating NSP in a seek, test, treat, and retain approach. Participants enrolled May-December 2012 from 10 sites. Respondent-driven sampling was used to reach n=1,785 PWID for HIV-1 prevalence and viral load determination and survey data. Estimated HIV prevalence, adjusted for differential network size and recruitment relationships, was 14.5% in Nairobi (95% CI 10.8-18.2) and 20.5% in the Coast region (95% CI 17.3-23.6). Viral load (log10 transformed) in Nairobi ranged from 1.71 to 6.12 (median 4.41; IQR 3.51-4.94) and in the Coast from 1.71 to 5.88 (median 4.01; IQR 3.44-4.72). Using log10 viral load 2.6 as a threshold for HIV viral suppression, the percentage of HIV-infected participants with viral suppression was 4.2% in Nairobi and 4.6% in the Coast. Heroin was the most commonly injected drug in both regions, used by 93% of participants in the past month typically injecting 2-3 times/day. Receptive needle/syringe sharing at last injection was more common in Nairobi (23%) than the Coast (4%). Estimated incidence among new injectors was 2.5/100 person-years in Nairobi and 1.6/100 person-years in the Coast. The HIV epidemic is well-established among PWID in both Nairobi and Coast regions. Public health scale implementation of combination HIV prevention has the potential to greatly limit the epidemic in this vulnerable and bridging population.

Gender and Ethnicity As Moderators: Integrative Data Analysis Of Multidimensional Family Therapy Randomized Clinical Trials Greenbaum PE, Wang W, Henderson CE, Kan L, Hall K, Dakof GA, Liddle HA. J Fam Psychol. 2015.
This study examined gender and ethnicity as moderators of Multidimensional Family Therapy (MDFT) effectiveness for adolescent drug abuse and illustrated the utility of integrative data analysis (IDA; Bauer & Hussong, 2009) for assessing moderation. By pooling participant data from 5 independent MDFT randomized clinical trials (RCTs), IDA increased power to test moderation. Participants were 646 adolescents receiving treatment for drug use, aged 11 to 17 years (M = 15.31, SD = 1.30), with 19% female (n = 126), 14% (n = 92) European American, 35% (n = 225) Hispanic, and 51% (n = 329) African American. Participants were randomized to MDFT or active comparison treatments, which varied by study. Drug use involvement (i.e., frequency and consequences) was measured at study entry, 6-, and 12-months by a 4-indicator latent variable. Growth curve change parameters from multiple calibration samples were regressed on treatment effects overall and by moderator subgroups. MDFT reduced drug use involvement ($p < .05$) for all participant groups. Pooled comparison groups reduced drug use involvement only for females and Hispanics ($ps < .05$). MDFT was more effective than comparisons for males, African Americans, and European Americans ($ps < .05$; Cohen's d = 1.17, 1.95, and 1.75, respectively). For females and Hispanics, there were no significant differences between MDFT and pooled comparison treatments, Cohen's d = 0.63 and 0.19, respectively. MDFT is an effective treatment for drug use among adolescents of both genders and varied ethnicity with males, African American, and European American non-Hispanic adolescents benefitting most from MDFT.

Evidence-based Interventions To Enhance Assessment, Treatment, and Adherence In the Chronic Hepatitis C Care Continuum Meyer JP, Moghimi Y, Marcus R, Lim JK, Litwin AH, Altice FL. Int J Drug Policy. 2015; 26(10): 922-935.
With the explosion of newly available direct acting antiviral (DAA) Hepatitis C virus (HCV) treatments that demonstrate 95% sustained virologic response (SVR) rates, evidence-based strategies are urgently needed to achieve real-world effectiveness in challenging patient populations. While HIV is incurable, lessons from over 30 years of experience overcoming obstacles to the HIV treatment cascade could be applied to the HCV context. Using Institute of Medicine guidelines, the authors conducted a systematic review of published interventions from PubMed, Medline, GoogleScholar, EmBASE, and PsychInfo bibliographic databases and citation indices. Abstracts were first screened by three independent reviewers and studies were included if they involved original research, described a specific intervention, were published in English in a peer-reviewed journal between 2001 and 2014, and had full text available. Evidence-based interventions to enhance HCV assessment, treatment, and adherence generally fell into one of 4 categories, including those involving: (1) diagnosis or case-finding; (2) linkage to HCV care; (3) pre-therapeutic evaluation or treatment initiation; or (4) treatment adherence. While most available eligible studies described interventions using non-contemporary interferon-based HCV treatments, future research will need to address how these interventions apply to the context of well-tolerated, simple, oral treatment regimens. In some cases, the authors explored how HIV-specific interventions might be modified to fit the HCV spectrum of care engagement. Evidence-based interventions should be strategically incorporated into HCV treatment implementation efforts to most effectively deliver treatment and maximize treatment outcomes.

Shortening The Screener and Opioid Assessment For Patients With Pain-Revised (SOAPP-R): A Proof-of-Principle Study For Customized Computer-Based Testing Finkelman MD, Kulich RJ, Zacharoff KL, Smits N, Magnuson BE, Dong J, Butler SF. Pain Med. 2015.
The Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) is a 24-item self-report instrument that was developed to aid providers in predicting aberrant medication-related behaviors among chronic pain patients. Although the SOAPP-R has garnered widespread use, certain patients may be dissuaded from taking it because of its length. Administrative barriers associated with lengthy questionnaires further limit its utility. The aim of this study was to investigate the extent to which two techniques for computer-based administration (curtailment and stochastic curtailment) reduce the average test length of the SOAPP-R without unduly affecting sensitivity and specificity. This was a retrospective study conducted at pain management centers. Subjects comprised four hundred and twenty-eight chronic non-cancer pain patients. Subjects had taken the full-length SOAPP-R and been classified by the Aberrant Drug Behavior Index (ADBI) as having engaged or not engaged in aberrant medication-related behavior. Curtailment and stochastic curtailment were applied to the data in post-hoc simulation. Sensitivity and specificity with respect to the ADBI, as well as average test length, were computed for the full-length test, curtailment, and stochastic curtailment. The full-length SOAPP-R exhibited a sensitivity of 0.745 and a specificity of 0.671 for predicting the ADBI. Curtailment reduced the average test length by 26% while exhibiting the same sensitivity and specificity as the full-length test. Stochastic curtailment reduced the average test length by as much as 65% while always exhibiting sensitivity and specificity for the ADBI within 0.035 of those of the full-length test. Curtailment and stochastic curtailment have potential to improve the SOAPP-R's efficiency in computer-based administrations.

The Relationship Between Electronic Goal Reminders and Subsequent Drug Use and Treatment Initiation In A Criminal Justice Setting Spohr SA, Taxman FS, Walters ST. Addict Behav. 2015; 51: 51-56.
Opportunities to influence behavior through the use of electronic reminders has not been examined in a criminal justice population. The purpose of this study was to assess probationer preferences for short-term goals from a web-based program and evaluate the role of voluntary electronic reminders (e.g., text messaging, email) in achieving early treatment and probation tasks. The authors used data from drug-involved offenders (n=76) participating in a clinical trial of a 2-session motivational computer program. As part of the program, participants could choose to receive text or email reminders about their probation and treatment goals for the next month. Poisson regression models were utilized to evaluate goal and reminder selection in relation to the days of substance use and treatment attendance at two-month follow-up. The most common goals were related to probation and treatment tasks, relationships, and cognitive reappraisals. Forty-five percent of probationers elected to receive electronic goal reminders at Session 1 with a slight increase at Session two (49%). Probationers who opted to receive electronic goal reminders at Session one selected significantly more goals on average (M=4.4, SD=2.1) than probationers who did not want reminders (M=3.4, SD=1.8), (t=2.41, p=.019). Reminder selection and total number of goals selected predicted days of substance use and treatment attendance at a two-month follow-up. Probationers who opted not to receive electronic reminders and those who only chose to receive reminders at one visit had more days of substance use compared to those who chose to receive reminders at both visits, 1.66 and 2.31 times respectively. Probationers who chose not to receive electronic reminders attended 56% fewer days of treatment compared to those who chose to receive reminders at both visits. People's choice of short-term goals and reminders can provide advance notification of the likelihood of

substance use and treatment initiation. Probation systems might use such information to triage at-risk probationers to a higher level of service, before problems have emerged.

Treatment Strategy Profiles In Substance Use Disorder Treatment Programs: A Latent Class Analysis Edmond MB, Aletraris L, Paino M, Roman PM. Drug Alcohol Depend. 2015; 153: 109-115.
Modern treatment options for substance use disorder are diverse. While studies have analyzed the adoption of individual evidence-based practices in treatment centers, little is known about the specific make-up of treatment strategy profiles in treatment centers throughout the United States. The current study used latent class analysis to profile underlying treatment strategies and to evaluate philosophical and structural supports associated with each profile. Utilizing three aggregated and secondary datasets of nationally representative samples of substance use disorder treatment centers (N=775), the authors employed latent class analysis to determine treatment strategy profiles. Using multinomial logistic regression, they then examined organizational characteristics associated with each profile. They found three distinct treatment strategy profiles: centers that primarily relied on motivational interviewing and motivational enhancement therapy, centers that utilized psychosocial and alternative therapies, and centers that employed comprehensive treatments including pharmacotherapy. The multinomial logistic regression revealed that philosophical and structural center characteristics were associated with membership in the comprehensive class. Centers with philosophical orientations conducive to holistic care and pharmacotherapy-acceptance, resource-rich infrastructures, and an entrepreneurial reliance on insured clients were more likely to offer diverse interventions. All associations were significant at the .05 level. The findings from this study help us understand the general strategies of treatment centers. From a practical perspective, practitioners and clients should be aware of the variation in treatment center practices where they may offer or receive treatment.

The Supply Of Physicians Waivered To Prescribe Buprenorphine For Opioid Use Disorders In The United States: A State-Level Analysis Knudsen HK. J Stud Alcohol Drugs. 2015; 76(4): 644-654.
The U.S. Food and Drug Administration's approval of buprenorphine in 2002 expanded options for treating opioid use disorder (OUD). Physicians who intend to treat OUD patients with buprenorphine must seek a waiver to prescribe it, which may contribute to state-by-state variation in the supply of waivered physicians. This study integrates data extracted from the U.S. Drug Enforcement Agency's database of waivered physicians with state-level indicators of the macro environment, health-related resources, and treatment demand. In December 2013, the average state had 8.0 waivered physicians per 100,000 residents (SD = 5.2). Large regional differences between states in the Northeast relative to states in the Midwest, South, and West were observed. The percentage of residents covered by Medicaid as well as the population-adjusted availability of opioid treatment programs and substance use disorder treatment facilities were positively associated with buprenorphine physician supply. Buprenorphine physician supply was positively correlated with states' rates of overdose deaths, suggesting that physicians may seek the waiver in response to the magnitude of the opioid problem in their state. States with greater health-related resources, particularly in terms of the supply of opioid treatment programs and substance use disorder treatment programs, had more waivered physicians in 2013. The finding regarding Medicaid coverage suggests that states implementing Medicaid expansion under health reform may experience additional growth in buprenorphine physician supply. However, large regional

disparities in the supply of waivered physicians may impede access to care for many Americans with OUD.

Where Is Buprenorphine Dispensed to Treat Opioid Use Disorders? The Role of Private Offices, Opioid Treatment Programs, and Substance Abuse Treatment Facilities in Urban and Rural Counties Stein BD, Pacula RL, Gordon AJ, Burns RM, Leslie DL, Sorbero MJ, Bauhoff S, Mandell TW, Dick AW. Milbank Q. 2015; 93(3): 516-583.
Opioid use disorders are a significant public health problem. In 2002, the FDA approved buprenorphine as an opioid use disorder treatment when prescribed by waivered physicians who were limited to treating 30 patients at a time. In 2006, federal legislation raised this number to 100 patients. Although federal legislators are considering increasing these limits further and expanding prescribing privileges to non-physicians, little information is available regarding the impact of such changes on buprenorphine use. The authors therefore examined the impact of the 2006 legislation—as well as the association between urban and rural waivered physicians, opioid treatment programs, and substance abuse treatment facilities—on buprenorphine distributed per capita over the past decade. Using 2004-2011 state-level data on buprenorphine dispensed and county-level data on the number of buprenorphine-waivered physicians and substance abuse treatment facilities using buprenorphine, the authors estimated a multivariate ordinary least squares regression model with state fixed effects of a state's annual total buprenorphine dispensed per capita as a function of the state's number of buprenorphine providers. The amount of buprenorphine dispensed has been increasing at a greater rate than the number of buprenorphine providers. The number of physicians waivered to treat 100 patients with buprenorphine in both rural and urban settings was significantly associated with increased amounts of buprenorphine dispensed per capita. There was no significant association in the growth of buprenorphine distributed and the number of physicians with 30-patient waivers. The greater amounts of buprenorphine dispensed are consistent with the potentially greater use of opioid agonists for opioid use disorder treatment, though they also make their misuse more likely. The changes after the 2006 legislation suggest that policies focused on increasing the number of patients that a single waivered physician could safely and effectively treat could be more effective in increasing buprenorphine use than would alternatives such as opening new substance abuse treatment facilities or raising the overall number of waivered physicians.

Provision Of Onsite HIV Services In Substance Use Disorder Treatment Programs: A Longitudinal Analysis Aletraris L, Roman PM. J Subst Abuse Treat. 2015; 57: 1-8.
The provision of HIV education and testing in substance use disorder (SUD) treatment programs is an important public health strategy for reducing HIV incidence. For many at-risk individuals, SUD treatment represents the primary point of access for testing and receiving HIV-related services. This study uses two waves of nationally representative data of 265 privately-funded SUD treatment programs in the U.S. to examine organizational and patient characteristics associated with offering a dedicated HIV/AIDS treatment track, onsite HIV/AIDS support groups, and onsite HIV testing. The authors' longitudinal analysis indicated that the majority of treatment programs reported providing education and prevention services, but there was a small, yet significant, decline in the number of programs providing these services. Programs placed more of an emphasis on providing information on the transmission of HIV rather than on acquiring risk-reduction skills. There was a notable and significant increase (from 26.0% to 31.7%) in programs that offered onsite HIV testing, including rapid HIV testing, and an increase in the percentage of patients who received testing in the programs. Larger programs were more likely to offer a dedicated HIV/AIDS treatment track and to offer onsite HIV/AIDS support groups, while accredited programs and programs with a medical

infrastructure were more likely to provide HIV testing. The percentage of injection drug users was positively linked to the availability of specialized HIV/AIDS tracks and HIV/AIDS support groups, and the percentage of female clients was associated with the availability of onsite support groups. The odds of offering HIV/AIDS support groups were also greater in programs that had a dedicated LGBT track. The findings suggest that access to hospitals and medical care services is an effective way to facilitate adoption of HIV services and that programs are providing a needed service among a group of patients who have a heightened risk of HIV transmission. Nonetheless, the fact that fewer than one third of programs offered onsite testing, and, of the ones that did, fewer than one third of their patients received testing, raises concern in light of federal guidelines.

The Effect Of Neighborhood Context On The Relationship Between Substance Misuse and Weapons Aggression In Urban Adolescents Seeking ED Care Goldstick JE, Lipton RI, Carter P, Stoddard SA, Newton MF, Reischl T, Walton M, Zimmerman MA, Cunningham RM. Subst Use Misuse. 2015; 50(5): 674-684.
Frameworks for studying the ecology of human behavior suggest that multiple levels of the environment influence behavior and that these levels interact. Applied to studies of weapons aggression, this suggests proximal risk factor (e.g., substance use) effects may differ across neighborhoods. The aim of this study was to estimate how the association between weapons aggression and substance use varies as a function of several community-level variables. Individual-level measures (demographics, behavioral measures) were obtained from a survey of youth aged 14-24Â years old seeking care at a Level-1 ED in Flint, Michigan. Community-level variables were obtained from public sources. Logistic generalized additive models were used to test whether community-level variables (crime rates, alcohol outlets, demographics) modify the link between individual-level substance use variables and the primary outcome measure: self-reported past 6-month weapon (firearm/knife) related aggression. The effect of marijuana misuse on weapons aggression varied significantly as a function of five community-level variables: racial composition, vacant housing rates, female headed household rates, density of package alcohol outlets, and nearby drug crime rates. The effect of high-risk alcohol use did not depend on any of the eight community variables tested. The relationship between marijuana misuse and weapons aggression differed across neighborhoods with generally less association in more disadvantaged neighborhoods, while high-risk alcohol use showed a consistently high association with weapons aggression that did not vary across neighborhoods. The results aid in understanding the contributions of alcohol and marijuana use to the etiology of weapon-related aggression among urban youth, but further study in the general population is required.

Provider Workforce Assessment In A Rural Hepatitis C Epidemic: Implications For Scale-up Of Antiviral Therapy Westergaard RP, Stockman LJ, Hyland HA, Guilfoyle SM, Fangman JJ, Vergeront JM. J Prim Care Community Health. 2015; 6(3): 215-217.
New recommendations for birth cohort screening for hepatitis C virus (HCV) infection and the development of new, highly effective antiviral medications are expected to increase the demand for HCV treatment. In the past, antiviral therapy for HCV was almost exclusively prescribed by specialists in the field of gastroenterology and infectious diseases, meaning that people living in rural areas that are underserved by specialists may have poor access to treatment. The authors investigated the number and geographic distribution of medical providers who actively prescribed direct acting antiviral drugs for hepatitis C in Wisconsin during 2012. Using public health surveillance data and a state-wide prescription drug database, the authors found that there was 1 treatment provider for every 340 residents known to be living with HCV. However, 51 of 72

Wisconsin counties had no providers who provided HCV treatment in 2012. Scaling up antiviral treatment to address the epidemic of hepatitis C efficiently and equitably will require strategies to increase the number of treatment providers in rural communities. Providing education, training, and support to the primary care workforce serving rural communities should be considered a potentially effective and efficient approach to preventing future HCV-related illness.

Intergenerational Effects Of Parental Substance-related Convictions and Adult Drug Treatment Court Participation On Children's School Performance Gifford EJ, Sloan FA, Eldred LM, Evans KE. Am J Orthopsychiatry. 2015; 85(5): 452-468.
This study examined the intergenerational effects of parental conviction of a substance-related charge on children's academic performance and, conditional on a conviction, whether completion of an adult drug treatment court (DTC) program was associated with improved school performance. State administrative data from North Carolina courts, birth records, and school records were linked for 2005-2012. Math and reading end-of-grade test scores and absenteeism were examined for 5 groups of children, those with parents who: were not convicted on any criminal charge, were convicted on a substance-related charge and not referred by a court to a DTC, were referred to a DTC but did not enroll, enrolled in a DTC but did not complete, and completed a DTC program. Accounting for demographic and socioeconomic factors, the school performance of children whose parents were convicted of a substance-related offense was worse than that of children whose parents were not convicted on any charge. These differences were statistically significant but substantially reduced after controlling for socioeconomic characteristics; for example, mother's educational attainment. The authors found no evidence that parent participation in an adult DTC program led to improved school performance of their children. While the children of convicted parents fared worse on average, much-but not all-of this difference was attributed to socioeconomic factors, with the result that parental conviction remained a risk factor for poorer school performance. Even though adult DTCs have been shown to have other benefits, the authors could detect no intergenerational benefit in improved school performance of their children.

