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STAFF REPORT to the NIDA DIRECTOR

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RESEARCH FINDINGS

BASIC AND BEHAVIORAL RESEARCH

AT-1001: A High Affinity α3β4 nAChR Ligand with Novel Nicotine-Suppressive Pharmacology Cippitelli A, Wu J, Gaiolini KA, Mercatelli D, Schoch J, Gorman M, Ramirez A, Ciccocioppo R, Khroyan TV, Tasuda D, Zaveri NT, Pascual C, Xie XS, Toll L. Br J Pharmacol. 2014 Dec 2 [Epub ahead of print].

The α3β4 subtype of nicotinic acetylcholine receptors (nAChR) has been implicated in mediating nicotine reinforcement processes. AT-1001 has been recently described as a high affinity and selective α3β4 nAChR antagonist that blocks nicotine self-administration in rats. The aim of this study was to investigate the mechanism of action underlying the nicotine suppressive effects of AT-1001. Effects of AT-1001 were determined using in vitro assays and rat models of nicotine addiction, and compared to varenicline. AT-1001 and its analog AT-1012 were functionally selective as antagonists for α3β4 over α4β2 nAChR, but not to the same extent as the binding selectivity, and had partial agonist activity at α3β4 nAChR. In contrast, varenicline was a partial agonist at α4β2, a weak agonist at α3β4 and inhibited α4β2 at a much lower concentration than it inhibited α3β4 nAChR. AT-1001 and varenicline also had very different in vivo properties. First, AT-1001 did not exhibit reinforcing properties per se while varenicline was self-administered. Secondly, systemic treatment with AT-1001 did not induce reinstatement of nicotine seeking but rather attenuated reinstatement induced by varenicline, as well as nicotine. Finally, unlike varenicline, AT-1001 selectively blocked nicotine self-administration without altering alcohol lever pressing as assessed in an operant co-administration paradigm. These findings describe a more complex AT-1001 in vitro profile than previously appreciated and provide further support for the potential of AT-1001 and congeners as clinically useful compounds for smoking cessation, with a mechanism of action distinct from currently available medications.

Bidirectional Modulation Of Incubation Of Cocaine Craving By Silent Synapse-Based Remodeling Of Prefrontal Cortex To Accumbens Projections Ma Y-Y, Lee BR, Wang X, Guo C, Liu L, Cui R, Lan Y, Balcita-Pedicino JJ, Wolf ME, Sesack SR, Shaham Y, Schluter OM, Huang YH, Dong Y. Neuron (2014): 83(6), 1453-1467.

Glutamatergic projections from the medial prefrontal cortex (mPFC) to nucleus accumbens (NAc) contribute to cocaine relapse. Here the authors show that silent synapse-based remodeling of the two major mPFC-to-NAc projections differentially regulated the progressive increase in cue-induced cocaine seeking after withdrawal (incubation of cocaine craving). Specifically, cocaine self-administration in rats generated AMPA receptor-silent glutamatergic synapses within both infralimbic (IL) and prelimbic mPFC (PrL) to NAc projections, measured after 1 day of withdrawal. After 45 days of withdrawal, IL-to-NAc silent synapses became unsilenced/matured by recruiting calcium-permeable (CP) AMPARs, whereas PrL-to-NAc silent synapses matured by recruiting non-CP-AMPARs, resulting in differential remodeling of these projections. Optogenetic reversal of silent synapse-based remodeling of IL-to-NAc and PrL-to-NAc projections potentiated and inhibited, respectively, incubation of cocaine craving on withdrawal day 45. Thus, pro- and antirelapse circuitry remodeling is induced in parallel after cocaine self-administration. These results may provide substrates for utilizing endogenous antirelapse mechanisms to reduce cocaine relapse.

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

Reactivation Of Cocaine Reward Memory Engages the Akt/GSK3/Mtor Signaling Pathway and Can Be Disrupted By GSK3 Inhibition Shi X, Miller JS, Harper LJ, Poole RL, Gould TJ, Unterwald EM. Psychopharmacology (Berl). 2014 Aug;231(16):3109-3118.
Memories return to a labile state following their retrieval and must undergo a process of reconsolidation to be maintained. Thus, disruption of cocaine reward memories by interference with reconsolidation may be therapeutically beneficial in the treatment of cocaine addiction. The objectives of this study were to elucidate the signaling pathway involved in reconsolidation of cocaine reward memory and to test whether targeting this pathway could disrupt cocaine-associated contextual memory. Using a mouse model of conditioned place preference, regulation of the activity of glycogen synthase kinase-3 (GSK3), mammalian target of Rapamycin complex 1 (mTORC1), P70S6K, β-catenin, and the upstream signaling molecule Akt, was studied in cortico-limbic-striatal circuitry after re-exposure to an environment previously paired with cocaine. Levels of phosporylated Akt-Thr308, GSK3α-Ser21, GSK3β-Ser9, mTORC1, and P70S6K were reduced in the nucleus accumbens and hippocampus 10 min after the reactivation of cocaine cue memories. Levels of pAkt and pGSK3 were also reduced in the prefrontal cortex. Since reduced phosphorylation of GSK3 indicates heightened enzyme activity, the effect of a selective GSK3 inhibitor, SB216763, on reconsolidation was tested. Administration of SB216763 immediately after exposure to an environment previously paired with cocaine abrogated a previously established place preference, suggesting that GSK3 inhibition interfered with reconsolidation of cocaine-associated reward memories. These findings suggest that the Akt/GSK3/mTORC1 signaling pathway in the nucleus accumbens, hippocampus, and/or prefrontal cortex is critically involved in the reconsolidation of cocaine contextual reward memory. Inhibition of GSK3 activity during memory retrieval can erase an established cocaine place preference.

The G Protein-Biased K-Opioid Receptor Agonist RB-64 Is Analgesic With A Unique Spectrum Of Activities In Vivo White KL, Robinson JE, Zhu H, DiBerto JF, Polepally PR, zjawiony JK, Nichols DE, Malanga CJ, Roth BL. J Pharmacol Exp Ther. 2015 Jan;352(1):98-109.
The hypothesis that functionally selective G protein-coupled receptor (GPCR) agonists may have enhanced therapeutic benefits has revitalized interest for many GPCR targets. In particular, although κ-opioid receptor (KOR) agonists are analgesic with a low risk of dependence and abuse, their use is limited by a propensity to induce sedation, motor incoordination, hallucinations, and

dysphoria-like states. Several laboratories have produced a body of work suggesting that G protein-biased KOR agonists might be analgesic with fewer side effects. Although that has been an intriguing hypothesis, suitable KOR-selective and G protein-biased agonists have not been available to test this idea. Here we provide data using a G protein-biased agonist, RB-64 (22-thiocyanato-salvinorin A), which suggests that KOR-mediated G protein signaling induces analgesia and aversion, whereas β-arrestin-2 signaling may be associated with motor incoordination. Additionally, unlike unbiased KOR agonists, the G protein-biased ligand RB-64 does not induce sedation and does not have anhedonia-like actions, suggesting that a mechanism other than G protein signaling mediates these effects. These findings provide the first evidence for a highly selective and G protein-biased tool compound for which many, but not all, of the negative side effects of KOR agonists can be minimized by creating G protein-biased KOR agonists.