Impact Of Illicit Drug Use On Health-Related Quality Of Life In Opioid Dependent Patients Undergoing HIV Treatment Aden B, Dunning A, Nosyk B, Wittenberg E, Bray JW, Schackman BR. J Acquir Immune Defic Syndr. 2015.
To assess the impact of illicit drug use on health-related quality of life (health utility) among opioid-dependent, HIV-infected patients. Secondary analyses of data from the Buprenorphine-HIV Evaluation and Support (BHIVES) cohort of HIV-infected patients with opioid dependence in 9 U.S. HIV clinics between 2004 and 2009. Health status (Short Form-12 (SF-12)), combination antiretroviral treatment (ART) status, CD4 cell count, HCV antibody status, current drug use, and demographics were assessed at an initial visit and quarterly follow-up visits for up to one year. Short Form-6D health utility scores were derived from the SF-12. Multivariate mixed effects regression models were used to assess the impact of illicit drug use on health utility controlling for demographic, clinical and social characteristics. Health utility was assessed among 307 participants, 67% male, with median age 46 at 1089 quarterly assessments. In multivariate analyses, illicit opioid use, non-opioid illicit drug use, not being on ART and being on ART with poor adherence were associated with lower health utility. The observed decrement in health utility associated with illicit opioid use was larger for those on ART with good adherence (beta = -0.067; $p<0.01$) or poor adherence (-0.049; $p<0.01$) than for those not on ART. Illicit opioid and non-opioid drug use are negatively associated with health utility in patients with HIV, however the relative effect of illicit opioid use is smaller than that of not being on ART. Postponing ART until initiation of opioid

substitution therapy or abstinence may have limited benefits from the perspective of maximizing health utility.

The Medicaid Expansion Gap and Racial and Ethnic Minorities With Substance Use Disorders Andrews CM, Guerrero EG, Wooten NR, Lengnick-Hall R. Am J Public Health. 2015; 105 Suppl 3: S452-454.
The authors compared the race and ethnicity of individuals residing in states that did and did not expand Medicaid in 2014. Findings indicated that African Americans and Native Americans with substance use disorders who met new federal eligibility criteria for Medicaid were less likely than those of other racial and ethnic groups to live in states that expanded Medicaid. These findings suggest that the uneven expansion of Medicaid may exacerbate racial and ethnic disparities in insurance coverage for substance use disorder treatment.

Risk Factors For Stimulant Use Among Homeless and Unstably Housed Adult Women Riley ED, Shumway M, Knight KR, Guzman D, Cohen J, Weiser SD. Drug Alcohol Depend. 2015; 153: 173-179.
One of the most common causes of death among homeless and unstably housed women is acute intoxication where cocaine is present. While correlates of stimulant use have been determined in prior research, few studies have assessed risk factors of use specifically in this high-risk population. The authors sampled biological women with a history of housing instability from community-based venues to participate in a cohort study. Baseline and 6-month follow-up data were used to determine the relative risk of stimulant use (crack cocaine, powder cocaine or methamphetamine) among individuals who did not use at baseline. Among 260 study participants, the median age was 47 years, 70% were women of color; 47% reported having unmet subsistence needs and 53% reported abstinence from stimulants at baseline. In analyses adjusting for baseline socio-demographics and drug treatment, the risk of using stimulants within 6 months was significantly higher among women who reported recent sexual violence (Adjusted Relative Risk [ARR]=4.31; 95% CI:1.97-9.45), sleeping in a shelter or public place (ARR=2.75; 95% CI:1.15-6.57), and using un-prescribed opioid analgesics (ARR=2.54; 95% CI:1.01-6.38).We found that almost half of homeless and unstably housed women used stimulants at baseline and 14% of those who did not use began within 6 months. Addressing homelessness and sexual violence is critical to reduce stimulant use among impoverished women.

Preferences For Aftercare Among Persons Seeking Short-term Opioid Detoxification Stein MD, Anderson BJ, Bailey GL. J Subst Abuse Treat. 2015.
Without aftercare treatment, the period following discharge from short-term inpatient detoxification for opioid dependence presents a high risk of relapse. Yet the role of patient preference in treatment selection is rarely discussed in the substance-abuse literature. The authors surveyed 485 persons initiating inpatient opioid detoxification who were predominantly male (71.3%) and had detoxed in the past (73.2%). When asked to choose the one treatment that would work best for them after discharge, 43% of participants selected medication-assisted treatment (MAT), 29% preferred residential, 12% selected drug-free counseling, 12% NA/AA meetings only, and 4% preferred no additional treatment. Residential treatment preference was significantly associated with homelessness, having been in a detox program within the past year, and having pending legal problems, indicating that there is a distinct profile of detox patients who prefer residential treatment despite its limited availability. Detox program staff should work with patients to understand reasons for treatment preferences to optimize aftercare services.

Prescription Monitoring Programs and Emergency Department Visits Involving Benzodiazepine Misuse: Early Evidence From 11 United States Metropolitan Areas Bachhuber MA, Maughan BC, Mitra N, Feingold J, Starrels JL. Int J Drug Policy. 2015.
Emergency department (ED) visits involving benzodiazepines have increased in the United States. Most states have created prescription monitoring programs (PMPs) to improve drug prescribing safety. To determine the association between PMP implementation and ED visits involving benzodiazepine misuse, the authors conducted a retrospective analysis of data from 11 metropolitan areas in the United States from 2004 to 2011. They estimated rates of ED visits per 100,000 residents involving benzodiazepine misuse from the Drug Abuse Warning Network dataset. Dates of PMP implementation were obtained from program administrators. The authors used linear regression models to assess whether PMP implementation was associated with a change in ED visits involving benzodiazepines. Models were adjusted for calendar quarter, metropolitan area, and metropolitan area-specific linear time trends. Rates of ED visits involving benzodiazepine misuse increased in all metropolitan areas during the study period. PMP implementation was not associated with a change in ED visits (mean difference: 0.9 [95% CI: -0.09 to 1.9] visits per 100,000 population per quarter; p=0.08). When analyzed by number of years after implementation, PMPs were associated with a higher visit rate in year one (0.8 [95% CI: 0.2-1.5]; p=0.01]), but not in year two (0.3 [95% CI: -2.1-2.8]; p=0.78) or year three or later (2.1 [95% CI: -0.4-4.7]; p=0.10). The authors did not find evidence that PMP implementation was associated with reductions in ED visits involving benzodiazepine misuse. Future work should identify PMP features and capabilities that improve benzodiazepine safety.

Lessons From Medicaid's Divergent Paths On Mental Health and Addiction Services Andrews C, Grogan CM, Brennan M, Pollack HA. Health Aff (Millwood). 2015; 34(7): 1131-1138.
Over the past fifty years Medicaid has taken divergent paths in financing mental health and addiction treatment. In mental health, Medicaid became the dominant source of funding and had a profound impact on the organization and delivery of services. But it played a much more modest role in addiction treatment. This is poised to change, as the Affordable Care Act is expected to dramatically expand Medicaid’s role in financing addiction services. In this article the authors consider the different paths these two treatment systems have taken since 1965 and identify strategic lessons that the addiction treatment system might take from mental health’s experience under Medicaid. These lessons include leveraging optional coverage categories to tailor Medicaid to the unique needs of the addiction treatment system, providing incentives to addiction treatment programs to create and deliver high-quality alternatives to inpatient treatment, and using targeted Medicaid licensure standards to increase the quality of addiction services.

Characterizing Retention In HAART As A Recurrent Event Process: Insights Into 'Cascade Churn' Nosyk B, Lourenco L, Min JE, Shopin D, Lima VD, Montaner JSG, STOP HIVAIDS Study Group. AIDS. 2015; 29(13): 1681-1689.
The benefits of HAART rely on continuous lifelong treatment retention. The authors used linked population-level health administrative data to characterize durations of HAART retention and non-retention. This is a retrospective cohort study. The authors considered individuals initiating HAART in British Columbia (1996-2012). An HAART episode was considered discontinued if individuals had a gap of at least 30 days between days in which medication was prescribed. The authors considered durations of HAART retention and non-retention separately, and used Cox proportional hazards frailty models to identify demographic and treatment-related factors associated with durations of HAART retention and non-retention. Six thousand one hundred fifty-two individuals

were included in the analysis; 81.2% were male, 40.6% were people who inject drugs, and 42.8% initiated treatment with $CD4^+$ cell count less than 200 cells/[mu]I. Overall, 29% were continuously retained on HAART through the end of follow-up. HAART episodes were a median 6.8 months (25th, 75th percentile: 2.3, 19.5), whereas off-HAART episodes lasted a median 1.9 months (1.2, 4.5). In Cox proportional hazards frailty models, durations of HAART retention improved over time. Successive treatment episodes tended to decrease in duration among those with multiple attempts, whereas off-HAART episodes remained relatively stable. Younger age, earlier stages of disease progression, and injection drug use were all associated with shorter durations of HAART retention and longer off-HAART durations. Metrics to monitor HAART retention, dropout, and reentry should be prioritized for HIV surveillance. Clinical strategies and public health policies are urgently needed to improve HAART retention, particularly among those at earlier stages of disease progression, the young, and people who inject drugs.

Improving Coordination Of Addiction Health Services Organizations With Mental Health and Public Health Services Guerrero EG, Andrews C, Harris L, Padwa H, Kong Y, Fenwick K. J Subst Abuse Treat. 2015.
In this mixed-method study, the authors examined coordination of mental health and public health services in addiction health services (AHS) in low-income racial and ethnic minority communities in 2011 and 2013. Data from surveys and semi-structured interviews were used to evaluate the extent to which environmental and organizational characteristics influenced the likelihood of high coordination with mental health and public health providers among outpatient AHS programs. Coordination was defined and measured as the frequency of interorganizational contact among AHS programs and mental health and public health providers. The analytic sample consisted of 112 programs at time 1 (T1) and 122 programs at time 2 (T2), with 61 programs included in both periods of data collection. Forty-three percent of AHS programs reported high frequency of coordination with mental health providers at T1 compared to 66% at T2. Thirty-one percent of programs reported high frequency of coordination with public health services at T1 compared with 54% at T2. Programs with culturally responsive resources and community linkages were more likely to report high coordination with both services. Qualitative analysis highlighted the role of leadership in leveraging funding and developing creative solutions to deliver coordinated care. Overall, these findings suggest that AHS program funding, leadership, and cultural competence may be important drivers of program capacity to improve coordination with health service providers to serve minorities in an era of health care reform.

A Longitudinal Study Of State Strategies and Policies To Accelerate Evidence-Based Practices In The Context Of Systems Transformation Rieckmann T, Abraham A, Zwick J, Rasplica C, McCarty D. Health Serv Res. 2015; 50(4): 1125-1145.
To profile state agency efforts to promote implementation of three evidence-based practices (EBPs): screening and brief intervention (SBIRT), psychosocial interventions, and medication-assisted treatment (MAT). Primary data collected from representatives of 50 states and the District of Columbia's Single State Authorities from 2007 to 2009. The study used mixed methods, in-depth, semi-structured interviews and quantitative surveys. Interviews assessed state and provider strategies to accelerate implementation of EBPs. Statewide implementation of psychosocial interventions and MAT increased significantly over 3 years. In the first two assessments, states that contracted directly with providers were more likely to link use of EBPs to reimbursement, and states with indirect contract, through counties and other entities, increased recommendations, and some requirements for provision of specific EBPs. The number of states using legislation as a

policy lever to promote EBPs was unchanged. Health care reform and implementation of parity in coverage increases access to treatment for alcohol and drug use. Science-based substance abuse treatment will become even more crucial as payers seek consistent quality of care. This study provides baseline data on service delivery, contracting, and financing as state agencies and treatment providers prepare for implementation of the Affordable Care Act.

Integration of Substance Abuse Treatment Organizations into Accountable Care Organizations: Results from a National Survey D'Aunno T, Friedmann PD, Chen Q, Wilson DA. Journal of Health Politics, Policy, and Law. 2015; 40(4): 1125-1145.
To meet their aims of managing population health to improve the quality and cost of health care in the United States, accountable care organizations (ACOs) will need to focus on coordinating care for individuals with substance abuse disorders. The prevalence of these disorders is high, and these individuals often suffer from comorbid chronic medical and social conditions. This article examines the extent to which the nation's fourteen thousand specialty substance abuse treatment (SAT) organizations, which have a daily census of more than 1 million patients, are contracting with ACOs across the country; the authors also examine factors associated with SAT organization involvement in ACOs. They draw on data from a recent (2014) nationally representative survey of executive directors and clinical supervisors from 635 SAT organizations. Results show that only 15 percent of these organizations had signed contracts with ACOs. Results from multivariate analyses show that directors' perceptions of market competition, organizational ownership, and geographic location are significantly related to SAT involvement with ACOs. The authors discuss implications for integrating the SAT specialty system with the mainstream health care system.

Knowledge Of Case Workers and Correctional Officers Towards HIV and HCV Infections: Opportunity For Public Health Education In The Correctional System Pérez CM, del Carmen SM, Torres A, Grana C, Albizu-García C.P R Health Sci J. 2015; 34(3): 135-141.
Given the heavy burden of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections in correctional facilities, the authors examined knowledge about these infections among case workers and correctional officers in penal institutions in Puerto Rico. They used data from a cross-sectional study of state prisons, commissioned by the Puerto Rico Department of Correction and Rehabilitation, to assess knowledge about HCV and HIV (10 items each) among 256 case workers and correctional officers from 18 penal institutions selected in the prison system. Total scores for each scale ranged from 0 to 10 points, with higher scores reflecting more knowledge. Of 256 participants, 64.8% were males, 39.6% were aged 30-39 years, and 70.3% were case workers. The percentage of correct responses for knowledge items ranged from 8.5% to 97.0% for HCV infection and from 38.7% to 99.6% for HIV infection. The vast majority (>96%) of participants knew that injection drug users should be tested for HCV infection and that sharing of needle injection equipment and multiple sex partners increase the risk of HIV infection. However, misconceptions about routes of transmission for these viral infections were found, with larger gaps in knowledge for HCV infection. Mean knowledge scores for HCV and HIV infections were 4.20±0.17 and 6.95±0.22, respectively, being significantly ($p<0.05$) higher for case workers.
The findings about HCV and HIV knowledge in an important segment of the correctional system staff support the urgent need for increasing educational opportunities for correctional staff.

Utilizing MHealth Methods To Identify Patterns Of High Risk Illicit Drug Use Linas BS, Latkin C, Genz A, Westergaard RP, Chang LW, Bollinger RC, Kirk GD. Drug Alcohol Depend. 2015; 151: 250-257.
The authors assessed patterns of illicit drug use using mobile health (mHealth) methods and subsequent health care indicators among drug users in Baltimore, MD. Participants of the EXposure Assessment in Current Time (EXACT) study were provided a mobile device for assessment of their daily drug use (heroin, cocaine or both), mood and social context for 30 days from November 2008 through May 2013. Real-time, self-reported drug use events were summed for individuals by day. Drug use risk was assessed through growth mixture modeling. Latent class regression examined the association of mHealth-defined risk groups with indicators of healthcare access and utilization.109 participants were a median of 48.5 years old, 90% African American, 52% male and 59% HIV-infected. Growth mixture modeling identified three distinct classes: low intensity drug use (25%), moderate intensity drug use (65%) and high intensity drug use (10%). Compared to low intensity drug users, high intensity users were younger, injected greater than once per day, and shared needles. At the subsequent study visit, high intensity drug users were nine times less likely to be medically insured (adjusted OR: 0.10, 95%CI: 0.01-0.88) and at greater risk for failing to attend any outpatient appointments (aOR: 0.13, 95%CI: 0.02-0.85) relative to low intensity drug users. Real-time assessment of drug use and novel methods of describing sub-classes of drug users uncovered individuals with higher-risk behavior who were poorly utilizing healthcare services. mHealth holds promise for identifying individuals engaging in high-risk behaviors and delivering real-time interventions to improve care outcomes.

Implementation and Operational Research: Linkage To Care Among Methadone Clients Living With HIV In Dar Es Salaam, Tanzania Tran OC, Bruce RD, Masao F, Ubuguyu O, Sabuni N, Mbwambo J, Lambdin BH. J Acquir Immune Defic Syndr. 2015; 69(2): e43-48.
The first methadone maintenance treatment clinic in Tanzania was launched in February 2011 to address an emerging HIV epidemic among people who inject drugs. The authors conducted a retrospective cohort study to understand factors associated with linkage to HIV care and explore how a methadone maintenance treatment clinic can serve as a platform for integrated HIV care and treatment. This study used routine programmatic and clinical data on clients enrolled in methadone at Muhimbili National Hospital from February 2011 to January 2013. Multivariable proportional hazards regression model was used to examine time to initial CD4 count.
Final analyses included 148 HIV-positive clients, contributing 31.7 person-years. At 30, 60, and 90 days, the probability of CD4 screening was 40% [95% confidence interval (CI): 32% to 48%], 55% (95% CI: 47% to 63%), and 63% (95% CI: 55% to 71%), respectively. Clients receiving high methadone doses (â‰¥ 85 mg/d) [adjusted hazard ratio (aHR): 1.68, 95% CI: 1.03 to 2.74] had higher likelihood of CD4 screening than those receiving low doses (<85 mg/d). Clients with primary education or lower (aHR: 1.62, 95% CI: 1.05 to 2.51) and self-reported poor health (aHR: 1.96, 95% CI: 1.09 to 3.51) were also more likely to obtain CD4 counts. Clients with criminal arrest history (aHR: 0.56, 95% CI: 0.37 to 0.85]) were less likely to be linked to care. Among 17 antiretroviral therapy eligible clients (CD4 ≤ 200), 12 (71%) initiated treatment, of which 7 (41%) initiated within 90 days. Levels of CD4 screening and antiretroviral therapy initiation were similar to Sub-Saharan programs caring primarily for people who do not inject drugs. Adequate methadone dosing is important in retaining clients to maximize HIV treatment benefits and allow for successful linkage to services.

Impact Of A Brief Patient and Provider Intervention To Improve the Quality Of Communication About Medication Adherence Among HIV Patients Beach MC, Roter DL, Saha S, Korthuis PT, Eggly S, Cohn J, Sharp V, Moore RD, Wilson IB. Patient Educ Couns. 2015; 98(9): 1078-1083.
Medication adherence is essential in HIV care, yet provider communication about adherence is often suboptimal. The authors designed this study to improve patient-provider communication about HIV medication adherence. They randomized 26 providers at three HIV care sites to receive or not receive a one-hour communication skills training based on motivational interviewing principles applied to medication adherence. Prior to routine office visits, non-adherent patients of providers who received the training were coached to discuss adherence with their providers. Patients of providers who did not receive the training providers were not coached. The authors audio-recorded and coded patient-provider interactions using the roter interaction analysis system (RIAS). There was more dialogue about therapeutic regimen in visits with intervention patients and providers (167 vs 128, respectively, p=.004), with the majority of statements coming from providers. These visits also included more brainstorming solutions to non-adherence (41% vs. 22%, p=0.026). Intervention compared with control visit providers engaged in more positive talk (44 vs. 38 statements, p=0.039), emotional talk (26 vs. 18 statements, p<0.001), and probing of patient opinion (3 vs. 2 statements, p=0.009). A brief provider training combined with patient coaching sessions, improved provider communication behaviors and increased dialogue regarding medication adherence.

Intersectionality Of Internalized HIV Stigma and Internalized Substance Use Stigma: Implications For Depressive Symptoms Earnshaw VA, Smith LR, Cunningham CO, Copenhaver MM. J Health Psychol. 2015; 20(8): 1083-1089.
The authors adopted an intersectionality framework and examined whether the relationship between internalized HIV stigma and depressive symptoms is moderated by internalized substance use stigma. A total of 85 people living with HIV with a history of substance use in the Bronx, New York, completed a survey. Results revealed evidence of moderation: Participants who internalized HIV stigma experienced greater depressive symptoms only if they also internalized substance use stigma. Researchers should examine stigma associated with multiple socially devalued characteristics to best understand how stigma impacts mental health among people living with HIV. Healthcare providers should address stigma associated with the full range of socially devalued characteristics with which people living with HIV live.

Partner Incarceration and African-American Women's Sexual Relationships and Risk: A Longitudinal Qualitative Study Cooper HLF, Caruso B, Barham T, Embry V, Dauria E, Clark CD, Comfort ML. J Urban Health. 2015; 92(3): 527-547.
Racialized mass incarceration is associated with racial/ethnic disparities in HIV and other sexually transmitted infections (STIs) in the US. The purpose of this longitudinal qualitative study was to learn about the processes through which partner incarceration affects African-American women's sexual risk. Four waves of in-depth qualitative interviews were conducted in 2010-2011 with 30 women in Atlanta, Georgia (US) who had recently incarcerated partners. Approximately half the sample misused substances at baseline. Transcripts were analyzed using grounded theory. For over half the sample (N = 19), partner incarceration resulted in destitution, and half of this group (N = 9) developed new partnerships to secure shelter or food; most misused substances. Other women (N = 9) initiated casual relationships to meet emotional or sexual needs. When considered with past research, these findings suggest that reducing incarceration rates among African-American men may reduce HIV/STIs among African-American women, particularly among substance-misusing

women, as might rapidly linking women with recently incarcerated partners to housing and economic support and drug treatment.

A Randomized Controlled Trial Of Personalized Text Message Reminders To Promote Medication Adherence Among HIV-Positive Adolescents and Young Adults Garofalo R, Kuhns LM, Hotton A, Johnson A, Muldoon A, Rice D. AIDS Behav. 2015.
HIV-positive adolescents and young adults often experience suboptimal medication adherence, yet few interventions to improve adherence in this group have shown evidence of efficacy. The authors conducted a randomized trial of a two-way, personalized daily text messaging intervention to improve adherence to antiretroviral therapy (ART) among N = 105 poorly adherent HIV-positive adolescents and young adults, ages 16-29. Adherence to ART was assessed via self-reported visual analogue scale (VAS; 0-100 %) at 3 and 6-months for mean adherence level and proportion ≥90 % adherent. The average effect estimate over the 6-month intervention period was significant for ≥90 % adherence (OR = 2.12, 95 % CI 1.01-4.45, p < .05) and maintained at 12-months (6 months post-intervention). Satisfaction scores for the intervention were very high. These results suggest both feasibility and initial efficacy of this approach. Given study limitations, additional testing of this intervention as part of a larger clinical trial with objective and/or clinical outcome measures of adherence is warranted.

An Organizational Readiness Intervention and Randomized Controlled Trial To Test Strategies For Implementing Substance Use Disorder Treatment Into Primary Care: SUMMIT Study Protocol Ober AJ, Watkins KE, Hunter SB, Lamp K, Lind M, Setodji CM. Implement Sci. 2015; 10: 66.
Millions of people who need treatment for substance use disorders (SUD) do not receive it. Evidence-based practices for treating SUD exist, and some are appropriate for delivery outside of specialty care settings. Primary care is an opportune setting in which to deliver SUD treatment because many individuals see their primary care providers at least once a year. Further, the Patient Protection and Affordable Care Act (PPACA) increases coverage for SUD treatment and is increasing the number of individuals seeking primary care services. In this article, the authors present the protocol for a study testing the effects of an organizational readiness and service delivery intervention on increasing the uptake of SUD treatment in primary care and on patient outcomes. In a randomized controlled trial, they test the combined effects of an organizational readiness intervention consisting of implementation tools and activities and an integrated collaborative care service delivery intervention based on the Chronic Care Model on service system (patient-centered care, utilization of substance use disorder treatment, utilization of health care services and adoption and sustainability of evidence-based practices) and patient (substance use, consequences of use, health and mental health, and satisfaction with care) outcomes. The authors also use a repeated measures design to test organizational changes throughout the study, such as acceptability, appropriateness and feasibility of the practices to providers, and provider intention to adopt the practices. They use provider focus groups, provider and patient surveys, and administrative data to measure outcomes. The present study responds to critical gaps in health care services for people with substance use disorders, including the need for greater access to SUD treatment and greater uptake of evidence-based practices in primary care. The authors designed a multi-level study that combines implementation tools to increase organizational readiness to adopt and sustain evidence-based practices (EBPs) and tests the effectiveness of a service delivery intervention on service system and patient outcomes related to SUD services.

Harm Reduction Agencies As A Potential Site For Buprenorphine Treatment Fox AD, Chamberlain A, Frost T, Cunningham CO. Subst Abus. 2015; 36(2): 155-160.
Harm reduction agencies complement addiction treatment by providing diverse services that improve the health of people who use drugs. Buprenorphine maintenance treatment (BMT) is an effective opioid addiction treatment that may be provided from flexible settings, potentially including harm reduction agencies. This study investigated attitudes toward different potential sites for BMT (harm reduction agencies, general medical clinics, and drug treatment programs) among harm reduction clients. Using computer-based interviews, participants indicated preferred potential site for BMT (harm reduction agency, drug treatment program, or general medical clinic), interest in BMT by potential site, motivation for treatment, and barriers to BMT. Multivariable logistic regression was used to determine factors associated with harm reduction agency preference. Of 102 opioid users, the most preferred potential site for BMT was a harm reduction agency (51%), whereas fewer preferred general medical clinics (13%), drug treatment programs (12%), or were not interested in BMT (25%). In multivariable analysis, experiencing ≥1 barrier to BMT was strongly associated with preferring harm reduction agencies (adjusted odds ratio [aOR] = 3.39, 95% confidence interval [CI]: 1.00-11.43). The potential to initiate BMT at harm reduction agencies is highly favorable among harm reduction clients, especially among those experiencing barriers to BMT. Offering BMT at harm reduction agencies could improve access to treatment, but studies are needed to determine safety and efficacy of this approach.

Gender Differences In Mortality Among Treated Opioid Dependent Patients Evans E, Kelleghan A, Li L, Min J, Huang D, Urada D, Hser YI, Nosyk B. Drug Alcohol Depend. 2015; 155(): 228-235.
To assess gender differences in characteristics, mortality rates, and the causes and predictors of death among treated opioid-dependent individuals. Linked vital statistics data were obtained for all individuals first enrolled in publicly funded pharmacological treatment for opioid dependence in California from 2006 to 2010. Standardized mortality ratios (SMR) were calculated by gender. Cox proportional hazards models with time-varying covariates were fitted to determine the effect of gender on the hazard of all-cause mortality, controlling for covariates. Over a median 2.6 years (interquartile range: 1.4-3.7), 1.031 deaths were observed, including 2.2% (259/11,564) of women and 3.7% (772/20,758) of men. Women had a greater increased risk of mortality compared to the general population (SMR 5.1 95% CI: 4.5, 5.7) than men (SMR 4.3 95% CI: 4.0, 4.6). The relative risk of death for women compared with men was 1.18 (95% CI: 1.02, 1.36). Women had a lower instantaneous hazard of all-cause mortality than men (HR 0.58, 95% CI 0.50, 0.68), controlling for other factors. Significant interaction effects indicated that among men, mortality risk was decreased by full-time employment and increased by non-daily heroin use (relative to daily use) and medical problems. Concurrent opioid and methamphetamine/cocaine use increased mortality risk among women and decreased it among men. Treatment for opioid dependence is likely to reduce mortality risk among men by addressing employment and medical problems, and via interventions to reduce overdose risk after heroin abstinence, and among women by attending to the concurrent use of methamphetamine/cocaine and opioids.

A Multicomponent Intervention To Improve Primary Care Provider Adherence To Chronic Opioid Therapy Guidelines and Reduce Opioid Misuse: A Cluster Randomized Controlled Trial Protocol Lasser KE, Shanahan C, Parker V, Beers D, Xuan Z, Heymann O, Lange A, Liebschutz JM. J Subst Abuse Treat. 2015.

Prescription opioid misuse is a significant public health problem as well as a patient safety concern. Primary care providers (PCPs) are the leading prescribers of opioids for chronic pain, yet few PCPs follow standard practice guidelines regarding assessment and monitoring. This cluster randomized controlled trial will determine whether four implementation strategies; nurse care management, use of a patient registry, academic detailing, and electronic tools, will increase PCP adherence to chronic opioid therapy guidelines and reduce opioid misuse among patients, relative to electronic tools alone. The implementation strategies and intervention content are based on the chronic care model. The authors include 53 PCPs from three Boston-area community health centers and one urban safety-net hospital-based primary care practice who have at least four patients meeting the following inclusion criteria: 1) age≥18; 2) one or more completed visits to the primary care practice in the past year; 3) long-term opioid treatment defined as three or more opioid prescriptions written at least 21days apart within 6months and 4) an inpatient or outpatient ICD-9-CM diagnosis for musculoskeletal or neuropathic pain. The authors consider PCPs to be study subjects, and obtained a waiver of informed consent for patients because the study is promoting an established standard of care. They enrolled participants (PCPs) from December 2012 through March 2015. PCPs were randomized to receive the intervention, which includes four components: 1) nurse care management, 2) use of a patient registry, 3) academic detailing, and 4) electronic tools, or a control condition, which includes only the use of the electronic tools. The intervention PCPs receive the services of a nurse-managed registry for planning individual patient care and conducting population-based care for patients receiving opioids for chronic pain. In academic detailing visits, trained co-investigators provide intervention PCPs with individualized education to change prescribing practice. Electronic tools, located on a web site external to the EMR, www.mytopcare.org, include validated instruments to assess patient status, and management resources to facilitate PCP adherence to suggested monitoring. Electronic tools are available to PCPs in both study arms. The primary outcomes are PCP adherence to chronic opioid therapy guidelines and patient opioid misuse. Secondary outcomes include measures of substance abuse, possible opioid diversion, and level of opioid risk among patients. The authors will follow PCPs and their estimated 1200 chronic pain patients for 1year after study enrollment. To determine whether the intervention condition achieves greater adherence to guidelines and reduced opioid misuse after 1year compared to the control condition, they will compare the baseline and follow-up measures of the individual patients, stratifying by intervention status and noting differences that are statistically significant at the p=0.05 level. Analyses will be based on intent-to-treat. Randomization resulted in groups with similar baseline characteristics. The ages of PCPs are evenly distributed, with inclusion of both PCPs who have recently completed training and those who have been in practice for more than 20years. Two-thirds of enrolled PCPs are women, and one-third are non-white. The study will determine the impact of this multicomponent intervention on improving PCP adherence to guidelines and reducing opioid misuse among patients.

Buprenorphine Dose Induction In Non-Opioid-Tolerant Pre-Release Prisoners Vocci FJ, Schwartz RP, Wilson ME, Gordon MS, Kinlock TW, Fitzgerald TT, O'Grady KE, Jaffe JH. Drug Alcohol Depend. 2015.

In a previously reported randomized controlled trial, formerly opioid-dependent prisoners were more likely to enter community drug abuse treatment when they were inducted in prison onto

buprenorphine/naloxone (hereafter called buprenorphine) than when they received counseling without buprenorphine in prison (47.5% vs. 33.7%, p=0.012) (Gordon et al., 2014). In this communication the authors report on the results of the induction schedule and the adverse event profile seen in pre-release prisoners inducted onto buprenorphine. This paper examines the dose induction procedure, a comparison of the proposed versus actual doses given per week, and side effects reported for 104 adult participants who were randomized to buprenorphine treatment in prison. Self-reported side effects were analyzed using generalized estimated equations to determine changes over time in side effects. Study participants were inducted onto buprenorphine at a rate faster than the induction schedule. Of the 104 (72 males, 32 females) buprenorphine recipients, 64 (37 males, 27 females) remained on medication at release from prison. Nine participants (8.6%) discontinued buprenorphine because of unpleasant opioid side effects. There were no serious adverse events reported during the in-prison phase of the study. Constipation was the most frequent symptom reported (69 percent). These findings suggest that buprenorphine administered to non-opioid-tolerant adults should be started at a lower, individualized dose than customarily used for adults actively using opioids, and that non-opioid-tolerant pre-release prisoners can be successfully inducted onto therapeutic doses prior to release.

CTN-RELATED RESEARCH

Hispanic Subgroups, Acculturation, and Substance Abuse Treatment Outcomes Chartier KG, Carmody T, Akhtar M, Stebbins MB, Walters ST, Warden D. J Subst Abuse Treat. 2015 Dec;59:74-82. Epub 2015 Jul 26.
This study explored Hispanic subgroup differences in substance use treatment outcomes, and the relationship of acculturation characteristics to these outcomes. Data were from a multisite randomized clinical trial of motivational enhancement therapy versus treatment as usual in a sample of Spanish-speaking substance abusers. Participants were Cuban American (n=34), Mexican American (n=209), Puerto Rican (n=78), and other Hispanic American (n=54). Results suggested that Cuban Americans and individuals with more connection to Hispanic culture had lower treatment retention. Hispanics born in the U.S and those who spoke English at home had a lower percentage of days abstinent during weeks 5-16, although Puerto Ricans born in the U.S. and Cuban Americans living more years in the U.S. had a higher percentage of days abstinent in weeks 1-4 and 5-16, respectively. Results may inform future hypothesis-driven studies in larger Hispanic treatment seeking samples of the relationship between acculturation and treatment outcome.

Long-Term Outcomes After Randomization To Buprenorphine/Naloxone Versus Methadone In A Multi-Site Trial Hser YI, Evans E, Huang D, Weiss R, Saxon A, Carroll KM, Woody G, Liu D, Wakim P, Matthews AG, Hatch-Maillette M, Jelstrom E, Wiest K, McLaughlin P, Ling W. Addiction. 2015 Nov 24. [Epub ahead of print].
The aims of the present study were to compare long-term outcomes among participants randomized to buprenorphine or methadone. Follow-up was conducted in 2011-2014 of 1,080 opioid-dependent participants entering 7 opioid treatment programs in the USA between 2006 and 2009 and randomized (within each program) to receive open-label buprenorphine/naloxone or methadone for up to 24 weeks; 795 participants completed in-person interviews (~74% follow-up interview rate) covering on average 4.5 years. Outcomes were indicated by mortality and opioid use. Covariates included demographics, site, cocaine use, and treatment experiences. Mortality was not different between the two randomized conditions with 23 (3.6%) of 630 participants randomized to buprenorphine having died, versus 26 (5.8%) of 450 participants randomized to methadone. Opioid use at follow-up was higher among participants randomized to buprenorphine relative to methadone (42.8% vs. 31.7% positive opioid urine specimens, $p < .01$, effect size (h) = 0.23 [0.09, 0.38]; 5.8 days vs. 4.4 days of past 30-day heroin use, $p < .05$, effect size (d) = 0.14 [0.00, 0.28]). Opioid use over the follow-up period by randomization condition was also significant ($F(7,39600) = 3.16$; $p < .001$) mostly due to less treatment participation among participants randomized to buprenorphine than methadone. Less opioid use was associated with both buprenorphine and methadone treatment (relative to no treatment); no difference was found between the two treatments. Individuals who are white or used cocaine at baseline responded better to methadone than to buprenorphine. The authors conclude that there are few differences in long-term outcomes between buprenorphine and methadone treatment for opioid dependence, and treatment with each medication is associated with a strong reduction in opioid use.

Depressive Symptoms and Associated Clinical Characteristics in Outpatients Seeking Community-Based Treatment for Alcohol and Drug Problems Sanchez K, Walker R, Campbell AN, Greer TL, Hu MC, Grannemann BD, Nunes EV, Trivedi MH. Subst Abus. 2015;36(3):297-303. Epub 2014 Aug 1.
Comorbid psychiatric and substance use disorders are common and associated with poorer treatment engagement, retention, and outcomes. This study examines the presence of depressive symptoms and the demographic and clinical correlates in a diverse sample of substance abuse treatment seekers to better characterize patients with co-occurring depressive symptoms and substance use disorders and understand potential treatment needs. Baseline data from a randomized clinical effectiveness trial of a computer-assisted, Web-delivered psychosocial intervention were analyzed. Participants (N = 507) were recruited from 10 geographically diverse outpatient drug treatment programs. Assessments included the self-report Patient Health Questionnaire, and measures of coping strategies, social functioning, physical health status, and substance use. One fifth (21%; n = 106) of the sample screened positive for depression; those screening positive for depression were significantly more likely to screen positive for anxiety (66.9%) and posttraumatic stress disorder (PTSD; 42.9%). After controlling for anxiety and PTSD symptoms, presence of depressive symptoms remained significantly associated with fewer coping strategies (P = .001), greater impairment in social adjustment (P < .001), and poorer health status (P < .001), but not to days of drug use in the last 90 days (P = .14). Depression is a clinically significant problem among substance abusers, and, in this study, patients who screened positive for depression were more likely to have co-occurring symptoms of anxiety and PTSD. Additionally, the presence of depressive symptoms was associated with fewer coping strategies and poorer social adjustment. Coping skills are a significant predictor of addiction outcomes, and it may be especially important to screen for and enhance coping among depressed patients. Evidence-based interventions that target coping skills and global functioning among substance abusers with depressive symptoms may be important adjuncts to usual treatment.

Substance Use, Depression and Sociodemographic Determinants of HIV Sexual Risk Behavior in Outpatient Substance Abuse Treatment Patients Tross S, Feaster DJ, Thorens G, Duan R, Gomez Z, Pavlicova M, Hu MC, Kyle T, Erickson S, Spector A, Haynes L, Metsch LR. J Addict Med. 2015 Dec;9(6):457-463.
The NIDA Clinical Trials Network trial of rapid HIV testing/counseling in 1281 patients was a unique opportunity to examine relationships among substance use, depressive symptoms, and sex risk behavior. Past 6-month substance use; substance use severity (Drug Abuse Screening Test - 10); depressive symptoms (Quick Inventory of Depressive Symptomatology); and three types of sex risk behavior (unprotected sex occasions [USOs] with primary partners; USOs with nonprimary partners; and USOs while high/drunk) were assessed. Zero-inflated negative binomial analyses provided: probability and rate of sex risk behavior (in risk behavior subsample). Levels of sexual risk behavior were high, while variable across the three types of sex risk behaviors. Among the patients, 50.4% had engaged in USOs with primary partners, 42% in sex while drunk or high, and 23.8% in USOs with nonprimary partners. Similar factors were significantly associated with all three types of sex risk behaviors. For all types, problem drinking, cocaine use, and substance use severity had an exacerbating effect. Older age was associated with lower risk behavior; other relationship categories (eg, married, separated/divorced, cohabitating) were associated with greater risk behavior than was single status. Depressive symptoms were associated with decreased likelihood of USOs with a primary partner. Sexual risk behavior is common among individuals in outpatient substance abuse treatment. Results highlight problem drinking (eg, up to three-fold) and

cocaine (eg, up to twice) in increasing sex risk behavior. They demonstrate the utility of distinguishing between partner types and presence/absence of alcohol/drugs during sex. Findings argue for the need to integrate sex risk reduction into drug treatment.