Increased Excitability of Lateral Habenula Neurons in Adolescent Rats following Cocaine Self-administration Neurmann PA, Ishikawa M, Otaka M, Huang YH, Schluter OM, Dong Y. Int J Neuropsychopharmacol. 2014 Dec 28. [Epub ahead of print].

The lateral habenula (LHb) is a brain region that has been critically implicated in modulating negative emotional states and responses to aversive stimuli. Exposure to addictive drugs such as cocaine negatively impacts affective states, an effect persisting longer than acute drug effects. However, the mechanisms of this effect are poorly understood. The authors hypothesized that drugs of abuse, such as cocaine, may contribute to drug-induced negative affective states by altering the firing properties of LHb neurons, thus changing the signaling patterns from the LHb to downstream circuits. Using whole-cell current-clamp recording of acutely prepared brain slices of rats after various periods of withdrawal from cocaine self-administration, the authors characterized an important heterogeneous subregion of the LHb based on membrane properties. They found two major relevant neuronal subtypes: burst firing neurons and regular spiking neurons. They also found that LHb regular spiking neurons had higher membrane excitability for at least 7 days following cocaine self-administration, likely due to a greater membrane resistance. Both the increase in LHb excitability and membrane resistance returned to baseline when tested after a more prolonged period of 45 days of withdrawal. This is the first study to look at intrinsic LHb neuron properties following cocaine exposure beyond acute drug effects. These results may help to explain how cocaine and other drugs negatively impact affect states.

Chronic Pain. Decreased Motivation During Chronic Pain Requires Long-Term Depression In The Nucleus Accumbens Schwartz N, Temkin P, Jurado S, Lim BK, Heifets BD, Polepalli JS, Malenka RC. Science (2014): 345(6196), 535-542.

Several symptoms associated with chronic pain, including fatigue and depression, are characterized by reduced motivation to initiate or complete goal-directed tasks. However, it is unknown whether maladaptive modifications in neural circuits that regulate motivation occur during chronic pain. Here, the authors demonstrate that the decreased motivation elicited in mice by two different models of chronic pain requires a galanin receptor 1-triggered depression of excitatory synaptic transmission in indirect pathway nucleus accumbens medium spiny neurons. These results demonstrate a previously unknown pathological adaption in a key node of motivational neural circuitry that is required for one of the major sequela of chronic pain states and syndromes.

Cocaine Self-Administration In Social Dyads Using Custom-Built Operant Conditioning Chambers Lacy RT, Strickland JC, Smith MA. J Neurosci Methods 2014: 236, 11-8.

Traditionally, the analysis of intravenous drug self-administration is limited to conditions in which subjects are tested in isolation. This limits the translational appeal of these studies because drug use

in humans often occurs in the presence of others. The authors used custom-built operant conditioning chambers that allowed social dyads visual, olfactory, auditory, and limited tactile contact while concurrently self-administering cocaine. Male rats were trained to respond according to a fixed interval schedule of reinforcement (with a limited hold) in order to determine if patterns of cocaine (0.75mg/kg/infusion) self-administration became more similar over time in social pairs. Cocaine self-administration was tested across five days according to a 10-min fixed interval schedule (with a 5-min limited hold). Quarter-life values (time at which 25% of responses were emitted per interval) were analyzed using intraclass correlations. The total number of reinforcers obtained did not vary across the five days of testing; however, quarter-life values became progressively more similar between individuals within the social dyads. Standard operant conditioning chambers are unable to assess responding in multiple animals due to their small size, the need to prevent subjects from responding on the lever of their partner, and the need to prevent infusion lines from entangling. By using custom-built social operant conditioning chambers, we assessed the effects of social contact on cocaine self-administration. Social operant conditioning chambers can be used as a preclinical method to examine social influences on drug self-administration under conditions that approximate human substance use.

Michael Acceptor Approach To the Design Of New Salvinorin A-Based High Affinity Ligands For the Kappa-Opioid Receptor Polepally PR, Huben K, Vardy E, Setola V, Mosier PD, Roth BL, Zjawiony JK. Eur J Med Chem. 2014 Oct 6;85:818-829.
The neoclerodane diterpenoid salvinorin A is a major secondary metabolite isolated from the psychoactive plant Salvia divinorum. Salvinorin A has been shown to have high affinity and selectivity for the κ-opioid receptor (KOR). To study the ligand-receptor interactions that occur between salvinorin A and the KOR, a new series of salvinorin A derivatives bearing potentially reactive Michael acceptor functional groups at C-2 was synthesized and used to probe the salvinorin A binding site. The κ-, δ-, and μ-opioid receptor (KOR, DOR and MOR, respectively) binding affinities and KOR efficacies were measured for the new compounds. Although none showed wash-resistant irreversible binding, most of them showed high affinity for the KOR, and some exhibited dual affinity to KOR and MOR. Molecular modeling techniques based on the recently-determined crystal structure of the KOR combined with results from mutagenesis studies, competitive binding, functional assays and structure-activity relationships, and previous salvinorin A-KOR interaction models were used to identify putative interaction modes of the new compounds with the KOR and MOR.

Cocaine Exposure Reorganizes Cell Type- and Input-Specific Connectivity In the Nucleus Accumbens MacAskill AF, Cassel JM, Carter AG. Nat Neurosci 2014; 17(9): 1198-1207.
Repeated exposure to cocaine alters the structural and functional properties of medium spiny neurons (MSNs) in the nucleus accumbens (NAc). These changes suggest a rewiring of the NAc circuit, with an enhancement of excitatory synaptic connections onto MSNs. However, it is unknown how drug exposure alters the balance of long-range afferents onto different cell types in the NAc. Here the authors used whole-cell recordings, two-photon microscopy, optogenetics and pharmacogenetics to show how repeated cocaine exposure alters connectivity in the mouse NAc medial shell. Cocaine selectively enhanced amygdala innervation of MSNs expressing D1 dopamine receptors (D1-MSNs) relative to D2-MSNs. They also found that amygdala activity was required for cocaine-induced changes to behavior and connectivity. Finally, they established how heightened amygdala innervation can explain the structural and functional changes evoked by cocaine. Their findings reveal how exposure to drugs of abuse fundamentally reorganizes cell type- and input-specific connectivity in the NAc.

Nicotine Consumption Is Regulated By A Human Polymorphism In Dopamine Neurons
Morel C, Fattore L, Pons S, Hay YA, Marti F, Lambolez B, De Biasi M, Lathrop M, Fratta W, Maskos U, Faure P. Mol Psychiatry 2014; 19(8): 930-936.
Smoking is the most important preventable cause of morbidity and mortality worldwide. Recent genome-wide association studies highlighted a human haplotype on chromosome 15 underlying the risk for tobacco dependence and lung cancer. Several polymorphisms in the CHRNA3-CHRNA5-CHRNB4 cluster coding for the nicotinic acetylcholine receptor (nAChR) α3, α5 and β4 subunits were implicated. In mouse models, the authors define a key role in the control of sensitivity to nicotine for the α5 subunit in dopaminergic (DAergic) neurons of the ventral tegmental area (VTA). They first investigated the reinforcing effects of nicotine in drug-naive α5(-/-) mice using an acute intravenous nicotine self-administration task and ex vivo and in vivo electrophysiological recordings of nicotine-elicited DA cell activation. They designed lentiviral re-expression vectors to achieve targeted re-expression of wild-type or mutant α5 in the VTA, in general, or in DA neurons exclusively. Their results establish a crucial role for α5*-nAChRs in DAergic neurons. These receptors are key regulators that determine the minimum nicotine dose necessary for DA cell activation and thus nicotine reinforcement. Finally, the authors demonstrate that a single-nucleotide polymorphism, the non-synonymous α5 variant rs16969968, frequent in many human populations, exhibits a partial loss of function of the protein in vivo. This leads to increased nicotine consumption in the self-administration paradigm. They thus define a critical link between a human predisposition marker, its expression in DA neurons and nicotine intake.

Effects of Oral and Intravenous Administration of Buspirone on Food-Cocaine Choice in Socially Housed Male Cynomolgus Monkeys Czoty PW, Nader MA. Neuropsychopharmacology (2014). [epub ahead of print].
Drugs acting at D3 dopamine receptors have been suggested as medications for cocaine dependence. These experiments examined the effects of intravenously and orally administered buspirone, a D2-like receptor antagonist with high affinity for D3 and D4 receptors, on the relative reinforcing strength of cocaine in group-housed male cynomolgus monkeys. Use of socially housed monkeys permitted the assessment of whether social status, known to influence D2-like receptor availability, modulates the behavioral effects of buspirone. Buspirone was administered acutely to monkeys self-administering cocaine under a food-drug choice procedure in which a cocaine self-administration dose-effect curve was determined daily. When administered by either route, buspirone significantly decreased cocaine choice in dominant-ranked monkeys. In subordinate monkeys, however, i.v. buspirone was ineffective on average, and oral buspirone increased choice of lower cocaine doses. The effects of buspirone only differed according to route of administration in subordinate monkeys. Moreover, it is noteworthy that the effects of buspirone were similar to those of the D3 receptor-selective antagonist PG01037 and qualitatively different than those of less selective drugs that act at D2-like or serotonin (5-HT)1A receptors, suggesting a D3 and possibly D4 receptor mechanism of action for buspirone. Taken together, the data support the utility of drugs targeting D3/D4 receptors as potential treatments for cocaine addiction, particularly in combination with enriching environmental manipulations.

Δ9-Tetrahydrocannabinol and Endocannabinoid Degradative Enzyme Inhibitors Attenuate Intracranial Self-Stimulation In Mice Wiebelhaus JM, Grim TW, Owens RA, Lazenka MF, SIm-Selley LJ, Abdullah RA, Niphakis MJ, Vann RE, Cravatt BF, Wiley JL, Negus SS, Lichtman AH. J Pharmacol Exp Ther. 2015 Feb;352(2):195-207.
A growing body of evidence implicates endogenous cannabinoids as modulators of the mesolimbic dopamine system and motivated behavior. Paradoxically, the reinforcing effects of Δ(9)-

tetrahydrocannabinol (THC), the primary psychoactive constituent of cannabis, have been difficult to detect in preclinical rodent models. In this study, the authors investigated the impact of THC and inhibitors of the endocannabinoid hydrolytic enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) on operant responding for electrical stimulation of the medial forebrain bundle [intracranial self-stimulation (ICSS)], which is known to activate the mesolimbic dopamine system. These drugs were also tested in assays of operant responding for food reinforcement and spontaneous locomotor activity. THC and the MAGL inhibitor JZL184 (4-[bis(1,3-benzodioxol-5-yl)hydroxymethyl]-1-piperidinecarboxylic acid 4-nitrophenyl ester) attenuated operant responding for ICSS and food, and also reduced spontaneous locomotor activity. In contrast, the FAAH inhibitor PF-3845 (N-3-pyridinyl-4-[[3-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenyl]methyl]-1-piperidinecarboxamide) was largely without effect in these assays. Consistent with previous studies showing that combined inhibition of FAAH and MAGL produces a substantially greater cannabimimetic profile than single enzyme inhibition, the dual FAAH-MAGL inhibitor SA-57 (4-[2-(4-chlorophenyl)ethyl]-1-piperidinecarboxylic acid 2-(methylamino)-2-oxoethyl ester) produced a similar magnitude of ICSS depression as that produced by THC. ICSS attenuation by JZL184 was associated with increased brain levels of 2-arachidonoylglycerol (2-AG), whereas peak effects of SA-57 were associated with increased levels of both N-arachidonoylethanolamine (anandamide) and 2-AG. The cannabinoid receptor type 1 receptor antagonist rimonabant, but not the cannabinoid receptor type 2 receptor antagonist SR144528, blocked the attenuating effects of THC, JZL184, and SA-57 on ICSS. Thus, THC, MAGL inhibition, and dual FAAH-MAGL inhibition not only reduce ICSS, but also decrease other reinforced and nonreinforced behaviors.

Loss Of BDNF Signaling In D1R-Expressing Nac Neurons Enhances Morphine Reward By Reducing GABA Inhibition Koo JW, Lobo MK, Chaudhury D, Labonte B, Friedman A, Heller E, Pena CJ, Han M-H, Nestler EJ. Neuropsychopharmacology 2014; 39(11): 2646-2653.
The nucleus accumbens (NAc) has a central role in the mechanism of action of drugs of abuse. The major neuronal type within the NAc is the GABAergic medium spiny neuron (MSN), with two major subpopulations defined-termed D1-type and D2-type MSNs-based on the predominant dopamine receptor expressed. However, very little is known about the contribution of altered GABAergic function in NAc MSNs to the neural and behavioral plasticity that contributes to the lasting actions of drugs of abuse. In the present study, the authors show that GABAergic activity is selectively modulated in D1-type MSNs of the NAc by signaling of brain-derived neurotrophic factor (BDNF) and its receptor, tyrosine receptor kinase B (TrkB), and that such adaptations control rewarding responses to morphine. Optical activation of D1-type MSNs, or the knockout of TrkB from D1-type MSNs (D1-TrkB KO), enhances morphine reward, effects not seen for D2-type MSNs. In addition, D1-TrkB KO mice, but not D2-TrkB KO mice, display decreased GABAA receptor (GABAAR) subunit expression and reduced spontaneous inhibitory postsynaptic currents (sIPSCs) in D1-type, but not D2-type, MSNs in the NAc. Furthermore, the authors found that GABAAR antagonism in the NAc enhances morphine reward and that morphine exposure decreases TrkB expression as well as GABAergic activity in D1-type MSNs. Together, these data provide evidence for the enhancement of morphine reward through reduction of inhibitory GABAAR responses, an adaptation mediated by morphine-induced reduction of BDNF-TrkB signaling in D1-type MSNs.