Substance Use and Mental Diagnoses Among Adults With and Without Type 2 Diabetes: Results From Electronic Health Records Data Wu LT, Ghitza UE, Batch BC, Pencina MJ, Rojas LF, Goldstein BA, Schibler T, Dunham AA, Rusincovitch S, Brady KT. Drug Alcohol Depend. 2015 Nov 1;156:162-9. Epub 2015 Sep 12.
Comorbid diabetes and substance use diagnoses (SUD) represent a hazardous combination, both in terms of healthcare cost and morbidity. To date, there is limited information about the association of SUD and related mental disorders with type 2 diabetes mellitus (T2DM). The authors examined the associations between T2DM and multiple psychiatric diagnosis categories, with a focus on SUD and related psychiatric comorbidities among adults with T2DM. They analyzed electronic health record (EHR) data on 170,853 unique adults aged ≥18 years from the EHR warehouse of a large academic healthcare system. Logistic regression analyses were conducted to estimate the strength of an association for comorbidities. Overall, 9% of adults (n=16,243) had T2DM. Blacks, Hispanics, Asians, and Native Americans had greater odds of having T2DM than whites. All 10 psychiatric diagnosis categories were more prevalent among adults with T2DM than among those without T2DM. Prevalent diagnoses among adults with T2MD were mood (21.22%), SUD (17.02%: tobacco 13.25%, alcohol 4.00%, drugs 4.22%), and anxiety diagnoses (13.98%). Among adults with T2DM, SUD was positively associated with mood, anxiety, personality, somatic, and schizophrenia diagnoses. The authors examined a large diverse sample of individuals and found clinical evidence of SUD and psychiatric comorbidities among adults with T2DM. These results highlight the need to identify feasible collaborative care models for adults with T2DM and SUD related psychiatric comorbidities, particularly in primary care settings, that will improve behavioral health and reduce health risk.

Presence or Absence of QTc Prolongation in Buprenorphine-Naloxone Among Youth With Opioid Dependence Poole SA, Pecoraro A, Subramaniam G, Woody G, Vetter VL. J Addict Med. 2015 Dec 17. [Epub ahead of print].
The aim of the study was to evaluate buprenorphine-naloxone effects on the QTc in youth with opioid dependence. Buprenorphine is a partial agonist that is an effective treatment for opioid dependence. Compared with methadone, it has a lower risk of QTc prolongation in adults, but is less studied in the youth. It may also reduce the risk of torsades de pointes (TdP)-an uncommon variant of polymorphic ventricular tachycardia-that can result in syncope, ventricular fibrillation, and sudden death. Secondary analysis of the electrocardiogram data from 95 individuals who participated in a multisite trial for youth with opioid dependence. The participants were randomized to a 2-week (DETOX) or a 12-week course of buprenorphine-naloxone (BUP). At baseline, 12-lead electrocardiograms were done at weeks 4 and 12, and QTc intervals were hand-measured and calculated using Bazett formula. Increases above 60 milliseconds were considered clinically significant, and readings above 450 milliseconds (in men) and 470 milliseconds (in women) indicated a prolonged QTc. Mean QTc intervals were higher for BUP than for DETOX participants at baseline, week 4, and week 12 ($P = 0.045$), and women had longer mean QTc intervals than men ($P < 0.0005$). Variations in the QTc intervals were observed in some; however, none were above 500 milliseconds-the level at which risk for TdP becomes more significant. In this randomized trial, the mean QTc at baseline, before randomization, was higher in BUP than in DETOX patients. Minimal changes in the QTc were seen at 4 and 12 weeks in a few patients in both groups. There

was no evidence that buprenorphine-naloxone alone increased the QTc to a level that increased the risk for TdP.

An Application of Analyzing the Trajectories of Two Disorders: A Parallel Piecewise Growth Model of Substance Use and Attention-Deficit/Hyperactivity Disorder Mamey MR, Barbosa-Leiker C, McPherson S, Burns GL, Parks C, Roll J. Exp Clin Psychopharmacol. 2015 Dec; 23(6):422-427. Epub 2015 Sep 21.
Researchers often want to examine 2 comorbid conditions simultaneously. One strategy to do so is through the use of parallel latent growth curve modeling (LGCM). This statistical technique allows for the simultaneous evaluation of 2 disorders to determine the explanations and predictors of change over time. Additionally, a piecewise model can help identify whether there are more than 2 growth processes within each disorder (e.g., during a clinical trial). A parallel piecewise LGCM was applied to self-reported attention-deficit/hyperactivity disorder (ADHD) and self-reported substance use symptoms in 303 adolescents enrolled in cognitive-behavioral therapy treatment for a substance use disorder and receiving either oral-methylphenidate or placebo for ADHD across 16 weeks. Assessing these 2 disorders concurrently allowed us to determine whether elevated levels of 1 disorder predicted elevated levels or increased risk of the other disorder. First, a piecewise growth model measured ADHD and substance use separately. Next, a parallel piecewise LGCM was used to estimate the regressions across disorders to determine whether higher scores at baseline of the disorders (i.e., ADHD or substance use disorder) predicted rates of change in the related disorder. Finally, treatment was added to the model to predict change. While the analyses revealed no significant relationships across disorders, this study explains and applies a parallel piecewise growth model to examine the developmental processes of comorbid conditions over the course of a clinical trial. Strengths of piecewise and parallel LGCMs for other addictions researchers interested in examining dual processes over time are discussed.

Exploring The Relationship Between Eating Disorder Symptoms and Substance Use Severity In Women With Comorbid PTSD And Substance Use Disorders Killeen T, Brewerton TD, Campbell A, Cohen LR, Hien DA. Am J Drug Alcohol Abuse. 2015 Nov;41(6):547-552. Epub 2015 Sep 14.
Eating disorders (ED) and substance use disorders (SUD) commonly co-occur, especially in conjunction with posttraumatic stress disorder (PTSD), yet little is known about ED and ED symptoms in women presenting to addiction treatment programs. The authors examined the association between ED symptoms and substance use frequency and severity in a sample of women with a DSM IV diagnosis of current SUD and PTSD enrolled in SUD treatment. Participants were 122 women from four substance abuse treatment sites who participated in a multi-site clinical trial through the National Institute of Drug Abuse Clinical Trials Network (NIDA CTN). The Eating Disorder Examination-Questionnaire (EDE-Q), the Clinician's Administered PTSD Scale (CAPS) and the Addiction Severity Index (ASI) were administered at baseline and correlational analyses were performed. Variables that significantly correlated with EDE-Q total and subscale scores were entered into a linear regression analysis. Scores on the EDE-Q Global scale, as well as the Eating Concern, Weight Concern and Shape Concern subscales of the EDE-Q were significantly associated with Caucasian race/ethnicity, past 30 day opiate use, higher ASI Psychiatric Subscale score and lower ASI Employment Subscale score. Although exploratory, these findings suggest that there may be a relationship between addiction severity, use of certain drugs of abuse and eating disorder symptoms, particularly those involving weight and shape concerns in women with comorbid PTSD and SUD.

Using E-Technologies In Clinical Trials Rosa C, Campbell AN, Miele GM, Brunner M, Winstanley EL. Contemp Clin Trials. 2015 Nov; 45(Pt A): 41-54. Epub 2015 Jul 12.
Clinical trials have been slow to incorporate e-technology (digital and electronic technology that utilizes mobile devices or the Internet) into the design and execution of studies. In the meantime, individuals and corporations are relying more on electronic platforms and most have incorporated such technology into their daily lives. This paper provides a general overview of the use of e-technologies in clinical trials research, specifically within the last decade, marked by rapid growth of mobile and Internet-based tools. Benefits of and challenges to the use of e-technologies in data collection, recruitment and retention, delivery of interventions, and dissemination are provided, as well as a description of the current status of regulatory oversight of e-technologies in clinical trials research. As an example of ways in which e-technologies can be used for intervention delivery, a summary of e-technologies for treatment of substance use disorders is presented. Using e-technologies to design and implement clinical trials has the potential to reach a wide audience, making trials more efficient while also reducing costs; however, researchers should be cautious when adopting these tools given the many challenges in using new technologies, as well as threats to participant privacy/confidentiality. Challenges of using e-technologies can be overcome with careful planning, useful partnerships, and forethought. The role of web- and smartphone-based applications is expanding, and the increasing use of those platforms by scientists and the public alike make them tools that cannot be ignored.

Using Electronic Health Record Data For Substance Use Screening, Brief Intervention, and Referral To Treatment Among Adults With Type 2 Diabetes: Design Of A National Drug Abuse Treatment Clinical Trials Network Study Wu LT, Brady KT, Spratt SE, Dunham AA, Heidenfelder B, Batch BC, Lindblad R, VanVeldhuisen P, Rusincovitch SA, Killeen TK, Ghitza UE. Contemp Clin Trials. 2015 Nov 10;46:30-38. [Epub ahead of print].
The Affordable Care Act encourages healthcare systems to integrate behavioral and medical healthcare, as well as to employ electronic health records (EHRs) for health information exchange and quality improvement. Pragmatic research paradigms that employ EHRs in research are needed to produce clinical evidence in real-world medical settings for informing learning healthcare systems. Adults with comorbid diabetes and substance use disorders (SUDs) tend to use costly inpatient treatments; however, there is a lack of empirical data on implementing behavioral healthcare to reduce health risk in adults with high-risk diabetes. Given the complexity of high-risk patients' medical problems and the cost of conducting randomized trials, a feasibility project is warranted to guide practical study designs. The authors describe the study design, which explores the feasibility of implementing substance use Screening, Brief Intervention, and Referral to Treatment (SBIRT) among adults with high-risk type 2 diabetes mellitus (T2DM) within a home-based primary care setting. This study includes the development of an integrated EHR datamart to identify eligible patients and collect diabetes healthcare data, and the use of a geographic health information system to understand the social context in patients' communities. Analysis will examine recruitment, proportion of patients receiving brief intervention and/or referrals, substance use, SUD treatment use, diabetes outcomes, and retention. By capitalizing on an existing T2DM project that uses home-based primary care, our study results will provide timely clinical information to inform the designs and implementation of future SBIRT studies among adults with multiple medical conditions.

Treatment Outcomes In Opioid Dependent Patients With Different Buprenorphine/Naloxone Induction Dosing Patterns and Trajectories Jacobs P, Ang A, Hillhouse MP, Saxon AJ, Nielsen S, Wakim PG, Mai BE, Mooney LJ, S Potter J, Blaine JD. Am J Addict. 2015 Oct; 24(7):667-675. Epub 2015 Sep 24.
Induction is a crucial period of opioid addiction treatment. This study aimed to identify buprenorphine/naloxone (BUP) induction patterns and examine their association with outcomes (opioid use, retention, and related adverse events [AEs]). The secondary analysis of a study of opioid-dependent adults seeking treatment in eight treatment settings included 740 participants inducted on BUP with flexible dosing. Latent class analysis models detected six distinctive induction trajectories: bup1-started and remained on low; bup2-started low, shifted slowly to moderate; bup3-started low, shifted quickly to moderate; bup4-started high, shifted to low; bup5-started and remained on moderate; bup6-started moderate, shifted to high dose. Baseline characteristics, including Clinical Opioid Withdrawal Scale (COWS), were important predictors of retention. When controlled for the baseline characteristics, bup6 participants were three times less likely to drop out the first 7 days than bup1 participants (adjusted hazard ratio (aHR) = .28, p = .03). Opioid use and AEs were similar across trajectories. Participants on ≥16 mg BUP compared to those on <16 mg at Day 28 were less likely to drop out (aHR = .013, p = .001) and less likely to have AEs during the first 28 days (aOR = .57, p = .03). BUP induction dosing was guided by an objective measure of opioid withdrawal. Participants with higher baseline COWS whose BUP doses were raised more quickly were less likely to drop out in the first 7 days than those whose doses were raised slower. This study supports the use of an objective measure of opioid withdrawal (COWS) during BUP induction to improve retention early in treatment.

Examining Longitudinal Stimulant Use and Treatment Attendance as Parallel Outcomes in Two Contingency Management Randomized Clinical Trials McPherson S, Brooks O, Barbosa-Leiker C, Lederhos C, Lamp A, Murphy S, Layton M, Roll J. J Subst Abuse Treat. 2016 Feb;61:18-25. Epub 2015 Sep 21.
The primary aim of this study was to examine stimulant use and longitudinal treatment attendance in one 'parallel outcomes' model in order to determine how these two outcomes are related to one another during treatment, and to quantify how the intervention impacts these two on- and off-target outcomes differently. Data came from two multi-site randomized clinical trials (RCTs) of contingency management (CM) that targeted stimulant use. The authors used parallel multilevel modeling to examine the impact of multiple pre-specified covariates, including selected Addiction Severity Index (ASI) scores, age and sex, in addition to CM on concurrent attendance and stimulant use in two separate analyses, i.e., one per trial. In one trial, CM was positively associated with attending treatment throughout the trial (β=0.060, $p<0.05$). In the second trial, CM predicted negative urinalysis (¯UA) over the 12-week treatment period (β=0.069, $p<0.05$). In both trials, there was a significant, positive relationship between attendance and ¯UA submission, but in the first trial a ¯UA at both baseline and over time was related to attendance over time (r=0.117; r=0.013, respectively) and in the second trial, a ¯UA submission at baseline was associated with increased attendance over time (r=0.055). These findings indicate that stimulant use and treatment attendance over time are related but distinct outcomes that, when analyzed simultaneously, portray a more informative picture of their predictors and the separate trajectories of each. This 'indirect reinforcement' between two clinically meaningful on-target (directly reinforced behavior) and off-target (indirectly reinforced behavior) outcomes is in need of further examination in order to fully exploit the potential clinical benefits that could be realized in substance use disorder treatment trials.

Treatment Strategy Profiles In Substance Use Disorder Treatment Programs: A Latent Class Analysis Edmond MB, Aletraris L, Paino M, Roman PM. Drug Alcohol Depend. 2015 Aug 1;153:109-15. Epub 2015 Jun 9.

Modern treatment options for substance use disorder are diverse. While studies have analyzed the adoption of individual evidence-based practices in treatment centers, little is known about the specific make-up of treatment strategy profiles in treatment centers throughout the United States. The current study used latent class analysis to profile underlying treatment strategies and to evaluate philosophical and structural supports associated with each profile. Utilizing three aggregated and secondary datasets of nationally representative samples of substance use disorder treatment centers (N=775), we employed latent class analysis to determine treatment strategy profiles. Using multinomial logistic regression, we then examined organizational characteristics associated with each profile. The authors found three distinct treatment strategy profiles: centers that primarily relied on motivational interviewing and motivational enhancement therapy, centers that utilized psychosocial and alternative therapies, and centers that employed comprehensive treatments including pharmacotherapy. The multinomial logistic regression revealed that philosophical and structural center characteristics were associated with membership in the comprehensive class. Centers with philosophical orientations conducive to holistic care and pharmacotherapy-acceptance, resource-rich infrastructures, and an entrepreneurial reliance on insured clients were more likely to offer diverse interventions. All associations were significant at the .05 level. The findings from this study help us understand the general strategies of treatment centers. From a practical perspective, practitioners and clients should be aware of the variation in treatment center practices where they may offer or receive treatment.

Technology Transfer for the Implementation of a Clinical Trials Network on Drug Abuse and Mental Health Treatment in Mexico Horigian VE, Marín-Navarrete RA, Verdeja RE, Alonso E, Perez MA, Fernández-Mondragón J, Berlanga C, Medina-Mora ME, Szapocznik J. PAJPH. 2015; 38(3): 233–242.

Low- and middle-income countries (LMIC) lack the research infrastructure and capacity to conduct rigorous substance abuse and mental health effectiveness clinical trials to guide clinical practice. A partnership between the Florida Node Alliance of the United States National Drug Abuse Treatment Clinical Trials Network and the National Institute of Psychiatry in Mexico was established in 2011 to improve substance abuse practice in Mexico. The purpose of this partnership was to develop a Mexican national clinical trials network of substance abuse researchers and providers capable of implementing effectiveness randomized clinical trials in community-based settings. A technology transfer model was implemented and ran from 2011–2013. The Florida Node Alliance shared the "know how" for the development of the research infrastructure to implement randomized clinical trials in community programs through core and specific training modules, role-specific coaching, pairings, modeling, monitoring, and feedback. The technology transfer process was bi-directional in nature in that it was informed by feedback on feasibility and cultural appropriateness for the context in which practices were implemented. The Institute, in turn, led the effort to create the national network of researchers and practitioners in Mexico and the implementation of the first trial. A collaborative model of technology transfer was useful in creating a Mexican researcher-provider network that is capable of changing national practice in substance abuse research and treatment. Key considerations for transnational technology transfer are presented.

Self-Report After Randomly Assigned Supervision Does not Predict Ability to Practice Motivational Interviewing Wain RM, Kutner BA, Smith JL, Carpenter KM, Hu MC, Amrhein PC, Nunes EV. J Subst Abuse Treat. 2015 Oct; 57:96-101. Epub 2015 Apr 14.
The objective of this study was to investigate the relation between self-report and objective assessment of motivational interviewing (MI) skills following training and supervision. After an MI workshop, 96 clinicians from 26 community programs (age 21-68, 65% female, 40.8% Black, 29.6% Caucasian, 24.5% Hispanic, 2.0% Asian, 3.1% other) were randomized to supervision (tele-conferencing or tape-based), or workshop only. At four time points, trainees completed a self-report of MI skill, using items from the MI understanding questionnaire (MIU), and were objectively assessed by raters using the Motivational Interviewing Treatment Integrity (MITI) system. Correlations were calculated between MIU and MITI scores. A generalized linear mixed model was tested on MIU scores, with MITI scores, supervision condition and time as independent variables. MIU scores increased from pre-workshop (mean = 4.74, SD = 1.79) to post-workshop (mean = 6.31, SD = 1.03) ($t = 8.69$, $p < .0001$). With supervision, scores continued to increase, from post-workshop to week 8 (mean = 7.07, SD = 0.91, $t = 5.60$, $p < .0001$) and from week 8 to week 20 (mean = 7.28, SD = 0.94, $t = 2.43$, $p = .02$). However, MIU scores did not significantly correlate with MITI scores, with or without supervision. Self-reported ability increased with supervision, but self-report was not an indicator of objectively measured skill. This suggests that training does not increase correspondence between self-report and objective assessment, so community treatment programs should not rely on clinician self-report to assess the need for ongoing training and supervision and it may be necessary to train clinicians to accurately assess their own skill.

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 Jun;24(4):336-40. Epub 2015 Feb 17.
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.

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. 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.

INTRAMURAL RESEARCH

Molecular Targets and Medications Discovery Branch
Medicinal Chemistry Section

Binding Mode Selection Determines the Action Of Ecstasy Homologs At Monoamine Transporters Sandtner W, Stockner T, Hasenhuetl PS, Partilla JS, Seddik A, Zhang Y-W, Cao J, Holy M, Steinkellner T, Rudnick G, Baumann MH, Ecker GF, Newman AH, Sitte HH. Mol Pharmacol 2015, e-pub October 30, 2015.

Determining the structural elements that define substrates and inhibitors at the monoamine transporters is critical to elucidating mechanisms underlying these disparate functions. In this study, the authors addressed this structure-activity question directly by generating a series of N-substituted-3,4-methylenedioxyamphetamine analogs that differ only in the number of methyl substituents on the terminal amine group. Starting with 3,4,-methylenedioxy-N-methylamphetamine (MDMA), 3,4-methylenedioxy-N,N-dimethylamphetamine (MDDMA) and 3,4,-methylenedioxy-N,N,N-trimethylamphetamine (MDTMA) were prepared. The authors evaluated functional activities of the compounds at all three monoamine transporters in native brain tissue and in cells expressing transporters, and used ligand docking to generate models of the respective protein-ligand complexes. This approach allowed us to relate experimental findings to available structural information. The results suggest that the 3,4-methylenedioxy amphetamine analogs bind at the monoamine transporter orthosteric binding site by adopting one of two mutually exclusive binding modes. MDA and MDMA adopt a high-affinity binding mode, whereas MDDMA and MDTMA adopt a low-affinity binding mode in which the ligand orientation is inverted. Importantly, MDDMA can alternate between both binding modes while MDTMA exclusively binds to the low affinity mode. The authors' experimental results are consistent with the idea that the initial orientation of bound ligands is critical for subsequent interactions that lead to transporter conformational changes and substrate translocation.