Beyond Cigarettes Per Day. A Genome-Wide Association Study Of The Biomarker Carbon Monoxide Bloom AJ, Hartz SM, Baker TB, Chen LS, Piper ME, Fox L, Martinez M, Hatsukami D, Johnson EO, Laurie CC, Saccone NL, Goate A, Bierut LJ. Ann Am Thorac Soc. 2014 Sep;11(7):1003-1010.

The CHRNA5-CHRNA3-CHRNB4 locus is associated with self-reported smoking behavior and also harbors the strongest genetic associations with chronic obstructive pulmonary disease (COPD) and lung cancer. Because the associations with lung disease remain after adjustment for self-reported smoking behaviors, it has been asserted that CHRNA5-CHRNA3-CHRNB4 variants increase COPD and lung cancer susceptibility independently of their effects on smoking. The objectives of this study were to compare the genetic associations of exhaled carbon monoxide (CO), a biomarker of current cigarette exposure, with self-reported smoking behaviors. A total of 1,521 European American and 247 African American current smokers recruited into smoking cessation studies were assessed for CO at intake before smoking cessation. DNA samples were genotyped using the Illumina Omni2.5 microarray. Genetic associations with CO and smoking behaviors (cigarettes smoked per day, Fagerstrom test for nicotine dependence) were studied. Variants in the CHRNA5-CHRNA3-CHRNB4 locus, including rs16969968, a nonsynonymous variant in CHRNA5, are genomewide association study-significantly associated with CO ($\beta = 2.66$; 95% confidence interval [CI], 1.74-3.58; $P = 1.65 \times 10(-8)$), and this association remains strong after adjusting for smoking behavior ($\beta = 2.18$; 95% CI, 1.32-3.04; $P = 7.47 \times 10(-7)$). The correlation between CO and cigarettes per day is statistically significantly lower ($z = 3.43$; $P = 6.07 \times 10(-4)$) in African Americans ($r = 0.14$; 95% CI, 0.02-0.26; $P = 0.003$) than in European-Americans ($r = 0.36$; 95% CI, 0.31-0.40; $P = 0.0001$). Exhaled CO, a biomarker that is simple to measure, captures aspects of cigarette smoke exposure in current smokers beyond the number of cigarettes smoked per day. Behavioral measures of smoking are therefore insufficient indices of cigarette smoke exposure, suggesting that genetic associations with COPD or lung cancer that persist after adjusting for self-reported smoking behavior may still reflect genetic effects on smoking exposure.

Effects Of Adolescent Caffeine Consumption On Cocaine Sensitivity O'Neill CE, Levis SC, Schreiner DC, Amat J, Maier SF, Bachtell RK. Neuropsychopharmacology 2014. [epub ahead of print].

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

adolescence produced changes in the NAc that are evident in adulthood and may contribute to increases in cocaine-mediated behaviors.

Inhibition Of Monoacylglycerol Lipase Enzyme Reduces Nicotine Withdrawal Muldoon PP, Chen J, Harenza JL, Abdullah RA, Sim-Selley LJ, Cravatt BF, Miles MF, Chen X, Lichtman AH, Damaj MI. Br J Pharmacol. 2014 Sep 26. [Epub ahead of print].
Abrupt discontinuation of nicotine, the main psychoactive component in tobacco, induces a withdrawal syndrome in nicotine-dependent animals, consisting of somatic and affective signs, avoidance of which contributes to drug maintenance. While blockade of fatty acid amide hydrolase (FAAH), the primary catabolic enzyme of the endocannabinoid arachidonoylethanolamine (anandamide; AEA), exacerbates withdrawal responses in nicotine-dependent mice, the role of monoacylglycerol lipase (MAGL), the main hydrolytic enzyme of a second endocannabinoid 2-arachidonylglycerol (2-AG), in nicotine withdrawal remains unexplored. To evaluate the role of MAGL enzyme inhibition in nicotine withdrawal, the authors initially performed a genetic correlation approach using the BXD recombinant inbred mouse panel. They then assessed nicotine withdrawal intensity in the mouse after treatment with the selective MAGL inhibitor JZL184 and after genetic deletion of the enzyme. Lastly, they assessed the association between genotypes and smoking withdrawal phenotypes in two human data sets. BXD mice displayed significant positive correlations between basal MAGL mRNA expression and nicotine withdrawal responses, consistent with the idea that increased 2-AG brain levels may attenuate withdrawal responses. Strikingly, the MAGL inhibitor JZL184 dose-dependently reduced somatic and aversive withdrawal signs, which was blocked by rimonabant, indicating a CB1 receptor-dependent mechanism. MAGL-knockout mice also showed attenuated nicotine withdrawal. Lastly, genetic analyses in humans revealed associations of the MAGL gene with smoking withdrawal in humans.

NIH Electronic Cigarette Workshop: Developing a Research Agenda Walton KM, Abrams DB, Bailey WC, Clark D, Connolly GN, Djordjevic MV, Eissenberg TE, Fiore MC, Goniewicz ML, Haverkos L, Hecht SS, Henningfield JE, Hughes JR, Oncken CA, Postow L, Rose JE, Wanke KL, Yang L, Hatsukami DK. Nicotine Tob Res. 2014 Oct 21 [Epub ahead of print].
Electronic cigarettes (e-cigarettes) represent an emerging public health issue. These devices deliver nicotine along with other constituents, including flavorants, via an inhalable aerosol. Their uptake is rapidly increasing in both adults and youths, primarily in current smokers. Public debate is increasing on how these devices should be regulated and used, yet only limited peer-reviewed research exists. An informed policy for e-cigarettes needs to be developed and their effects on human behavior, physiology, and health need to be understood. This paper describes proceedings from a National Institutes of Health-sponsored workshop, held in November 2013, to identify research needs relating to the effects of e-cigarettes. Discussion topics included e-cigarette risks and abuse potential, the potential role for e-cigarettes in harm reduction and smoking cessation, unintended consequences of e-cigarette use such as becoming a gateway to conventional cigarettes and dual use of both e-cigarettes and conventional cigarettes. The research needs identified by the workshop participants included: standards to measure the contents and emissions of e-cigarettes; biomarkers of exposure; physiological effects of e-cigarettes on tissues and organ systems including pulmonary and cardiovascular; information on e-cigarette users, how the devices are used, and identification of the best tools to assess these measures; factors that drive use and influence patterns of use; and appropriate methods to evaluate a potential role for e-cigarettes in smoking or nicotine cessation. To understand fully the challenges and opportunities that e-cigarettes represent, expertise will be needed in basic, behavioral, translational, and clinical sciences.

Phasic Dopamine Release In the Nucleus Accumbens In Response To Pro-Social 50 Khz Ultrasonic Vocalizations In Rats Willuhn I, Tose A, Wanat MJ, Hart AS, Hollon NG, Phillips PEM, Schwarting RKW, Wohr M. J Neurosci 2014; 34(32): 10616-19623.
Rats emit ultrasonic vocalizations (USVs) that are thought to serve as situation-dependent affective signals and accomplish important communicative functions. In appetitive situations, rats produce 50 kHz USVs, whereas 22 kHz USVs occur in aversive situations. Reception of 50 kHz USVs induces social approach behavior, while 22 kHz USVs lead to freezing behavior. These opposite behavioral responses are paralleled by distinct brain activation patterns, with 50 kHz USVs, but not 22 kHz USVs, activating neurons in the nucleus accumbens (NAcc). The NAcc mediates appetitive behavior and is critically modulated by dopaminergic afferents that are known to encode the value of reward. Therefore, the authors hypothesized that 50 kHz USVs, but not 22 kHz USVs, elicit NAcc dopamine release. While recording dopamine signaling with fast-scan cyclic voltammetry, freely moving rats were exposed to playback of four acoustic stimuli via an ultrasonic speaker in random order: (1) 50 kHz USVs, (2) 22 kHz USVs, (3) time-and amplitude-matched white noise, and (4) background noise. Only presentation of 50 kHz USVs induced phasic dopamine release and elicited approach behavior toward the speaker. Both of these effects, neurochemical and behavioral, were most pronounced during initial playback, but then declined rapidly with subsequent presentations, indicating a close temporal relationship between the two measures. Moreover, the magnitudes of these effects during initial playback were significantly correlated. Collectively, our findings show that NAcc dopamine release encodes pro-social 50 kHz USVs, but not alarming 22 kHz USVs. Thus, these results support the hypothesis that these call types are processed in distinct neuroanatomical regions and establish a functional link between pro-social communicative signals and reward-related neurotransmission.

Direct Regulation Of Diurnal Drd3 Expression and Cocaine Reward By NPAS2 Ozburn AR, Falcon E, Twaddle A, Nugent AL, Gillman AG, Spencer SM, Arey RN, Mukherjee S, Lyons-Weiler J, Self DW, McClung CA. Biol Psychiatry 2014 [epub ahead of print].
Circadian gene disruptions are associated with the development of psychiatric disorders, including addiction. However, the mechanisms by which circadian genes regulate reward remain poorly understood. The authors used mice with a mutation in Npas2 and adeno-associated virus-short hairpin RNA mediated knockdown of Npas2 and Clock in the nucleus accumbens (NAc). They performed conditioned place preference assays. They utilized cell sorting quantitative real-time polymerase chain reaction, and chromatin immunoprecipitation followed by deep sequencing. Npas2 mutants exhibit decreased sensitivity to cocaine reward, which is recapitulated with a knockdown of neuronal PAS domain protein 2 (NPAS2) specifically in the NAc, demonstrating the importance of NPAS2 in this region. Interestingly, reducing circadian locomotor output cycles kaput (CLOCK) (a homologue of NPAS2) in the NAc had no effect, suggesting an important distinction in NPAS2 and CLOCK function. Furthermore, the authors found that NPAS2 expression is restricted to Drd1 expressing neurons while CLOCK is ubiquitous. Moreover, NPAS2 and CLOCK have distinct temporal patterns of DNA binding, and they identified novel and unique binding sites for each protein. The authors identified the Drd3 dopamine receptor as a direct transcriptional target of NPAS2 and found that NPAS2 knockdown in the NAc disrupts its diurnal rhythm in expression. Chronic cocaine treatment likewise disrupts the normal rhythm in Npas2 and Drd3 expression in the NAc, which may underlie behavioral plasticity in response to cocaine. Together, these findings identify an important role for the circadian protein, NPAS2, in the NAc in the regulation of dopamine receptor expression and drug reward.

Enhanced Nicotine Self-Administration And Suppressed Dopaminergic Systems In A Rat Model Of Diabetes O'Dell LE, Natividad LA, Pipkin JA, Roman F, Torres I, Jurado J, Torres OV, Friedman TC, Tenayuca JM, Nazarian A. Addict Biol. 2014 Nov;19(6):1006-1019.
Patients with diabetes display a heightened propensity to use tobacco; however, it is unclear whether they experience enhanced rewarding effects of nicotine. Thus, this study examined the reinforcing effects of nicotine in a rodent model of diabetes involving administration of streptozotocin (STZ), a drug that is toxic to pancreatic insulin-producing cells. The first study compared STZ- and vehicle-treated rats that had 23-hour access to intravenous self-administration (IVSA) of nicotine or saline and concomitant access to food and water. In order to examine the contribution of dopamine to our behavioral effects, dopamine transporter (DAT), D1 and D2 receptor levels were compared in the nucleus accumbens (NAc) following 10 days of nicotine or saline IVSA. Dopamine levels in the NAc were also compared following nicotine administration. Lastly, nicotine metabolism and dose-dependent effects of nicotine IVSA were assessed. The results revealed that STZ-treated rats displayed enhanced nicotine intake and a robust increase in food and water intake relative to controls. Protein analysis revealed an increase in DAT and a decrease in D1 receptor levels in the NAc of STZ- versus vehicle-treated rats regardless of IVSA condition. STZ-treated rats also displayed suppressed NAc dopamine levels during baseline and in response to nicotine. STZ treatment did not alter our assessment of nicotine metabolism. Furthermore, STZ treatment increased nicotine IVSA in a dose-dependent manner. These findings suggest that STZ-treatment increased the rewarding effects of nicotine. This suggests that strong reinforcing effects of nicotine may contribute to greater tobacco use in patients with diabetes.

Probing the Carboxyester Side Chain in Controlled Deactivation (-)-Δ8-Tetrahydro-cannabinols Nikas SP, Sharma R, Paronis CA, Kulkarni S, Thakur GA, Hurst D, Wood JT, Gifford RS, Rajarshi G, Liu Y, Raghav JG, Guo JJ, Jarbe TU, Reggio PH, Bergman J, Makriyannis A. J Med Chem. 2014 Dec 16. [Epub ahead of print].
The authors recently reported on a controlled deactivation/detoxification approach for obtaining cannabinoids with improved druggability. Their design incorporates a metabolically labile ester group at strategic positions within the THC structure. They have now synthesized a series of (-)-Δ8-THC analogues encompassing a carboxyester group within the 3-alkyl chain in an effort to explore this novel cannabinergic chemotype for CB receptor binding affinity, in vitro and in vivo potency and efficacy, as well as controlled deactivation by plasma esterases. They have also probed the chain's polar characteristics with regard to fast onset and short duration of action. The authors lead molecule, namely 2-[(6aR,10aR)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6H-dibenzo [b,d]pyran-3-yl]-2-methyl-propanoic acid 3-cyano-propyl ester (AM7438), showed picomolar affinity for CB receptors and is deactivated by plasma esterases while the respective acid metabolite is inactive. In further in vitro and in vivo experiments, the compound was found to be a remarkably potent and efficacious CB1 receptor agonist with relatively fast onset/offset of action.