High Affinity Dopamine D3 Receptor (D3R)-Selective Antagonists Attenuate Heroin Self-Administration In Wildtype But Not D3R Knockout Mice Boateng CA, Bakare OM, Zhan J, Banala AK, Burzynski C, Pommier E, Keck TM, Donthamsetti P, Javitch JA, Rais R, Slusher BS, Xi Z-X, Newman AH J Med Chem 2015; 58(15): 6195-6213.

The dopamine D3 receptor (D3R) is a promising target for the development of pharmacotherapeutics to treat substance use disorders. Several D3R-selective antagonists are effective in animal models of drug abuse, especially in models of relapse. Nevertheless, poor bioavailability, metabolic instability, and/or predicted toxicity have impeded success in translating these drug candidates to clinical use. Herein, the authors report a series of D3R-selective 4-phenylpiperazines with improved metabolic stability. A subset of these compounds was evaluated for D3R functional efficacy and off target binding at selected 5-HT receptor subtypes, where significant overlap in SAR with D3R has been observed. Several high affinity D3R antagonists, including compounds 16 (Ki = 0.12 nM) and 32 (Ki = 0.35 nM), showed improved metabolic stability compared to the parent compound, PG648 (6). Notably, 16 and the classic D3R antagonist SB277011A (2) were effective in reducing self-administration of heroin in wildtype but not D3R knockout mice.

Clinical Pharmacology and Therapeutics Research Branch
Chemistry and Drug Metabolism Section

Cocaine and Metabolites Concentrations In Dried Blood Spots and Venous Blood After Controlled Intravenous Administration Ellefsen KN, da Costa JL, Concheiro M, Anizan S, Barnes AJ, Pirard S, Gorelick DA, Huestis MA. Bioanalysis. 2015; 7(16): 2041-2056.
Dried blood spots (DBS) are an increasingly common clinical matrix. Sensitive and specific methods for DBS and venous blood cocaine and metabolite detection by liquid chromatography-high resolution mass spectrometry (LC-HRMS) and two dimensional-gas chromatography-mass spectrometry (2D-GC-MS), respectively, were validated to examine correlation between concentrations following controlled intravenous cocaine administration. Linear ranges from 1-200 µg/L were achieved, with acceptable bias and imprecision. Authentic matched specimens' (392 DBS, 97 venous blood) cocaine and benzoylecgonine concentrations were qualitatively similar, but DBS had much greater variability (21.4-105.9 % coefficient of variation (CV)) and were lower than in blood. Conclusion: DBS offer advantages for monitoring cocaine intake; however, differences between capillary and venous blood and DBS concentration variability must be addressed.

In Silico Prediction, Metabolic Stability, and Metabolite Identification By Human Hepatocytes and High Resolution-Mass Spectrometry Ellefsen KN, Wohlfarth A, Swortwood MJ, Diao X, Concheiro M, Huestis MA. Forensic Toxicology. 2015, e-pub Oct 1, 2015.
Novel psychoactive substances are continuously developed to circumvent legislative and regulatory efforts. A new synthetic cathinone, 4-methoxy-a-PVP, was identified for the first time in illegal products; however, the metabolism of this compound is not known. Complete metabolic profiles are needed for these novel psychoactive substances to enable identification of their intake and to link adverse effects to the causative agent. This study assessed 4-methoxy-a-PVP metabolic stability with human liver microsomes (HLMs) and identified its metabolites after HLM and hepatocyte incubations followed by high-resolution mass spectrometry (HRMS). A Thermo QExactive high-resolution mass spectrometer (HRMS) was used with full scan data-dependent mass spectrometry, with (1) and without (2) an inclusion list of predicted metabolite, and with full scan and all-ion fragmentation (3) to identify potential unexpected metabolites. In silico predictions were performed and compared to in vitro results. Scans were thoroughly mined with different data processing algorithms using WebMetabase (Molecular Discovery). 4-Methoxy-a- PVP exhibited a long half-life of 79.7 min in HLM, with an intrinsic clearance of 8.7 lL min-1 mg-1. In addition, this compound is predicted to be a low-clearance drug with an estimated human hepatic clearance of 8.2 mL min-1 kg-1.

High-Resolution Mass Spectrometry For Characterizing the Metabolism Of Synthetic Cannabinoid THJ-018 and Its 5-Fluoro Analog THJ-2201 After Incubation In Human Hepatocytes Diao X, Wohlfarth A, Pang S, Scheidweiler KB, Huestis MA. Clinical Chemistry, 2015, e-pub Oct 1, 2015.
Despite increasing prevalence of novel psychoactive substances, no human metabolism data are currently available, complicating laboratory documentation of intake in urine samples and assessment of the drugs' pharmacodynamic, pharmacokinetic, and toxicological properties. In 2014, THJ-018 and THJ-2201, synthetic cannabinoid indazole analogs of JWH-018 and AM-2201, were identified, with the National Forensic Laboratory Information System containing 220 THJ-2201 reports. Because of numerous adverse events, the Drug Enforcement Administration listed THJ-2201 as Schedule I in January 2015. The authors used high-resolution mass spectrometry (HR-MS)

(TripleTOF 5600+) to identify optimal metabolite markers after incubating 10 µmol/L THJ-018 and THJ-2201 in human hepatocytes for 3 h. Data were acquired via full scan and information-dependent acquisition triggered product ion scans with mass defect filter. In silico metabolite predictions were performed with MetaSite and compared with metabolites identified in human hepatocytes. Thirteen THJ-018 metabolites were detected, with the major metabolic pathways being hydroxylation on the N-pentyl chain and further oxidation or glucuronidation. For THJ-2201, 27 metabolites were observed, predominantly oxidative defluorination plus subsequent carboxylation or glucuronidation, and glucuronidation of hydroxylated metabolites. Dihydrodiol formation on the naphthalene moiety was observed for both compounds. MetaSite prediction matched well with THJ-018 hepatocyte metabolites but underestimated THJ-2201 oxidative defluorination. With HR-MS for data acquisition and processing, the authors characterized THJ-018 and THJ-2201 metabolism in human hepatocytes and suggest appropriate markers for laboratories to identify THJ-018 and THJ-2201 intake and link observed adverse events to these new synthetic cannabinoids.

Plasma Cannabinoid Pharmacokinetics After Controlled Smoking and Ad Libitum Cannabis Smoking In Chronic Frequent Users Lee D, Bergamaschi MM, Milman G, Barnes AJ, Queiroz RH, Vandrey R, Huestis MA. Journal of Analytical Toxicology. 2015, Oct; 39(8): 580-587.
More Americans are dependent on cannabis than any other illicit drug. The main analytes for cannabis testing include the primary psychoactive constituent, Δ(9)-tetrahydrocannabinol (THC), equipotent 11-hydroxy-THC (11-OH-THC) and inactive 11-nor-9-carboxy-THC (THCCOOH). Eleven adult chronic frequent cannabis smokers resided on a closed research unit with unlimited access to 5.9% THC cannabis cigarettes from 12:00 to 23:00 during two ad libitum smoking phases, followed by a 5-day abstinence period in seven participants. A single cigarette was smoked under controlled topography on the last day of the smoking and abstinence phases. Plasma cannabinoids were quantified by two-dimensional gas chromatography-mass spectrometry. Median plasma maximum concentrations (Cmax) were 28.3 (THC), 3.9 (11-OH-THC) and 47.0 µg/L (THCCOOH) 0.5 h after controlled single cannabis smoking. Median Cmax 0.2-0.5 h after ad libitum smoking was higher for all analytes: 83.5 (THC), 14.2 (11-OH-THC) and 155 µg/L (THCCOOH). All 11 participants' plasma samples were THC and THCCOOH-positive, 58.3% had THC ≥5 µg/L and 79.2% were 11-OH-THC-positive 8.1-14 h after last cannabis smoking. Cannabinoid detection rates in seven participants 106-112 h (4-5 days) after last smoking were 92.9 (THC), 35.7 (11-OH-THC) and 100% (THCCOOH), with limits of quantification of 0.5 µg/L for THC and THCCOOH, and 1.0 µg/L for 11-OH-THC. These data greatly expand prior research findings on cannabinoid excretion profiles in chronic frequent cannabis smokers during ad libitum smoking. Smoking multiple cannabis cigarettes led to higher Cmax and AUC compared with smoking a single cigarette. The chronic frequent cannabis smokers exhibited extended detection windows for plasma cannabinoids, reflecting a large cannabinoid body burden.

Extended Detection Of Amphetamine and Methamphetamine In Oral Fluid Andås HT, Enger A, Øiestad ÅML, Vindenes V, Christophersen AS, Huestis MA, Øiestad EL. Therapeutic Drug Monitoring 2015, e-pub Sep 22, 2015.
Amphetamine and methamphetamine are popular drugs of abuse worldwide, and are important components of drug monitoring programs. Windows of detection for amphetamine and methamphetamine in oral fluid after high doses have not been investigated. Repeated high dose ingestions are likely to cause positive samples for extended time periods. Common routes of administration of amphetamine/ methamphetamine in Norway are oral intake or injection. The aim of this study was to investigate windows of detection for amphetamine and methamphetamine in

oral fluid from drug addicts under sustained abstinence during detoxification. Twenty-five patients admitted to a closed detoxification unit were included in this study. Oral fluid samples were collected daily in the morning and evening, and urine every morning for 10 days. A blood sample was drawn during the first five days after admission, if the patient consented. Oral fluid results were compared to urine results to determine if a new ingestion occurred. Oral fluid was collected with the Intercept oral fluid collection device. In-house cut-off concentrations for amphetamine and methamphetamine were 6.8 and 7.5 µg/L, respectively, in oral fluid and 135 and 149 µg/L, respectively, in urine. Amphetamines were detected in 11 oral fluid, five urine, and two blood specimens from 25 patients. Patients self-reported amphetamines intake of up to 0.5-2 g daily. Windows of detection for amphetamine and methamphetamine in oral fluid were up to 8 days, longer than in urine at the applied cut-off values. These data confirm that oral fluid is a viable alternative to urine for monitoring amphetamine abuse, and that these substances might be detected in oral fluid for at least one week after ingestion of high doses. Such long detection times were, as far as we are aware, never reported previously for oral fluid amphetamines.

One Hundred False-Positive Amphetamine Specimens Analyzed By Liquid Chromatography Time-Of-Flight Mass Spectrometry Marin SJ, Chang A, Doyle K, Concheiro-Guisan M, Huestis MA, Johnson-Davis KL. Drug Test Analysis. 2015, e-pub Sep 4, 2015.
Some amphetamine (AMP) and ecstacy (MDMA) urine immunoassay (IA) kits are prone to false-positive results due to poor specificity of the antibody. The authors employed two techniques, high-resolution mass spectrometry (HRMS) and an in silico structure search, to identify compounds likely to cause false-positive results. Hundred false-positive IA specimens for AMP and/or MDMA were analyzed by an Agilent 6230 time-of-flight (TOF) mass spectrometer. Separately, SciFinder (Chemical Abstracts) was used as an in silico structure search to generate a library of compounds that are known to cross-react with AMP/MDMA IAs. Chemical formulas and exact masses of 145 structures were then compared against masses identified by TOF. Compounds known to have cross-reactivity with the IAs were identified in the structure-based search. The chemical formulas and exact masses of 145 structures (of 20 chemical formulas) were compared against masses identified by TOF. Urine analysis by HRMS correlates accurate mass with chemical formulae, but provides little information regarding compound structure. Structural data of targeted antigens can be utilized to correlate HRMS-derived chemical formulas with structural analogs.

Metabolic Characterization Of AH-7921, A Synthetic Opioid Designer Drug: In Vitro Metabolic Stability Assessment and Metabolite Identification, Evaluation Of In Silico Prediction, and In Vivo Confirmation Wohlfarth A, Scheidweiler KB, Pang S, Zhu M, Castaneto M, Kronstrand R, Huestis MA. Drug Test Analysis. 2015, e-pub Sep 1, 2015.
AH-7921 (3,4-dichloro-N-[(1-dimethylamino)cyclohexylmethyl]benzamide) is a new synthetic opioid and has led to multiple non-fatal and fatal intoxications. To comprehensively study AH-7921 metabolism, the authors assessed human liver microsome (HLM) metabolic stability, determined AH-7921's metabolic profile after human hepatocytes incubation, confirmed their findings in a urine case specimen, and compared results to in silico predictions. For metabolic stability, 1 µmol/L AH-7921 was incubated with HLM for up to 1 h; for metabolite profiling, 10 µmol/L was incubated with pooled human hepatocytes for up to 3 h. Hepatocyte samples were analyzed by liquid chromatography quadrupole/time-of-flight high-resolution mass spectrometry (MS). High-resolution full scan MS and information-dependent acquisition MS/MS data were analyzed with MetabolitePilot™ (SCIEX) using multiple data processing algorithms. The presence of AH-7921 and metabolites was confirmed in the urine case specimen. In silico prediction of metabolite

structures was performed with MetaSite™ (Molecular Discovery). AH-7921 in vitro half-life was 13.5 ± 0.4 min. The authors identified 12 AH-7921 metabolites after hepatocyte incubation, predominantly generated by demethylation, less dominantly by hydroxylation, and combinations of different biotransformations. Eleven of 12 metabolites identified in hepatocytes were found in the urine case specimen. One metabolite, proposed to be di-demethylated, N-hydroxylated and glucuronidated, eluted after AH-7921 and was the most abundant metabolite in non-hydrolyzed urine. MetaSite™ correctly predicted the two most abundant metabolites and the majority of observed biotransformations. The two most dominant metabolites after hepatocyte incubation (also identified in the urine case specimen) were desmethyl and di-desmethyl AH-7921. Together with the glucuronidated metabolites, these are likely suitable analytical targets for documenting AH-7921 intake.

Molecular Neuropsychiatry Research Branch

Mouse Model For PTPRD Associations With WED/RLS and Addiction: Reduced Expression Alters Locomotion, Sleep Behaviors and Cocaine-Conditioned Place Preference Drgonova J, Walther D, Wang KJ, Hartstein GL, Lochte B, Troncoso J, Uetani N, Iwakura Y, Uhl GR.. Molecular Medicine 2015, DOI: 10.2119/molmed.2015.00017.
The receptor type protein tyrosine phosphatase D (PTPRD) gene encodes a cell adhesion molecule likely to influence development and connections of addiction-, locomotion- and sleep-related brain circuits in which it is expressed. The PTPRD gene harbors genome wide association signals in studies of restless leg syndrome (Willis-Ekbom/RLS; $p < 10\text{-}8$) and addiction- related phenotypes (clusters of nearby SNPs with $10\text{-}2 > p > 10\text{-}8$ associations in several reports). The authors now report work that seeks a) association between PTPRD genotypes and expression of its mRNA in postmortem human brains and b) RLS-related, addiction-related and comparison behavioral phenotypes in hetero- and homozygous PTPRD knockout mice. The authors identify associations between PTPRD SNPs and levels of PTPRD mRNA in human brain samples that support validity of mouse models with altered PTPRD expression. Knockouts display less behaviorally-defined sleep at the end of their active periods. Heterozygotes move more despite motor weakness/impersistence. Heterozygotes display shifted dose-response relationships for cocaine reward. They display greater preference for places paired with 5 mg/kg cocaine and less preference for places paired with 10 or 20 mg/kg. The combined data provide support for roles for common, level-of-expression PTPRD variation in locomotor, sleep and drug reward phenotypes relevant to RLS and addiction. Taken together, mouse and human results identify PTPRD as a novel therapeutic target for RLS and addiction phenotypes.

Altered CSMD1 Expression Alters Cocaine-Conditioned Place Preference: Mutual Support For a Complex Locus From Human and Mouse Models Drgonova J, Walther D, Singhal S, Johnson K, Kessler B, Troncoso J, Uhl GR. PLoS One. 2015 doi: 10.1371/journal.pone.0120908.
The CUB and sushi multiple domains 1 (CSMD1) gene harbors signals provided by clusters of nearby SNPs with $10\text{-}2 > p > 10\text{-}8$ associations in genome wide association (GWAS) studies of addiction-related phenotypes. A CSMD1 intron 3 SNP displays $p < 10\text{-}8$ association with schizophrenia and more modest associations with individual differences in performance on tests of cognitive abilities. CSDM1 encodes a cell adhesion molecule likely to influence development, connections and plasticity of brain circuits in which it is expressed. The authors tested association between CSMD1 genotypes and expression of its mRNA in postmortem human brains ($n = 181$).

Expression of CSMD1 mRNA in human postmortem cerebral cortical samples differs 15-25%, in individuals with different alleles of simple sequence length and SNP polymorphisms located in the gene's third/fifth introns, providing nominal though not Bonferroni-corrected significance. These data support mice with altered CSMD1 expression as models for common human CSMD1 allelic variation. The authors tested baseline and/or cocaine-evoked addiction, emotion, motor and memory-related behaviors in +/- and -/- csmd1 knockout mice on mixed and on C57-backcrossed genetic backgrounds. Initial csmd1 knockout mice on mixed genetic backgrounds displayed a variety of coat colors and sizable individual differences in responses during behavioral testing. Backcrossed mice displayed uniform black coat colors. Cocaine conditioned place preference testing revealed significant influences of genotype ($p = 0.02$). Homozygote knockouts displayed poorer performance on aspects of the Morris water maze task. They displayed increased locomotion in some, though not all, environments. The combined data thus support roles for common level-of-expression CSMD1 variation in a drug reward phenotype relevant to addiction and in cognitive differences that might be relevant to schizophrenia. Mouse model results can complement data from human association findings of modest magnitude that identify likely polygenic influences.

Pretreatment Or Posttreatment With Aripiprazole Attenuates Methamphetamine-Induced Stereotyped Behavior In Mice Kitanaka N, Kitanaka J, Hall FS, Kayama M, Sugimori H, Uhl GR, Takemura M. J Exp Neurosci. 2015; 9(Suppl 1): 1-10.
Aripiprazole is a third-generation atypical antipsychotic and a dopamine D2 receptor partial agonist. In the present study, we investigated whether a single administration of aripiprazole to mice, either as a pretreatment or as a posttreatment, would affect stereotypy induced by methamphetamine (METH). Pretreatment of male ICR mice with aripiprazole (1 or 10 mg/kg, i.p.) attenuated the incidence of METH-induced stereotypical behavior in a dose-dependent manner. Pretreatment of mice with 1 mg/kg aripiprazole produced an increase in the locomotor activity in mice treated with METH compared with mice treated with vehicle plus METH and with 10 mg/kg aripiprazole plus METH. This increase in locomotion is indicative of a rightward shift in the dose-response curve for METH, consistent with a shift in the type of stereotypical behavior observed from biting to sniffing. Aripiprazole posttreatment, after METH-induced stereotypical behavior, was fully expressed and also significantly attenuated overall stereotypy in an aripiprazole dose-dependent manner. These data suggest that the antagonism of METH effects by aripiprazole should be investigated as a potential treatment for acute METH overdose.