Ultrasensitive Detection Of 3D Cerebral Microvascular Network Dynamics In Vivo Pan Y, You J, Volkow ND, Park K, Du C. Neuroimage. 2014 Dec;103:492-501.
Despite widespread applications of multiphoton microscopy in microcirculation, its small field of view and inability to instantaneously quantify cerebral blood flow velocity (CBFv) in vascular networks limit its utility in investigating the heterogeneous responses to brain stimulations. Optical Doppler tomography (ODT) provides 3D images of CBFv networks, but it suffers poor sensitivity for measuring capillary flows. Here the authors report on a new method, contrast-enhanced ODT with Intralipid that significantly improves quantitative CBFv imaging of capillary networks by obviating the errors from long latency between flowing red blood cells (low hematocrit ~20% in

capillaries). This enhanced sensitivity allowed us to measure the ultraslow microcirculation surrounding a brain tumor and the abnormal ingrowth of capillary flows in the tumor as well as in ischemia triggered by chronic cocaine in the mouse brain that could not be detected by regular ODT. It also enabled significantly enhanced sensitivity for quantifying the heterogeneous CBFv responses of vascular networks to acute cocaine exposure. Inasmuch as lipid emulsions are widely used for parenteral nutrition the Intralipid contrast method has translational potential for clinical applications.

Genome-Wide Association Study of Copy Number Variations (CNVs) with Opioid Dependence Li D, Zhao H, Kranzler HR, Li MD, Jensen KP, Zayats T, Farrer LA, Gelernter J. Neuropsychopharmacology 2014 [epub ahead of print].
Single-nucleotide polymorphisms that have been associated with opioid dependence (OD) altogether account for only a small proportion of the known heritability. Most of the genetic risk factors are unknown. Some of the 'missing heritability' might be explained by copy number variations (CNVs) in the human genome. The authors used Illumina HumanOmni1 arrays to genotype 5152 African-American and European-American OD cases and screened controls and implemented combined CNV calling methods. After quality control measures were applied, a genome-wide association study (GWAS) of CNVs with OD was performed. For common CNVs, two deletions and one duplication were significantly associated with OD genome-wide (eg, $P=2 \times 10\text{-}8$ and OR (95% CI)=0.64 (0.54-0.74) for a chromosome 18q12.3 deletion). Several rare or unique CNVs showed suggestive or marginal significance with large effect sizes. This study is the first GWAS of OD using CNVs. Some identified CNVs harbor genes newly identified here to be of biological importance in addiction, whereas others affect genes previously known to contribute to substance dependence risk. These findings augment our specific knowledge of the importance of genomic variation in addictive disorders, and provide an addiction CNV pool for further research. These findings require replication

Rapid Dopamine Transmission Within the Nucleus Accumbens: Dramatic Difference Between Morphine and Oxycodone Delivery Vander Weele CM, Porter-Stransky KA, Mabrouk OS, Lovic V, Singer BF, Kennedy RT, Aragona BJ. Eur J Neurosci. 2014 Oct;40(7):3041-3054.
While most drugs of abuse increase dopamine neurotransmission, rapid neurochemical measurements show that different drugs evoke distinct dopamine release patterns within the nucleus accumbens. Rapid changes in dopamine concentration following psychostimulant administration have been well studied; however, such changes have never been examined following opioid delivery. Here, the authors provide novel measures of rapid dopamine release following intravenous infusion of two opioids, morphine and oxycodone, in drug-naïve rats using fast-scan cyclic voltammetry and rapid (1 min) microdialysis coupled with high-performance liquid chromatography - tandem mass spectrometry (HPLC-MS). In addition to measuring rapid dopamine transmission, microdialysis HPLC-MS measures changes in GABA, glutamate, monoamines, monoamine metabolites and several other neurotransmitters. Although both opioids increased dopamine release in the nucleus accumbens, their patterns of drug-evoked dopamine transmission differed dramatically. Oxycodone evoked a robust and stable increase in dopamine concentration and a robust increase in the frequency and amplitude of phasic dopamine release events. Conversely, morphine evoked a brief (~ 1 min) increase in dopamine that was coincident with a surge in GABA concentration and then both transmitters returned to baseline levels. Thus, by providing rapid measures of neurotransmission, this study reveals previously unknown differences in opioid-induced neurotransmitter signaling. Investigating these differences may be essential for

understanding how these two drugs of abuse could differentially usurp motivational circuitry and powerfully influence behavior.

CB2-Selective Cannabinoid Receptor Ligands: Synthesis, Pharmacological Evaluation, and Molecular Modeling Investigation of 1,8-Naphthyridin-2(1H)-one-3-carboxamides Lucchesi V, Hurst DP, Shore DM, Bertini S, EHrmann BM, Allara M, Lawrence L, Ligresti A, Minutolo F, Saccomanni G, Sharir H, Macchia M, Di Marzo V, Abood ME, Reggio PH, Manera C. J Med Chem. 2014 Nov 13;57(21):8777-8791.

The authors have recently identified 1,8-naphthyridin-2(1H)-one-3-carboxamide as a new scaffold very suitable for the development of new CB2 receptor potent and selective ligands. In this paper they describe a number of additional derivatives in which the same central scaffold has been variously functionalized in position 1 or 6. All new compounds showed high selectivity and affinity in the nanomolar range for the CB2 receptor. Furthermore, they found that their functional activity is controlled by the presence of the substituents at position C-6 of the naphthyridine scaffold. In fact, the introduction of substituents in this position determined a functionality switch from agonist to antagonists/inverse agonists. Finally, docking studies showed that the difference between the pharmacology of these ligands may be in the ability/inability to block the Toggle Switch W6.48(258) (χ1 g+ $\rightarrow$ trans) transition.

Estradiol Facilitation Of Cocaine-Induced Locomotor Sensitization In Female Rats Requires Activation Of Mglur5 Martinez LA, Peterson BM, Meisel RL, Mermelstein PG. Behav Brain Res. 2014 Sep 1;271:39-42.

In comparison to men, women exhibit enhanced responsiveness to the stimulating and addictive properties of cocaine. A growing body of evidence implicates the steroid hormone estradiol in mediating this sex difference, yet the mechanisms underlying estradiol enhancement of behavioral responses to cocaine in females are not known. Recently, the authors have found that estrogen receptor alpha (ERα) functionally couples with the metabotropic glutamate receptor 5 (mGluR5) to mediate the effects of estradiol on both cellular activation as well as dendritic spine plasticity in brain regions involved in cocaine-induced behavioral sensitization. Thus, they sought to determine whether mGluR5 activation is required for the facilitative effects of estradiol on locomotor responses to cocaine. To test this hypothesis, ovariectomized (OVX) female rats were tested for locomotor activity on the first and fifth days of daily systemic injections of cocaine. For the 2 days prior to each locomotor test, animals were injected with the mGluR5 antagonist MPEP (or vehicle) and estradiol (or oil). MPEP treatment blocked the facilitative effects of estradiol on cocaine-induced locomotor sensitization, without affecting acute responses to cocaine or the inhibitory actions of estradiol on weight gain. Considered together, these data indicate that mGluR5 activation is critical for the actions of estradiol on cocaine-induced behavioral sensitization.

Differential Roles of α6β2* and α4β2* Neuronal Nicotinic Receptors in Nicotine- and Cocaine-Conditioned Reward in Mice Sanjakdar SS, Maldoon PP, Marks MJ, Brunzell DH, Maskos U, McIntosh JM, Bowers MS, Damaj MI. Neuropsychopharmacology 2015; 40(2): 350-360.

Mesolimbic α6* nicotinic acetylcholine receptors (nAChRs) are thought to have an important role in nicotine behavioral effects. However, little is known about the role of the various α6*-nAChRs subtypes in the rewarding effects of nicotine. In this report, the authors investigated and compared the role of α6*-nAChRs subtypes and their neuro-anatomical locus in nicotine and cocaine reward-like effects in the conditioned place preference (CPP) paradigm, using pharmacological antagonism of α6β2* nAChRs and genetic deletion of the α6 or α4 subunits in mice. They found that α6 KO mice exhibited a rightward shift in the nicotine dose-response curve compared with WT littermates

but that α4 KO failed to show nicotine preference, suggesting that α6α4β2*-nAChRs are involved. Furthermore, α6β2* nAChRs in nucleus accumbens were found to have an important role in nicotine-conditioned reward as the intra-accumbal injection of the selective α6β2* α-conotoxin MII [H9A; L15A], blocked nicotine CPP. In contrast to nicotine, α6 KO failed to condition to cocaine, but cocaine CPP in the α4 KO was preserved. Intriguingly, α-conotoxin MII [H9A; L15A], blocked cocaine conditioning in α4 KO mice, implicating α6β2* nAChRs in cocaine reward. Importantly, these effects did not generalize as α6 KO showed both a conditioned place aversion to lithium chloride as well as CPP to palatable food. Finally, dopamine uptake was not different between the α6 KO or WT mice. These data illustrate that the subjective rewarding effects of both nicotine and cocaine may be mediated by mesolimbic α6β2* nAChRs and that antagonists of these receptor subtypes may exhibit therapeutic potential.

Individual Differences In Anhedonic and Accumbal Dopamine Responses To Chronic Social Stress and Their Link To Cocaine Self-Administration In Female Rats Shimamoto A, Holly EN, Boyson CO, DeBold JF, Miczek KA. Psychopharmacology (Berl). 2014 Sep 3. [Epub ahead of print].

Women are twice as likely as men to develop major depressive disorder. Exposure to chronic stress can induce depression in some vulnerable individuals, while others are resistant to depressive-like symptoms after equivalent levels of chronic stress. In female rats, individual differences in saccharin intake during chronic social defeat stress may predict subsequent cocaine self-administration, and may be attributed to alterations in mesolimbic dopamine activity. Female rats were exposed to 21 days of chronic social defeat stress, during which they were evaluated for their anhedonia-like responses in the form of saccharin intake. After chronic social defeat stress, the rats were tested for behavioral cross-sensitization to cocaine and escalated cocaine self-administration in a 24-h "binge." A separate group of animals underwent in vivo microdialysis of the nucleus accumbens (NAc) shell to assess dopamine (DA) in response to acute cocaine challenge. Cluster analysis revealed two phenotypes among the stressed female rats based on their saccharin intake while being exposed to stress, termed stress-resistant (SR, 28 %) and stress-sensitive (SS, 72 %). The amount of cocaine self-administered during the 24-h "binge" was positively correlated with preceding saccharin intake. The NAc DA response to a cocaine challenge was significantly lower in SR rats than in the SS and non-stressed control rats. No other significant differences were observed in behavioral cross-sensitization or cocaine self-administration prior to the "binge." Female rats showed individual differences in their anhedonic-like response to chronic social defeat stress, and these differences were reliably associated with subsequent cocaine-taking behavior.

Differential Activation Of Intracellular Versus Plasmalemmal CB2 Cannabinoid Receptors Brailoiu GC, Deliu E, Marcu J, Hoffman NE, Console-Bram L, Zhao P, Madesh M, Abood ME, Brailoiu E. Biochemistry. 2014 Aug 5;53(30):4990-4999.

The therapeutic and psychoactive properties of cannabinoids have long been recognized. The type 2 receptor for cannabinoids (CB2) has emerged as an important therapeutic target in several pathologies, as it mediates beneficial effects of cannabinoids while having little if any psychotropic activity. Difficulties associated with the development of CB2-based therapeutic agents have been related to its intricate pharmacology, including the species specificity and functional selectivity of the CB2-initiated responses. The authors postulated that a plasmalemmal or subcellular location of the receptor may contribute to the differential signaling pathways initiated by its activation. To differentiate between these two, they used extracellular and intracellular administration of CB2 ligands and concurrent calcium imaging in CB2-expressing U2OS cells. They found that extracellular administration of anandamide was ineffective, whereas 2-arachidonoyl glycerol (2-

AG) and WIN55,212-2 triggered delayed, CB2-dependent Ca(2+) responses that were Gq protein-mediated. When microinjected, all agonists elicited fast, transient, and dose-dependent elevations in intracellular Ca(2+) concentration upon activation of Gq-coupled CB2 receptors. The CB2 dependency was confirmed by the sensitivity to AM630, a selective CB2 antagonist, and by the unresponsiveness of untransfected U2OS cells to 2-AG, anandamide, or WIN55,212-2. Moreover, the authors provide functional and morphological evidence that CB2 receptors are localized at the endolysosomes, while their activation releases Ca(2+) from inositol 1,4,5-trisphosphate-sensitive- and acidic-like Ca(2+) stores. Their results support the functionality of intracellular CB2 receptors and their ability to couple to Gq and elicit Ca(2+) signaling. These findings add further complexity to CB2 receptor pharmacology and argue for careful consideration of receptor localization in the development of CB2-based therapeutic agents.

A Heroin Addiction Severity-Associated Intronic Single Nucleotide Polymorphism Modulates Alternative Pre-Mrna Splicing Of The M Opioid Receptor Gene OPRM1 Via Hnrnph Interactions Xu J, Lu Z, Xu M, Pan L, Deng Y, Xie X, Liu H, Ding S, Hurd YL, Pasternak GW, Klein RJ, Cartegni L, Zhou W, Pan Y-X. J Neurosci 2014; 34(33): 11048-11066.
Single nucleotide polymorphisms (SNPs) in the OPRM1 gene have been associated with vulnerability to opioid dependence. The current study identifies an association of an intronic SNP (rs9479757) with the severity of heroin addiction among Han-Chinese male heroin addicts. Individual SNP analysis and haplotype-based analysis with additional SNPs in the OPRM1 locus showed that mild heroin addiction was associated with the AG genotype, whereas severe heroin addiction was associated with the GG genotype. In vitro studies such as electrophoretic mobility shift assay, minigene, siRNA, and antisense morpholino oligonucleotide studies have identified heterogeneous nuclear ribonucleoprotein H (hnRNPH) as the major binding partner for the G-containing SNP site. The G-to-A transition weakens hnRNPH binding and facilitates exon 2 skipping, leading to altered expressions of OPRM1 splice-variant mRNAs and hMOR-1 proteins. Similar changes in splicing and hMOR-1 proteins were observed in human postmortem prefrontal cortex with the AG genotype of this SNP when compared with the GG genotype. Interestingly, the altered splicing led to an increase in hMOR-1 protein levels despite decreased hMOR-1 mRNA levels, which is likely contributed by a concurrent increase in single transmembrane domain variants that have a chaperone-like function on MOR-1 protein stability. These studies delineate the role of this SNP as a modifier of OPRM1 alternative splicing via hnRNPH interactions, and suggest a functional link between an SNP-containing splicing modifier and the severity of heroin addiction.