Chemical Biology Research Branch
Drug Design and Synthesis Section

Quantification Of Methylone and Metabolites In Rat and Human Plasma By Liquid Chromatography-Tandem Mass Spectrometry Ellefsen KN, Concheiro M, Suzuki M, Rice KC, Elmore JS, Baumann MH, Huestis MA. Forensic Toxicol. 2015; 33: 202-212.
Methylone is a commonly abused synthetic cathinone derivative marketed as a “legal” alternative to “ecstasy” or cocaine. Previous studies examined the metabolism of methylone in vitro and in vivo; 4-hydroxy-3-methoxymethcathinone (HMMC) was identified as the primary metabolite, with other reported minor metabolites, 3,4-methylenedioxycathinone (MDC) and 3,4-dihydroxymethcathinone (HHMC). However, limited information is known about methylone and its metabolites’ pharmacokinetics. The authors developed and fully validated a method for the simultaneous quantification of methylone, HMMC, MDC and HHMC by liquid chromatography-tandem mass

spectrometry in 100 µl rat and human plasma. β-Glucuronidase was utilized for plasma hydrolysis, followed by perchloric acid protein precipitation and solid-phase extraction utilizing cation exchange columns. Chromatographic separation was performed with a Synergi Polar column in gradient mode, and analytes were determined by two multiple reaction monitoring (MRM) transitions. Linear ranges of 0.5–1,000 µg/l (methylone, HMMC and MDC) and 10–1,000 µg/l (HHMC) were achieved. Bias and imprecision were generally acceptable, although quantification of HHMC exhibited variability (16.2–37 %). Extraction efficiencies and ion suppression were 89.9–104 % (for HHMC, 15.9–16.2 %) and < 11.4 %, respectively. Methylone and metabolites were stable in plasma for 24 h at room temperature, 72 h at 4 °C, and after three freeze–thaw cycles (except for a 60 % HMMC increase). Human and rat plasma were cross-validated, documenting that rat plasma quality control samples were accurately quantified against a human plasma calibration curve (−23.8 to 12 % bias). As proof of method, rat plasma specimens were analyzed pre-injection and after subcutaneous administration of methylone at 6 mg/kg from 15 to 480 min post-dosing. Methylone, HMMC, MDC and HHMC concentrations ranged from 1.1 to 1,310, 11.2 to 194, 1.9 to 152 and 24.7 to 188 µg/l, respectively.

Corticotropin-Releasing Factor Receptor-1 Antagonism Mitigates Beta Amyloid Pathology and Cognitive and Synaptic Deficits In A Mouse Model Of Alzheimer's Disease Zhang C, Kuo CC, Moghadam SH, Monte L, Campbell SN, Rice KC, Sawchenko PE, Masliah E, Rissman RA. Alzheimers Dement. 2015, epub Nov 7, 2015.

Stress and corticotropin-releasing factor (CRF) have been implicated as mechanistically involved in Alzheimer's disease (AD), but agents that impact CRF signaling have not been carefully tested for therapeutic efficacy or long-term safety in animal models. To test whether antagonism of the type-1 corticotropin-releasing factor receptor (CRFR1) could be used as a disease-modifying treatment for AD, the authors used a preclinical prevention paradigm and treated 30-day-old AD transgenic mice with the small-molecule, CRFR1-selective antagonist, R121919, for 5 months, and examined AD pathologic and behavioral end points. R121919 significantly prevented the onset of cognitive impairment in female mice and reduced cellular and synaptic deficits and beta amyloid and C-terminal fragment-β levels in both genders. The authors observed no tolerability or toxicity issues in mice treated with R121919. CRFR1 antagonism presents a viable disease-modifying therapy for AD, recommending its advancement to early-phase human safety trials.

Pharmacological Characterization Of the Opioid Inactive Isomers (+)-Naltrexone and (+)-Naloxone As Toll-Like Receptor 4 Antagonists Wang X, Zhang Y, Peng Y, Hutchinson MR, Rice KC, Yin H, Watkins LR. Br J Pharmacol. 2015, epub Nov 25, 2015.

Recent evidence implicates toll-like receptor 4 (TLR4) in neuropathic pain and drug reward/reinforcement. Previous work in the authors' laboratory showed that the opioid inactive isomers (+)-naltrexone and (+)-naloxone act as TLR4 antagonists, reversing neuropathic pain and reducing opioid and cocaine reward and reinforcement. However, how these agents modulate TLR4 signaling is not clear. Herein, the authors elucidated the molecular mechanism of (+)-naltrexone and (+)-naloxone on TLR4 signaling. BV-2 mouse microglia cell line, primary rat microglia and primary rat peritoneal macrophages were stimulated with lipopolysaccharide (LPS) and TLR4 signaling inhibitor(s). (+)-Naltrexone and (+)-naloxone each inhibited, with similar potencies the LPS-induced TLR4 downstream signaling and induction of the pro-inflammatory factors nitric oxide (NO) and tumor necrosis factor-α (TNF-α). Similarly, (+)-naltrexone and (+)-naloxone each inhibited LPS-induced reactive oxygen species (ROS) and LPS-induced increase in microglial phagocytosis. However, (+)-naltrexone and (+)-naloxone did not directly inhibit LPS-induced

interleukin-1β (IL-1β) increased production. The drug interaction of (+)-naloxone and (+)-naltrexone is additive. (+)-Naltrexone and (+)-naloxone each inhibited LPS-induced interferon regulatory factor 3 (IRF3) activation and interferon-β (IFN-β) increased production. However, they did not inhibit TLR4 signaling via the activation of either nuclear factor kappa B (NF-κB), p-38 or Jun N-terminal kinase (JNK) in these cellular models. These data show (+)-naltrexone and (+)-naloxone are TRIF-IRF3 axis biased TLR4 antagonists. They block TLR4 downstream signaling leading to NO, TNF-α and ROS. This pattern may explain, at least in part, the in vivo therapeutic effects of (+)-naltrexone and (+)-naloxone.

Directly Observable Behavioral Effects Of Lorcaserin In Rats Serafine KM, Rice KC, France C. J Pharmacol Exp Ther. 2015; 355(3): 381-385.
(1R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (lorcaserin) is approved by the United States Food and Drug Administration for treating obesity, and its therapeutic effects are thought to result from agonist activity at serotonin (5-HT)2C receptors. Lorcaserin has affinity for other 5-HT receptor subtypes, although its activity at those subtypes is not fully described. The current study compared the behavioral effects of lorcaserin (0.0032-32.0 mg/kg) to the effects of other 5-HT receptor selective agonists in rats (n = 8). The 5-HT2C receptor selective agonist 1-(3-chlorophenyl)piperazine (mCPP, 0.032-1.0 mg/kg) and lorcaserin induced yawning which was attenuated by the 5-HT2C receptor selective antagonist 6-chloro-5-methyl-N-(6-[(2-methylpyridin-3-yl)oxy]pydidin-3-yl)indoline-1-carboxamide (1.0 mg/kg). The 5-HT2A receptor selective agonist 2,5-dimethoxy-4-methylamphetamine (0.1-3.2 mg/kg) induced head twitching, which was attenuated by the 5-HT2A receptor selective antagonist R-(+)-2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol] (MDL 100907, 0.01 mg/kg), lorcaserin (3.2 mg/kg), and mCPP (3.2 mg/kg). In rats pretreated with MDL 100907 (1.0 mg/kg), lorcaserin also induced head twitching. At larger doses, lorcaserin produced forepaw treading, which was attenuated by the 5-HT1A receptor selective antagonist N-(2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl)-N-(2-pyridyl)cyclohexane-carboxamide (0.178 mg/kg). While the behavioral effects of lorcaserin in rats are consistent with it having agonist activity at 5-HT2C receptors, these data suggest that at larger doses it also has agonist activity at 5-HT2A and possibly 5-HT1A receptors. Mounting evidence suggests that 5-HT2C receptor agonists might be effective for treating drug abuse. A more complete description of the activity of lorcaserin at 5-HT receptor subtypes will facilitate a better understanding of the mechanisms that mediate its therapeutic effects.

Neurokinin 1 Receptor Blockade In the Medial Amygdala Attenuates Alcohol Drinking In Rats With Innate Anxiety But Not In Wistar Rats Ayanwuyi LO, Stopponi S, Ubaldi M, Cippitelli A, Nasuti C, Damadzic R, Heilig M, Schank J, Cheng K, Rice KC, Ciccocioppo R. Br J Pharmacol. 2015; 172(21): 5136-5146.
Substance P and its preferred neurokinin receptor NK1 have been implicated in stress and anxiety and have been proposed as possible therapeutic targets for the treatment of anxiety/depression. Attention is also being focused on the role this neuropeptide system may play in drug addiction, because stress-related mechanisms promote drug abuse. The effects of the rat-specific NK1 receptor antagonist, L822429, on alcohol intake and seeking behaviour was investigated in genetically selected Marchigian Sardinian alcohol preferring rats. These rats demonstrate an anxious phenotype and are highly sensitive to stress and stress-induced drinking. Systemic administration of L822429 significantly reduced operant alcohol self-administration in Marchigian Sardinian alcohol preferring rats, but did not reduce alcohol self-administration in stock Wistar rats. NK1 receptor antagonism also attenuated yohimbine-induced reinstatement of alcohol seeking at all doses tested but had no

effect on cue-induced reinstatement of alcohol seeking. L822429 reduced operant alcohol self-administration when injected into the lateral cerebroventricles or the medial amygdala. L822429 injected into the medial amygdala also significantly reduced anxiety-like behaviour in the elevated plus maze test. No effects on alcohol intake were observed following injection of L822429 into the dorsal or the ventral hippocampus. The authors' results suggest that NK1 receptor antagonists may be useful for the treatment of alcohol addiction associated with stress or comorbid anxiety disorders. The medial amygdala appears to be an important brain site of action of NK1 receptor antagonism.

Sex Differences In 3,4-Methylenedioxypyrovalerone (MDPV)-Induced Taste Avoidance and Place Preferences King HE, Wakeford A, Taylor W, Wetzell B, Rice KC, Riley AL. Pharmacol Biochem Behav. 2015; 137: 16-22.
Synthetic cathinones, otherwise known as "bath salts", have gained significant attention in the last few years as a result of increased use and abuse. One such compound, 3,4-methylenedioxy-pyrovalerone (MDPV), is pharmacologically and behaviorally similar to cocaine and has been shown to possess both aversive and rewarding effects. For a host of other drugs, each of these effects (and their relative balance) can be influenced by a variety of factors, including sex, which in turn impacts drug taking behavior. In this context, the present assessment sought to determine whether males and females differed in MDPV-induced CTA and CPP. Both male and female Sprague-Dawley rats underwent a combined CTA/CPP procedure, in which an injection of one of three doses of MDPV (1.0, 1.8 or 3.2mg/kg) was paired with both a novel saccharin solution and a novel environment and changes in preferences for these stimuli were examined. Taste avoidance was evident in both sexes, although this avoidance was weaker in females compared to males. MDPV also produced place preferences in all drug-treated animals, but these preferences did not vary as a function of sex. The fact that females showed a weaker avoidance response compared to males (despite comparable preferences) suggests that females may have a heightened susceptibility to use and abuse of MDPV, paralleling results seen with cocaine and other stimulants. The present findings extend the behavioral characterization of MDPV and the factors that may alter its aversive and rewarding effects.

Neurokinin-1 Receptor Antagonism Attenuates Neuronal Activity Triggered By Stress-Induced Reinstatement Of Alcohol Seeking Schank JR, Nelson BS, Damadzic R, Tapocik JD, Yao M, King CE, Rowe KE, Cheng K, Rice KC, Heilig M. Neuropharmacology. 2015; 99: 106-114.
Substance P (SP) and its cognate neurokinin-1 receptor (NK1R) are involved in alcohol-related behaviors. The authors have previously reported that NK1R antagonism attenuates stress-induced reinstatement of alcohol seeking and suppresses escalated alcohol self-administration, but does not affect primary reinforcement or cue-induced reinstatement. Here, they administered an NK1R antagonist or vehicle prior to footshock-induced reinstatement of alcohol seeking, and mapped the resulting neuronal activation using Fos immunohistochemistry. As expected, vehicle treated animals exposed to footshock showed induction of Fos immunoreactivity in several regions of the brain stress circuitry, including the amygdala (AMG), nucleus accumbens (NAC), dorsal raphe nucleus (DR), prefrontal cortex (PFC), and bed nucleus of the stria terminalis (BNST). NK1R antagonism selectively suppressed the stress-induced increase in Fos in the DR and NAC shell. In the DR, Fos-induction by stress largely overlapped with tryptophan hydroxylase (TrpH), indicating activation of serotonergic neurons. Of NAC shell neurons activated during stress-induced reinstatement of alcohol seeking, about 30% co-expressed dynorphin (DYN), while 70% co-expressed enkephalin (ENK). Few (<1%) activated NAC shell neurons coexpressed choline acetyltransferase (ChAT),

which labels the cholinergic interneurons of this region. Infusion of the NK1R antagonist L822429 into the NAC shell blocked stress-induced reinstatement of alcohol seeking. In contrast, L822429 infusion into the DR had no effect, suggesting that the influence of NK1R signaling on neuronal activity in the DR is indirect. Taken together, our results outline a potential pathway through which endogenous NK1R activation mediates stress-induced alcohol seeking.

Integrative Neuroscience Research Branch
Neuronal Networks Section

Rewarding Effects Of Optical Stimulation Of Ventral Tegmental Area Glutamatergic Neurons Wang HL, Qi J, Zhang S, Wang H and Morales M. J Neurosci 2015; 35:15948-15954.
Ventral tegmental area (VTA) neurons play roles in reward and aversion. The VTA has three major neuronal phenotypes: dopaminergic, GABAergic, and glutamatergic. VTA glutamatergic neurons-expressing vesicular glutamate transporter-2 (VGluT2)-project to limbic and cortical regions, but also excite neighboring dopaminergic neurons. Here, the authors test whether local photoactivation of VTA VGluT2 neurons expressing Channelrhodopsin-2 (ChR2) under the VGluT2 promoter causes place preference and supports operant responding for the stimulation. By using a Cre-dependent viral vector, ChR2 (tethered to mCherry) was expressed in VTA glutamatergic neurons of VGluT2::Cre mice. The mCherry distribution was evaluated by immunolabeling. By confocal microscopy, we detected expression of mCherry in VTA cell bodies and local processes. In contrast, VGluT2 expression was restricted to varicosities, some of them coexpressing mCherry. By electron microscopy, we determined that mCherry-VGluT2 varicosities correspond to axon terminals, forming asymmetric synapses on neighboring dopaminergic neurons. These findings indicate that ChR2 was present in terminals containing glutamatergic synaptic vesicles and involved in local synaptic connections. Photoactivation of VTA slices from ChR2-expressing mice induced AMPA/NMDA receptor-dependent firing of dopaminergic neurons projecting to the nucleus accumbens. VTA photoactivation of ChR2-expressing mice reinforced instrumental behavior and established place preferences. VTA injections of AMPA or NMDA receptor antagonists blocked optical self-stimulation and place preference. These findings suggest a role in reward function for VTA glutamatergic neurons through local excitatory synapses on mesoaccumbens dopaminergic neurons.

The Brain On Drugs: From Reward To Addiction Volkow ND, Morales M. Cell, 2015; 162: 712-725.
Advances in neuroscience identified addiction as a chronic brain disease with strong genetic, neurodevelopmental, and sociocultural components. The authors here discuss the circuit- and cell-level mechanisms of this condition and its co-option of pathways regulating reward, self-control, and affect. Drugs of abuse exert their initial reinforcing effects by triggering supraphysiologic surges of dopamine in the nucleus accumbens that activate the direct striatal pathway via D1 receptors and inhibit the indirect striato-cortical pathway via D2 receptors. Repeated drug administration triggers neuroplastic changes in glutamatergic inputs to the striatum and midbrain dopamine neurons, enhancing the brain's reactivity to drug cues, reducing the sensitivity to non-drug rewards, weakening self-regulation, and increasing the sensitivity to stressful stimuli and dysphoria. Drug-induced impairments are long lasting; thus, interventions designed to mitigate or even reverse them would be beneficial for the treatment of addiction.

Integrative Neuroscience Branch
Cellular Pathobiology Section

Sigma-1 Receptor Mediates Cocaine-Induced Transcriptional Regulation By Recruiting Chromatin-Remodeling Factors At the Nuclear Envelope Tsai SY, Chuang JY, Tsai MS, Wang XF, Xi ZX, Hong JJ, Chang WC, Bonci A, Su TP. Proceedings of the National Academy of Sciences, U.S.A. 2015; 112: E6562-E6570.
The sigma-1 receptor (Sig-1R) chaperone at the endoplasmic reticulum (ER) plays important roles in cellular regulation. Here the authors found a new function of Sig-1R in that it translocates from the ER to the nuclear envelope to recruit chromatin-remodeling molecules and regulate the gene transcription thereof. Sig-1Rs mainly reside at the ER-mitochondrion interface. However, upon stimulation by agonists like cocaine, Sig-1Rs translocate from ER to the nuclear envelope (NE) where Sig-1Rs bind NE protein emerin and recruit chromatin-remodeling molecules including lamin A/C, BAF, and HDAC to form a complex with the gene repressor Sp3. Knockdown of Sig-1Rs attenuates the complex formation. Cocaine was found to suppress the gene expression of monoamine oxidase B (MAOB) in the brain of wild type but not Sig-1R knockout mouse. A single dose of cocaine (20 mg/kg) in rats suppresses the level of MAOB at nuclear accumbens without affecting the level of dopamine transporter. Daily injections of cocaine in rats caused behavioral sensitization. Withdrawal from cocaine in cocaine-sensitized rats induced an apparent time-dependent rebound of the MAOB protein level to about at a 200% over control on day 14 after withdrawal. Treatment of cocaine-withdrawn rats with the MAOB inhibitor deprenyl completely alleviated the behavioral sensitization to cocaine. The authors' results demonstrate a role of Sig-1R in transcriptional regulation and suggest that cocaine may work through this newly discovered genomic action to achieve its addictive action. Results also suggest the MAOB inhibitor deprenyl as a therapeutic agent to block certain action of cocaine during withdrawal.

Behavioral Neuroscience Branch
Preclinical Pharmacology Section,

The Novel Metabotropic Glutamate Receptor 2 Positive Allosteric Modulator, AZD8529, Decreases Nicotine Self-Administration and Relapse In Squirrel Monkeys Justinova Z, Panlilio LV, Secci ME,, Redhi GH, Schindler CW, Cross AJ, Mrzljak L, Medd A, Shaham Y, Goldberg SR Biological Psychiatry 2015;78: 452-462.
Based on rodent studies, group II metabotropic glutamate receptors (mGluR2 and mGluR3) were suggested as targets for addiction treatment. However, LY379268 and other group II agonists do not discriminate between the mainly presynaptic inhibitory mGluR2 (the proposed treatment target) and mGluR3. These agonists also produce tolerance over repeated administration and are no longer considered for addiction treatment. Here, the authors determined the effects of AZD8529, a selective positive allosteric modulator of mGluR2, on abuse-related effects of nicotine in squirrel monkeys and rats. The authors first assessed modulation of mGluR2 function by AZD8529 using functional in vitro assays in membranes prepared from a cell line expressing human mGluR2 and in primate brain slices. They then determined AZD8529 (.03-10 mg/kg, intramuscular injection) effects on intravenous nicotine self-administration and reinstatement of nicotine seeking induced by nicotine priming or nicotine-associated cues. They also determined AZD8529 effects on food self-administration in monkeys and nicotine-induced dopamine release in accumbens shell in rats. AZD8529 potentiated agonist-induced activation of mGluR2 in the membrane-binding assay and in

primate cortex, hippocampus, and striatum. In monkeys, AZD8529 decreased nicotine self-administration at doses (.3-3 mg/kg) that did not affect food self-administration. AZD8529 also reduced nicotine priming- and cue-induced reinstatement of nicotine seeking after extinction of the drug-reinforced responding. In rats, AZD8529 decreased nicotine-induced accumbens dopamine release. These results provide evidence for efficacy of positive allosteric modulators of mGluR2 in nonhuman primate models of nicotine reinforcement and relapse. This drug class should be considered for nicotine addiction treatment.

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; 40: 2185-2197.
Inhibition of the enzyme fatty acid amide hydrolase (FAAH) counteracts reward-related effects of nicotine in rats, but it 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 α-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 reexposure 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 of the FAAH inhibitors 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 because of their ability to block the rewarding effects of nicotine and prevent nicotine priming-induced and cue-induced reinstatement.

Neuroimaging Research Branch

Multivariate Classification Of Smokers and Nonsmokers Using SVM-RFE On Structural MRI Images Ding, X, Yang, Y, Stein, EA and Ross, TJ. Human Brain Mapping 2015 Oct 24. doi: 10.1002/hbm.22956. [Epub ahead of print].
Voxel-based morphometry (VBM) studies have revealed gray matter alterations in smokers, but this type of analysis has poor predictive value for individual cases, which limits its applicability in clinical diagnoses and treatment. A predictive model would essentially embody a complex biomarker that could be used to evaluate treatment efficacy. In this study, the authors applied VBM along with a multivariate classification method consisting of a support vector machine with recursive feature elimination to discriminate smokers from nonsmokers using their structural MRI data. Mean gray matter volumes in 1,024 cerebral cortical regions of interest created using a

subparcellated version of the Automated Anatomical Labeling template were calculated from 60 smokers and 60 nonsmokers, and served as input features to the classification procedure. The classifier achieved the highest accuracy of 69.6% when taking the 139 highest ranked features via 10-fold cross-validation. Critically, these features were later validated on an independent testing set that consisted of 28 smokers and 28 nonsmokers, yielding a 64.04% accuracy level (binomial P = 0.01). Following classification, exploratory post hoc regression analyses were performed, which revealed that gray matter volumes in the putamen, hippocampus, prefrontal cortex, cingulate cortex, caudate, thalamus, pre-/postcentral gyrus, precuneus, and the parahippocampal gyrus, were inversely related to smoking behavioral characteristics. These results not only indicate that smoking related gray matter alterations can provide predictive power for group membership, but also suggest that machine learning techniques can reveal underlying smoking-related neurobiology.

Resting-State Functional Connectivity and Nicotine Addiction: Prospects For Biomarker Development Fedota, J and Stein, EA. Annals NY Academy Science 2015; 1349: 64-82.
Given conceptual frameworks of addiction as a disease of intercommunicating brain networks, examinations of network interactions may provide a holistic characterization of addiction-related dysfunction. One such methodological approach is the examination of resting-state functional connectivity, which quantifies correlations in low-frequency fluctuations of the blood oxygen level-dependent magnetic resonance imaging signal between disparate brain regions in the absence of task performance. Here, evidence of differentiated effects of chronic nicotine exposure, which reduces the efficiency of network communication across the brain, and acute nicotine exposure, which increases connectivity within specific limbic circuits, is discussed. Several large-scale resting networks, including the salience, default, and executive control networks, have also been implicated in nicotine addiction. The dynamics of connectivity changes among and between these large-scale networks during nicotine withdrawal and satiety provide a heuristic framework with which to characterize the neurobiological mechanism of addiction. The ability to simultaneously quantify effects of both chronic (trait) and acute (state) nicotine exposure provides a platform to develop a neuroimaging-based addiction biomarker. While such development remains in its early stages, evidence of coherent modulations in resting-state functional connectivity at various stages of nicotine addiction suggests potential network interactions on which to focus future addiction biomarker development.

Neurobiological Impact Of Nicotinic Acetylcholine Receptor Agonists: An ALE Meta-Analysis Of Pharmacological Neuroimaging Studies Sutherland, MT, Riedel, M, Ray, K, Stein, EA and Laird, AR. Biological Psychiatry 2015;78: 711-720.
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; 78: 496-504.
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.

Cellular Neurobiology Research Branch
Behavioral Neurophysiology Research Section

Brief Optogenetic Inhibition Of Dopamine Neurons Mimics Endogenous Negative Reward Prediction Errors Chang CY, Esber GR, Marrero-Garci Y, Yau HJ, Bonci A, Schoenbaum G. 2015. Nature Neuroscience. Epub ahead of print.
Correlative studies have strongly linked phasic changes in dopamine activity with reward prediction error signaling. But causal evidence that these brief changes in firing actually serve as error signals to drive associative learning is more tenuous. Although there is direct evidence that brief increases can substitute for positive prediction errors, there is no comparable evidence that similarly brief pauses can substitute for negative prediction errors. In the absence of such evidence, the effect of increases in firing could reflect novelty or salience, variables also correlated with dopamine activity. Here the authors provide evidence in support of the proposed linkage, showing in a modified

Pavlovian over-expectation task that brief pauses in the firing of dopamine neurons in rat ventral tegmental area at the time of reward are sufficient to mimic the effects of endogenous negative prediction errors. These results support the proposal that brief changes in the firing of dopamine neurons serve as full-fledged bidirectional prediction error signals.

Dialogue On Economic Choice, Learning Theory, and Neuronal Representations Padoa-Schioppa, C and Schoenbaum, G. Current Opinion in Behavioral Science. 2015; 5:16-23.
In recent years, two distinct lines of work have focused on the substrates of associative learning and on the mechanisms of economic decisions. While experiments often focused the same brain regions - most notably the orbitofrontal cortex - the two literatures have remained largely distinct. Here the authors engage in a dialogue with the intent to clarify the relationship between the two frameworks. They identify a potential correspondence between the concept of outcome defined in learning theory and that of good defined in neuroeconomics, and they specifically discuss the concept of value defined in the two frameworks. While many differences remain unresolved, a common idea is that good/outcome values are subjective, devaluation-sensitive and computed on the fly, not "cached" or pre-computed.

Synaptic Plasticity Section

Transcranial Magnetic Stimulation Of Dorsolateral Prefrontal Cortex Reduces Cocaine Use: A Pilot Study Terraneo A, Leggio L, Saladini M, Ermani M, Bonci A, Gallimberti L. European Neuropsychopharmacology 2015, online publication.
Recent animal studies demonstrate that compulsive cocaine seeking strongly reduces prelimbic frontal cortex activity, while optogenetic stimulation of this brain area significantly inhibits compulsive cocaine seeking, providing a strong rationale for applying brain stimulation to reduce cocaine consumption. Thus, the authors employed repetitive transcranial magnetic stimulation (rTMS), to test if dorsolateral prefrontal cortex (DLPFC) stimulation might prevent cocaine use in humans. Thirty-two cocaine-addicted patients were randomly assigned to either the experimental group (rTMS) on the left DLPFC, or to a control group (pharmacological agents) during a 29-day study (Stage 1). This was followed by a 63-day follow-up (Stage 2), during which all participants were offered rTMS treatment. Amongst the patients who completed Stage 1, 16 were in the rTMS group (100%) and 13 in the control group (81%). No significant adverse events were noted. During Stage 1, there were a significantly higher number of cocaine-free urine drug tests in the rTMS group compared to control ($p=0.004$). Craving for cocaine was also significantly lower in the rTMS group compared to the controls ($p=0.038$). Out of 13 patients who completed Stage 1 in the control group, 10 patients received rTMS treatment during Stage 2 and showed significant improvement with favorable outcomes becoming comparable to those of the rTMS group. The present preliminary findings support the safety of rTMS in cocaine-addicted patients, and suggest its potential therapeutic role for rTMS-driven PFC stimulation in reducing cocaine use, providing a strong rationale for developing larger placebo-controlled studies.

D-Serine and D-Cycloserine Reduce Compulsive Alcohol Intake In Rats Seif T, Simms JA, Lei K, Wegner S, Bonci A, Messing RO, Hopf FW. Neuropsychopharmacology 2015; 40: 2357–2367.
There is considerable interest in NMDAR modulators to enhance memory and treat neuropsychiatric disorders such as addiction, depression, and schizophrenia. D-serine and D-cycloserine, the NMDAR activators at the glycine site, are of particular interest because they have

been used in humans without serious adverse effects. Interestingly, D-serine also inhibits some NMDARs active at hyperpolarized potentials (HA-NMDARs), and the authors previously found that HA-NMDARs within the nucleus accumbens core (NAcore) are critical for promoting compulsion-like alcohol drinking, where rats consume alcohol despite pairing with an aversive stimulus such as quinine, a paradigm considered to model compulsive aspects of human alcohol use disorders (AUDs). Here, the authors examined the impact of D-serine and D-cycloserine on this aversion-resistant alcohol intake (that persists despite adulteration with quinine) and consumption of quinine-free alcohol. Systemic D-serine reduced aversion-resistant alcohol drinking, without altering consumption of quinine-free alcohol or saccharin with or without quinine. Importantly, D-serine within the NAcore but not the dorsolateral striatum also selectively reduced aversion-resistant alcohol drinking. In addition, D-serine inhibited EPSCs evoked at −70 mV in vitro by optogenetic stimulation of mPFC–NAcore terminals in alcohol-drinking rats, similar to reported effects of the NMDAR blocker AP5. Further, D-serine preexposure occluded AP5 inhibition of mPFC-evoked EPSCs, suggesting that D-serine reduced EPSCs by inhibiting HA-NMDARs. Systemic D-cycloserine also selectively reduced intake of quinine-adulterated alcohol, and D-cycloserine inhibited NAcore HA-NMDARs in vitro. These results indicate that HA-NMDAR modulators can reduce aversion-resistant alcohol drinking, and support testing of D-serine and D-cycloserine as immediately accessible, FDA-approved drugs to treat AUDs.

Optogenetics In Freely Moving Mammals: Dopamine and Reward Zhang F, Tsai HC, Airan RD, Stuber GD, Adamantidis AR, de Lecea L, Bonci A, Deisseroth K. Cold Spring Harb Protoc. 2015. Online Publication.
Brain reward systems play a central role in the cognitive and hedonic behaviors of mammals. Multiple neuron types and brain regions are involved in reward processing, posing fascinating scientific questions, and major experimental challenges. Using diverse approaches including genetics, electrophysiology, imaging, and behavioral analysis, a large body of research has focused on both normal functioning of the reward circuitry and on its potential significance in neuropsychiatric diseases. In this introduction, the authors illustrate a real-world application of optogenetics to mammalian behavior and physiology, delineating procedures and technologies for optogenetic control of individual components of the reward circuitry. They describe the experimental setup and protocol for integrating optogenetic modulation of dopamine neurons with fast-scan cyclic voltammetry, conditioned place preference, and operant conditioning to assess the causal role of well-defined electrical and biochemical signals in reward-related behavior.

Optogenetics: 10 Years After Chr2 In Neurons-Views From the Community Adamantidis A, Arber S, Bains JS, Bamberg E, Bonci A, Buzsáki G, Wilson RI. Nat Neurosci. 2015 Aug 26; 18(9): 1202-1212.
Neuroscientists have long dreamed of the ability to control neuronal activity with exquisite spatiotemporal precision. In this issue, the authors celebrate the tenth anniversary of a paper published in the September 2005 issue of Nature Neuroscience by a team led by Karl Deisseroth (Nat. Neurosci. 8, 1263–1268 (2005)). In this study, the authors expressed a light-sensitive microbial protein, Channelrhodopsin-2 (ChR2), in neurons and showed that exposing these neurons to pulses of light could activate them in a temporally precise and reliable manner. In the decade since this paper, 'optogenetic' approaches have been widely and enthusiastically adopted by the field and applied to a vast array of questions both in neuroscience and beyond. In the intervening years, improvements to early techniques have provided the community with an optogenetics tool box that has opened the door to experiments we could have once only dreamed of. Controlling neuronal

activity in real time, we now have the ability to determine causality between activity patterns in specific neuronal circuits and brain function and behavior, enabling researchers to definitively test long-held views and advance our understanding of brain function in both health and disease. Anniversaries are often a time to reflect and, in light of the seminal influence this technique has had on neuroscience, the authors were curious to know how researchers in the field feel the advances in optogenetic approaches have influenced their work, what they think the future holds in terms of the application of these techniques and what they see as the obstacles we need to overcome to get there. Toward this end, the authors have asked a number of scientists to share their thoughts with us in this Q&A. Although they weren't able to ask more than a small fraction of the field, their answers give an exciting view of the power and potential of optogenetic approaches for understanding, and even potentially repairing, the nervous system.

Associative Learning Drives the Formation Of Silent Synapses In Neuronal Ensembles Of the Nucleus Accumbens Whitaker LR, Carneiro de Oliveira PE, McPherson KB, Fallon RV, Planeta CS, Bonci A, Hope BT. Biol Psychiatry. 2015. Online publication.
Learned associations between environmental stimuli and rewards play a critical role in addiction. Associative learning requires alterations in sparsely distributed populations of strongly activated neurons, or neuronal ensembles. Until recently, assessment of functional alterations underlying learned behavior was restricted to global neuroadaptations in a particular brain area or cell type, rendering it impossible to identify neuronal ensembles critically involved in learned behavior.
The authors used Fos-GFP transgenic mice that contained a transgene with a Fos promoter driving expression of green fluorescent protein (GFP) to detect neurons that were strongly activated during associative learning, in this case, context-independent and context-specific cocaine-induced locomotor sensitization. Whole-cell electrophysiological recordings were used to assess synaptic alterations in specifically activated GFP-positive (GFP+) neurons compared with surrounding nonactivated GFP-negative (GFP-) neurons 90 min after the sensitized locomotor response. After context-independent cocaine sensitization, cocaine-induced locomotion was equally sensitized by repeated cocaine injections in two different sensitization contexts. Correspondingly, silent synapses in these mice were induced in GFP+ neurons, but not GFP- neurons, after sensitization in both of these contexts. After context-specific cocaine sensitization, cocaine-induced locomotion was sensitized exclusively in mice trained and tested in the same context (paired group), but not in mice that were trained in one context and then tested in a different context (unpaired group). Silent synapses increased in GFP+ neurons, but not in GFP- neurons from mice in the paired group, but not from mice in the unpaired group. These results indicate that silent synapses are formed only in neuronal ensembles of the nucleus accumbens shell that are related to associative learning.

Sigma-1 Receptor Mediates Cocaine-Induced Transcriptional Regulation By Recruiting Chromatin-Remodeling Factors At the Nuclear Envelope Tsai SY, Chuang JY, Tsai MS, Wang XF, Xi ZX, Jung JJ, Chang WC, Bonci A, Su T-S. PNAS. 2015; 112(47): E6562-656270 . Online publication.
The sigma-1 receptor (Sig-1R) chaperone at the endoplasmic reticulum (ER) plays important roles in cellular regulation. Here the authors found a new function of Sig-1R, in that it translocates from the ER to the nuclear envelope (NE) to recruit chromatin-remodeling molecules and regulate the gene transcription thereof. Sig-1Rs mainly reside at the ER-mitochondrion interface. However, on stimulation by agonists such as cocaine, Sig-1Rs translocate from ER to the NE, where Sig-1Rs bind NE protein emerin and recruit chromatin-remodeling molecules, including lamin A/C, barrier-to-autointegration factor (BAF), and histone deacetylase (HDAC), to form a complex with the gene

repressor specific protein 3 (Sp3). Knockdown of Sig-1Rs attenuates the complex formation. Cocaine was found to suppress the gene expression of monoamine oxidase B (MAOB) in the brain of wild-type but not Sig-1R knockout mouse. A single dose of cocaine (20 mg/kg) in rats suppresses the level of MAOB at nuclear accumbens without affecting the level of dopamine transporter. Daily injections of cocaine in rats caused behavioral sensitization. Withdrawal from cocaine in cocaine-sensitized rats induced an apparent time-dependent rebound of the MAOB protein level to about 200% over control on day 14 after withdrawal. Treatment of cocaine-withdrawn rats with the MAOB inhibitor deprenyl completely alleviated the behavioral sensitization to cocaine. These results demonstrate a role of Sig-1R in transcriptional regulation and suggest cocaine may work through this newly discovered genomic action to achieve its addictive action. Results also suggest the MAOB inhibitor deprenyl as a therapeutic agent to block certain actions of cocaine during withdrawal.

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; 78: 463-473.
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 methamphet-amine 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 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.

Cellular Neurobiology Branch
Electrophysiology Research Section

Cocaine-Induced Endocannabinoid Mobilization In The Ventral Tegmental Area Wang H, Treadway T, Covey DP, Cheer JF, Lupica CR. Cell Reports, 2015; 12: 1997-2008. doi: 10.1016/j.celrep.2015.08.041. Epub 2015 Sep 10.
Cocaine is a highly addictive drug that acts upon the brain's reward circuitry via the inhibition of monoamine uptake. Endogenous cannabinoids (eCB) are lipid molecules released from midbrain dopamine (DA) neurons that modulate cocaine's effects through poorly understood mechanisms. The authors find that cocaine stimulates release of the eCB, 2-arachidonoylglycerol (2-AG), in the rat ventral midbrain to suppress GABAergic inhibition of DA neurons, through activation of presynaptic cannabinoid CB1 receptors. Cocaine mobilizes 2-AG via inhibition of Norepinephrine uptake and promotion of a cooperative interaction between Gq/11-coupled type-1 metabotropic glutamate and α1-adrenergic receptors to stimulate internal calcium stores and activate phospholipase C. The disinhibition of DA neurons by cocaine-mobilized 2-AG is also functionally relevant because it augments DA release in the nucleus accumbens in vivo. The authorsr results identify a mechanism through which the eCB system can regulate the rewarding and addictive properties of 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. Journal of Neurosci. 2015;35: 3460-3469.
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, the authors 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. Nat Neuroscience, 2015; 18: 386-392.
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.

Molecular Targets and Medications Discovery Branch
Psychobiology Section

Dopamine D2-Like Receptors and Behavioral Economics Of Food Reinforcement Soto P, Hiranita T, Xu M, Hursh S, Grandy D, Katz JL. Neuropsychopharmacology, doi:10.1038/npp.2015.223
Previous studies suggest dopamine (DA) D2-like receptor involvement in the reinforcing effects of food. To determine contributions of the three D2-like receptor subtypes, knockout (KO) mice completely lacking DA receptors (D2R, D3R, or D4R KO mice) and their wild-type littermates were exposed to a series of fixed-ratio (FR) food-reinforcement schedules in two contexts: an open economy with additional food provided outside the experimental setting and a closed economy with all food earned within the experimental setting. A behavioral-economic model was used to quantify reinforcer effectiveness with food pellets obtained as a function of price (FR schedule value) plotted to assess elasticity of demand. Under both economies, as price increased, food pellets obtained decreased more rapidly (i.e., food demand was more elastic) in DA D2R KO mice compared to WT littermates. Extinction of responding was studied in two contexts: by eliminating food deliveries and by delivering food independently of responding. A hyperbolic model quantified rates of extinction. Extinction in DA D2R KO mice occurred less rapidly compared to WT mice in both contexts. Elasticity of food demand was higher in DA D4R KO than WT mice in the open, but not closed, economy. Extinction of responding in DA D4R KO mice was not different from that in WT littermates in either context. No differences in elasticity of food demand or extinction rate were obtained in D3R KO mice and WT littermates. These results indicate that the D2R is the primary DA D2-like receptor subtype mediating the reinforcing effectiveness of food.

A Role For Σrs In Stimulant Self-Administration and Addiction Katz JL, Hong WC, Hiranita T. Su T-.P. Behavioural Pharmacology, DOI: 10.1097/FBP.0000000000000209
Sigma-1 receptors (σ1Rs) are structurally unique intracellular proteins that function as chaperones. σ1Rs translocate from the mitochondria-associated membrane to other sub-cellular compartments, and can influence a host of targets, including ion channels, G-protein-coupled receptors, lipids, and other signaling proteins. Drugs binding to σRs can induce or block the actions of σRs. Studies indicate that stimulant self-administration induces reinforcing effects of σR agonists, due to dopamine transporter actions. Once established the reinforcing effects of σR agonists are independent of dopaminergic mechanisms traditionally thought to be critical in the reinforcing effects of stimulants. Self-administered doses of σR agonists do not increase dopamine concentrations in the nucleus accumbens shell, a transmitter and brain region considered important

for reinforcing effects of abused drugs. However, the self-administration of σR agonists is blocked by σR antagonists. Several effects of stimulants have been blocked by σR antagonists, including reinforcing effects assessed by a place-conditioning procedure. However, the self-administration of stimulants is largely unaffected by σR antagonists, indicating fundamental differences in the mechanisms underlying these two procedures used to assess reinforcing effects. When σR antagonists are administered in combination with dopamine uptake inhibitors an effective and specific blockade of stimulant self-administration is obtained. Actions of stimulant drugs related to their abuse induce unique changes in σR activity and the changes induced potentially create redundant, and once established, independent reinforcement pathways. Concomitant targeting of both dopaminergic pathways and σR proteins produces a selective antagonism of stimulant self-administration, suggesting new avenues for combination chemotherapies to specifically combat stimulant abuse.

Differential Modulation Of Methamphetamine-Mediated Behavioral Sensitization By Overexpression Of Mu Opioid Receptors In Nucleus Accumbens and Ventral Tegmental Area
Kuo CC, Shen H, Harvey BK, Yu SJ, Kopajtic T, Hinkle JJ, Kyrkanides S, Katz JL.Wang Y. Psychopharmacology, DOI 10.1007/s00213-015-4134-4
Repeated administration of methamphetamine (Meth) induces behavioral sensitization which is characterized by a progressive increase in locomotor response after each injection. Previous studies have shown that Mu opioid receptors (MORs) can regulate Meth-mediated behavioral sensitization. However, the reported interactions are controversial; systemic activation of MORs either enhanced or suppressed Meth sensitization. It is possible that alteration of Meth sensitization after systemic administration of MOR ligands reflects the sum of distinct MOR reactions in multiple brain regions. The purpose of the present study was to examine the actions of MORs on Meth sensitization after regionally selective overexpression of human MOR through an AAV6-based gene delivery system. The authors demonstrated that adeno-associated virus (AAV)-MOR increased MOR immunoreactivity and binding in vitro. AAV-MOR or AAV-green fluorescent protein (GFP) was injected into the nucleus accumbens (NAc) or ventral tegmental area (VTA) of adult mice. Two weeks after viral infection, animals received Meth or saline for five consecutive days. Locomotor behavior and striatal dopamine (DA) and 3,4-dihydroxyphenylacetic acid (DOPAC) level were determined. Repeated administration of Meth progressively increased locomotor activity; this sensitization reaction was attenuated by intra-NAc AAV-MOR microinjections. Infusion of AAV-MOR to VTA enhanced Meth sensitization. AAVMOR significantly enhanced DA levels in VTA after VTA infection but reduced DOPAC/DA turnover in the NAc after NAc injection. These data suggest a differential modulation of Meth sensitization by overexpression of MOR in NAc and VTA. Regional manipulation of MOR expression through AAV may be a novel approach to control Meth abuse and psychomimetic activity.

Clinical Psychoneuroendocrinology and Neuropsychopharmacology Section (CPN)

Development and Validation Of An Assay For Quantitative Analysis Of A Ghrelin Receptor Inverse Agonist In Human Or Rat Plasma and Rat Brain Ghareeb M, Leggio L, El-Kattan A, Akhlaghi F. Analytical and Bioanalytical Chemistry, 2015; 407(19): 5603-5613.
PF-5190457 is a ghrelin receptor inverse agonist that is currently undergoing clinical development for the treatment of alcoholism. The aim of the authors was to develop and validate a simple and sensitive assay for quantitative analysis of PF-5190457 in human or rat plasma and rat brain using

liquid chromatography-tandem mass spectrometry. The lower limit of quantification was 1 ng/mL in rat or human plasma and 0.75 ng/g in rat brain. Intra- and inter-run mean percent accuracies were between 85 and 115% and percent imprecision was ≤15%. The assays were successfully utilized to measure the concentration of PF-5190457 in pre-clinical and clinical pharmacology studies of the compound.

Leptin Levels Are Reduced By Intravenous Ghrelin Administration and Correlated With Cue-Induced Alcohol Craving Haass-Koffler CL, Aoun EG, Swift RM, de la Monte SM, Kenna GA, Leggio L. Translational Psychiatry 2015; 5: e646.
This study tested the hypothesis that intravenous exogenous ghrelin administration acutely decreases endogenous serum leptin levels, and that changes in leptin levels negatively correlate with alcohol craving. This was a double-blind, placebo-controlled human laboratory study. Non-treatment-seeking, alcohol-dependent, heavy drinkers (n=45) were randomized to receive intravenous ghrelin or placebo, followed by a cue-reactivity procedure, during which participants were exposed to neutral (juice) and alcohol trial cues. There was a main effect for intravenous ghrelin administration, compared with placebo, in reducing serum leptin levels. The change of serum leptin level at the alcohol trial correlated with the increase in alcohol urge, whereas urge to drink juice was not correlated with the leptin change at the juice trial. These findings provide preliminary evidence of ghrelin-leptin cross-talk in alcoholic individuals and suggest that their relationship may have a role in alcohol craving.

Management Of Alcohol Use Disorder In Patients Requiring Liver Transplant Lee MR, LeggioL, American Journal of Psychiatry 2015; 172(12): 1182-1189.
This paper critically reviews and discuss the clinical, public health and bioethical issues related to the treatment of alcohol use disorder in patients before and after liver transplant. The review also highlights the critical need to address smoking in this population. This paper was highlighted in the American Journal of Psychiatry as an article that addresses “Core Competencies” as defined by the ACGME and the American Board of Medical Specialties; it was selected to be accompanied by a video (http://ajp.psychiatryonline.org/doi/full/10.1176/appi.ajp.2015.15040567) and was selected by the American Journal of Psychiatry Deputy Editor among the December2015 highlights of the AJP Podcasts (http://ajp.psychiatryonline.org/audio).

Behavioral Neuroscience Research Branch
Neural Engineering Unit

Imaging the Insertion Of Supercliptic 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, supercliptic pHluorin, to the extracellular domain of the receptor. By imaging pHluorin-tagged receptors under total internal reflection fluorescence microscopy (TIRFM), the authors 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):1011-24. 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 the authors 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. IEEE Transactions on , 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.

STAFF HIGHLIGHTS

STAFF AWARDS

Wilson Compton, M.D., NIDA Deputy Director**,** and **Jack Stein, Ph.D.**, and **Maureen Boyle, Ph.D.**, OSPC, received the HHS award for Distinguished Service for their work on the Secretary's Opioid Initiative.

Peter Hartsock, Ph.D., DESPR, was inducted as a Fellow in to The College of Physicians of Philadelphia, November 20th, Philadelphia, PA. The College is one of the oldest such institutions in the U.S. and is the birthplace of American public health. Other Fellows have included Dr. Benjamin Rush, signer of the Declaration of Independence, and the late Surgeon General C. Everett Koop with whom Dr. Hartsock served as co-author of the "Surgeon General's Report on AIDS."

David Thomas, Ph.D., DESPR, was awarded the NIH Director's Award for his part in developing the DHHS National Pain Strategy.

2015 NIDA Director's Awards

The CCTN Scientific Collaborator Group
Udi Ghitza, Ph.D., CCTN
David Liu, M.D., CCTN
Carmen Rosa, M.S., CCTN
Steven Sparenborg, Ph.D., CCTN

The ABCD Planning Group
Ishmael Amarreh, Ph.D., NIMH
Carol Alderson, DER
Cheryl Boyce, Ph.D., DESPR
Kevin Conway, Ph.D., DESPR
Bethany Deeds, Ph.D., DESPR
Matthew Finger, DESPR
Pamela Fleming, DESPR
Joe Frascella, Ph.D., OD
Steven Grant, Ph.D., DNB
Steve Gust, Ph.D., OD
Katia Howlett, Ph.D., DER
Donna Jones, OM
Marya Levintova, Ph.D., FIC
Roger Little, Ph.D., DNB
Vani Pariyadath, Ph.D., DNB
Thomas Radman, Ph.D., DNB
Mark Swieter, Ph.D., DER
Susan Weiss, Ph.D., DER

Christine Salaita, DER

Roger Sorensen, Ph.D., DNB

Kevin Conway, Ph.D., DESPR

Brain Imaging Drug Use Prevention Message Team
Usha Charya. OSPC
Bethany Deeds, Ph.D., DESPR
Steven Grant, Ph.D., DNB
Mary Kautz, Ph.D., DNB
Jacqueline Lloyd, Ph.D, DESPR
Harold Perl, Ph.D., DESPR

The Naloxone Team
Nora Chiang, Ph.D., DTMC
Shwe Gyaw, M.D., DTMC
Phillip Krieter, Ph.D, DTMC
David McCann, Ph.D., DTMC
Moo Park, Ph.D., DTMC
Robert Walsh, DTMC

Will Aklin, Ph.D., DTMC

Marisela Morales, Ph.D., IRP

The NIDA Strategic Planning Workgroup
Ishmael Amarreh, Ph.D., NIMH
Albert Avila, Ph.D, OD
Ruben Baler, Ph.D., OSPC
Jamie Biswas, Ph.D., DTMC
Maureen Boyle, Ph.D., OSPC
Katherine Davenny, M.P.H., OD
Meyer Glantz, Ph.D., DESPR
Elena Koustova, Ph.D, OD
Michelle Leff, M.D., IRP
Roger Little, Ph.D., DNB
Geetha Subramaniam, M.D., CCTN
David Thomas, Ph.D., DESPR
Eric Wargo, Ph.D., OSPC
Susan Weiss, Ph.D., DER

2015 NIDA Director's Innovator Award
Amy Newman, Ph.D, IRP

2015 NIDA Director's Award for Plain Language Writing
Eric Wargo, Ph.D., OSPC

2015 NIDA Director's Award for EEO, Diversity and Quality of Worklife
Susan Harrelson, IRP

30 Years of Government Service Awards
Montrue Crawford, OM
Hirsch Davis, DTMC
Lynda Erinoff, Ph.D., OD
Douglas Janes, OM
Brenda Monarque, OD
Vishnudutt Purohit, D.V.M., Ph.D.,DNB

40 Years of Government Service Awards
Marguerite Lewis, OM
Patricia Ballerstadt, IRP

STAFF CHANGES

New Appointments/Employees

Joellen Austin, MPAff, MSM, joined NIDA as the new Associate Director for Management /Executive Officer on October 19, 2015. Joellen comes to NIDA with 26 years of NIH experience, most recently serving for 4 years as EO for the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina. Prior to NIEHS, Joellen was the EO for the National Institute of Neurological Disorders and Stroke (NINDS). She received her Master of Science degree in Management upon graduation from the Sloan Fellows Program at the Graduate School of Business, Stanford University. She also holds a Master of Public Affairs degree from the Lyndon B. Johnson School of Public Affairs, University of Texas at Austin, and a Bachelor of Arts degree in Economics and Government from Skidmore College. She is a 2006 graduate of the HHS Senior Executive Service (SES) Candidate Development Program and was appointed to the SES in 2007.

Gayathri Dowling, Ph.D. rejoined NIDA on November 1, 2015 as the Director, Adolescent Brain and Cognitive Development (ABCD) Project, in the Division of Extramural Research at NIDA. Prior to that, she served as the Deputy Director of the Office of Science Policy, Engagement, Education, and Communications (OSPEEC) at the National Heart, Lung, and Blood Institute (NHLBI). While at NHLBI, she helped to reorganize the functions of the Institute's policy and communications offices to create OSPEEC, a comprehensive, coordinated, and technology-supported office that provides scientifically-based information to patients and their family members, health professionals, researchers, policy makers, and other stakeholders to inform policy and promote the prevention and treatment of heart, lung, blood, and sleep disorders. Dr. Dowling was also the Chief of the Science Policy Branch in the Office of Science Policy and Communications at NIDA. There she helped to educate a variety of audiences about the science of drug abuse and addiction—developing, guiding, and targeting communications for many different audiences, including Congress, the White House Office of National Drug Control Policy, other Federal Agencies, constituency organizations, physicians, and the general public. Dr. Dowling earned a Ph.D. in Neurobiology from the University of California at Davis, where she studied the developing

nervous system, and subsequently conducted research at the Parkinson's Institute in Sunnyvale, CA studying the role of nicotine in muscle cell degeneration and neuroprotection in a model of Parkinson's disease.

Katia Delrahim Howlett, Ph.D., M.P.P., M.B.A. joined NIDA as a Senior Scientific Program Manager in the Division of Extramural Research on November 1, 2015. She received her Ph.D. in Public Health from the University of California, San Diego, her Master's in Public Policy from Pepperdine University, and her Master of Business Administration from the Johns Hopkins University. At the University of California, San Diego she focused on health behavior and prevention of risky behaviors including those leading to Fetal Alcohol Spectrum Disorders. She has expertise in the fields of psychiatric disorders, public health and safety, health policy, health communication, and substance abuse and addiction. She is widely published in the field of mental illness and substance use disorders, on topics as varied as adolescent substance abuse, technology based health interventions, schizophrenia, antidepressant treatment, panic disorder, mood and anxiety disorders, the burden of phobias on the health-related quality of life, and minor depression. Before coming to NIDA, she served as Project Director of the NIDA Blending Initiative and the SAMHSA National Campaigns contracts. Prior to that, she served as Deputy Director of the Underage Drinking Prevention Education Initiatives contract with SAMHSA. Dr. Delrahim-Howlett became interested in substance abuse prevention and co-morbid mental health issues early in her education when she interned at the NIDA CCTN during her undergraduate studies at the University of California, San Diego. That interest grew as she took part in research projects in drug treatment, psychiatry, and drug trafficking. As Research Associate at the Cedars-Sinai Department of Psychiatry, she contributed to the design of new research protocols and served as lead clinical coordinator for industry sponsored clinical trials. Previously, she served as research assistant for several different psychiatric clinical trials and federal grants.

Bethany Deeds, Ph.D., is serving as Acting Chief of the Prevention Research Branch, Division of Epidemiology, Services and Prevention Research at NIDA.

Jessica Cotto, M.P.H. returned to the Science Policy Branch (SPB) in the Office of Science Policy and Communications (OSPC) in October 2015. Ms. Cotto left OSPC in October 2014, to serve as a Health Science Policy Analyst at NHLBI where she provided the Director and other NHLBI staff with reports on trends in morbidity, morality, and care patterns for diseases within the Institute's mandate. Ms. Cotto originally joined SPB as an Epidemiologist in January 2009 where she was a tremendous asset to the team and we are thrilled to have her back. Her primary responsibilities include analyzing data and synthesizing information from disparate sources to identify trends related to substance use. Prior to NIDA, Ms. Cotto served as a Clinical Research Associate for The Children's National Medical Center, the National Institute of Allergy and Infectious Diseases, and the National Cancer Institute.

Carolyn Tucker has joined NIDA's Division of Extramural Research as an Extramural Support Assistant. With over a decade of government administrative support experience, she assisted in the coordination of divisions and institutional workgroups as well as logistical and planning operations. Her educational experience includes coursework in applied sciences at the University of the District of Columbia and additional training in management and program analysis. She has been a dedicated member of the NIDA Work Life Advisory Committee (WAC) and was recently appointed as the Secretary in 2016. As a proud parent advocate for children's individual education and health

needs, she serves as the Secretary for the Parents of Children with Down syndrome of Prince George's County in Maryland.

Tracey Cain joined the NIDA Office of Management's Office of Acquisitions on January 10, 2016 as a NIDA R&D Contract Specialist. Tracey comes to NIDA from a position in the private sector.

Gweniffer Epps joined the NIDA Office of Management's Office of Acquisitions as a Contract Specialist on January 10, 2016. Gweniffer comes to NIDA from NCI.

Nancy Lamon-Kritikos joined the NIDA Office of Management's Office of Acquisitions as a Station Support Branch Lead Contract Specialist on November 29, 2015. Nancy comes to NIDA from NRC.

Mark McNally joined the NIDA Office of Management's Office of Acquisitions on September 20, 2015 as a NIDA R&D Contract Specialist.

Departures

Syreeta Evans, who has served as a key member of our DESPR operations and administrative team since 2008, accepted a position as Secretary at the Office of the Assistant Secretary for Health (OASH), within the Department of Health and Human Services. She will be supporting Dr. Nancy Lee, the Deputy Assistant Secretary of Health — Women's Health, and Director of the Office on Women's Health.

Cara Batenhorst, Contract Specialist in NIDA's Office of Management left NIDA on December 4, 2015.

Jesus Bonet, an IT Specialist in the NIDA Office of Management's Information & Resource Management Branch left NIDA on November 28, 2015 for a position at the SEC.

Paul Marsalese, a Contract Specialist in the NIDA Office of Management's Office of Acquisition's Station Support Branch left NIDA on October 3, 2015 for a position in the Office of the Secretary, DHHS

John Flannery, a Supervisory Contract Specialist in the NIDA Office of Management's Office of Acquisition's Station Support Branch left NIDA on October 31, 2015 for a position in the NIH Center for Information Technology.

Rodney Brooks, a Contract Specialist in the NIDA Office of Management's Office of Acquisition's Station Support Branch left NIDA on January 23, 2016 for a position in the Office of the Secretary, DHHS.

Retirements

Patricia Ballerstadt, IRP, retired from Federal service on October 1, 2015.

Jamie Biswas, Ph.D., retired from NIDA on December 31st, 2015. Jamie was the Chief of the Medications Research Grants Branch for 15 years. She was a Chemist by training and made significant contributions towards the development of medications to treat Substance Use Disorders. Ivan Montoya will serve as Acting Branch Chief.

Lynda Erinoff, Ph.D., OD, Associate Director, AIDS Research Program, retired on December 31, 2015 after 31 years of federal government service. She worked 2 years at the U.S. Environmental Protection Agency and 29 years at NIDA.

Diana Haikalis, a Grants Management Specialist in DER's Grants Management Branch, retired from Federal service on January 3, 2016 after serving for more than 36 years.

John Hamill, a NIDA R&D Supervisory Contract Specialist in NIDA's Office of Management, retired from Federal service on January 1, 2016.

Amy Siller, a Contract Specialist in NIDA's Office of Acquisitions, Office of Management retired from Federal service on October 2, 2015.

Hari Singh, Ph.D., a Chemist in DNB's Chemistry & Pharmacology Branch retired from Federal service on December 31, 2015.

Barbara Usher, Ph.D., a Program Analyst in DCNBR's Office of the Director, retired from Federal service on October 31, 2015.

GRANTEE HONORS

Kenneth A. Dodge, Ph.D., a William McDougall Professor at the Sanford School of Public Policy, Duke University, Durham, N.C., was recently inducted into the National Academy of Medicine, formerly the Institute of Medicine.

Frank Porreca, Ph.D., was selected for the Ronald Melzack Lecture Award at the 16th World Congress on Pain in Yokohama, Japan, September 2015.

Steffanie Strathdee, Ph.D., a NIDA T32 training program principal investigator at the University of California San Diego Department of Medicine's research was recently highlighted in "Means to an end: Cities, states and provinces are gearing up to halt their AIDS epidemics- though the definition of success varies." Joh Cohen. Science. 2015 July 15; 349 (6245): 226-231. The article featured several NIDA-funded research programs, including her former protégé and NIDA T32 fellow and recent NIDA K01 awardee, Dr. Laramie Smith's research on the HIV care cascade in Tijuana. In addition, it featured the work of Dr. Jose Luis Burgos, a former NIDA diversity supplement awardee. Dr. Strathdee directs a NIDA-funded T32 training program and Fogarty-funded HIV prevention training program grant focused on the Mexico-US border region. In 2010, she received a MERIT award from NIDA for her research on HIV prevention among drug users in Tijuana.