The Effects Of Post-Extinction Exercise On Cocaine-Primed And Stress-Induced Reinstatement Of Cocaine Seeking In Rats Ogbonmwan YE, Schroeder JP, Holmes PV, Weinshenker D. Psychopharmacology (Berl). 2014 Oct 31. [Epub ahead of print].
Voluntary aerobic exercise has shown promise as a treatment for substance abuse, reducing relapse in cocaine-dependent people. Wheel running also attenuates drug-primed and cue-induced reinstatement of cocaine seeking in rats, an animal model of relapse. However, in most of these studies, wheel access was provided throughout cocaine self-administration and/or extinction and had effects on several parameters of drug seeking. Moreover, the effects of exercise on footshock stress-induced reinstatement have not been investigated. The purposes of this study were to isolate and specifically examine the protective effect of exercise on relapse-like behavior elicited by a drug prime or stress. Rats were trained to self-administer cocaine at a stable level, followed by extinction training. Once extinction criteria were met, rats were split into exercise (24 h, continuous access to running wheel) and sedentary groups for 3 weeks, after which, drug-seeking behavior was assessed following a cocaine prime or footshock. The authors also measured galanin messenger RNA

(mRNA) in the locus coeruleus and A2 noradrenergic nucleus. Exercising rats ran ~4-6 km/day, comparable to levels previously reported for rats without a history of cocaine self-administration. Post-extinction exercise significantly attenuated cocaine-primed, but not footshock stress-induced, reinstatement of cocaine seeking, and increased galanin mRNA expression in the LC but not A2. These results indicate that chronic wheel running can attenuate some forms of reinstatement, even when initiated after the cessation of cocaine self-administration, supporting the idea that voluntary exercise programs may help maintain abstinence in clinical populations.

Salvinorin A Regulates Dopamine Transporter Function Via A Kappa Opioid Receptor And ERK1/2-Dependent Mechanism Neuropharmacology. 2014 Nov;86:228-240.
Salvinorin A (SalA), a selective κ-opioid receptor (KOR) agonist, produces dysphoria and pro-depressant like effects. These actions have been attributed to inhibition of striatal dopamine release. The dopamine transporter (DAT) regulates dopamine transmission via uptake of released neurotransmitter. KORs are apposed to DAT in dopamine nerve terminals suggesting an additional target by which SalA modulates dopamine transmission. SalA produced a concentration-dependent, nor-binaltorphimine (BNI)- and pertussis toxin-sensitive increase of ASP(+) accumulation in EM4 cells coexpressing myc-KOR and YFP-DAT, using live cell imaging and the fluorescent monoamine transporter substrate, trans 4-(4-(dimethylamino)-styryl)-N-methylpyridinium) (ASP(+)). Other KOR agonists also increased DAT activity that was abolished by BNI pretreatment. While SalA increased DAT activity, SalA treatment decreased serotonin transporter (SERT) activity and had no effect on norepinephrine transporter (NET) activity. In striatum, SalA increased the Vmax for DAT mediated DA transport and DAT surface expression. SalA up-regulation of DAT function is mediated by KOR activation and the KOR-linked extracellular signal regulated kinase-½ (ERK1/2) pathway. Co-immunoprecipitation and BRET studies revealed that DAT and KOR exist in a complex. In live cells, DAT and KOR exhibited robust FRET signals under basal conditions. SalA exposure caused a rapid and significant increase of the FRET signal. This suggests that the formation of KOR and DAT complexes is promoted in response to KOR activation. Together, these data suggest that enhanced DA transport and decreased DA release resulting in decreased dopamine signalling may contribute to the dysphoric and pro-depressant like effects of SalA and other KOR agonists.

The A3β4* Nicotinic Ach Receptor Subtype Mediates Physical Dependence To Morphine: Mouse And Human Studies Muldoon PP, Jackson KJ, Perez E, Harenza JL, Molas S, Rais B, Anwar H, Zaveri NT, Maldonado R, Maskos U, McIntosh JM, Dierssen M, Miles MF, Chen X, De Biasi M, Damaj MI. Br J Pharmacol. 2014 Aug;171(16):3845-3857
Recent data have indicated that α3β4* neuronal nicotinic (n) ACh receptors may play a role in morphine dependence. Here we investigated if nACh receptors modulate morphine physical withdrawal. To assess the role of α3β4* nACh receptors in morphine withdrawal, the authors used a genetic correlation approach using publically available datasets within the GeneNetwork web resource, genetic knockout and pharmacological tools. Male and female European-American (n = 2772) and African-American (n = 1309) subjects from the Study of Addiction: Genetics and Environment dataset were assessed for possible associations of polymorphisms in the 15q25 gene cluster and opioid dependence. BXD recombinant mouse lines demonstrated an increased expression of α3, β4 and α5 nACh receptor mRNA in the forebrain and midbrain, which significantly correlated with increased defecation in mice undergoing morphine withdrawal. Mice overexpressing the gene cluster CHRNA5/A3/B4 exhibited increased somatic signs of withdrawal. Furthermore, α5 and β4 nACh receptor knockout mice expressed decreased somatic withdrawal signs compared with their wild-type counterparts. Moreover, selective α3β4* nACh receptor

antagonists, α-conotoxin AuIB and AT-1001, attenuated somatic signs of morphine withdrawal in a dose-related manner. In addition, two human datasets revealed a protective role for variants in the CHRNA3 gene, which codes for the α3 nACh receptor subunit, in opioid dependence and withdrawal. In contrast, we found that the α4β2* nACh receptor subtype is not involved in morphine somatic withdrawal signs. Overall, these findings suggest an important role for the α3β4* nACh receptor subtype in morphine physical dependence.

Persistent Reduction Of Cocaine Seeking By Pharmacological Manipulation Of Adenosine A1 And A 2A Receptors During Extinction Training In Rats O'Neill CE, Hobson BD, Levis SC, Bachtell RK. Psychopharmacology (Berl). 2014 Aug;231(16):3179-3188.
Adenosine receptor stimulation and blockade have been shown to modulate a variety of cocaine-related behaviors. These studies identify the direct effects of adenosine receptor stimulation on cocaine seeking during extinction training and the persistent effects on subsequent reinstatement to cocaine seeking. Rats self-administered cocaine on a fixed ratio one schedule in daily sessions over 3 weeks. Following a 1-week withdrawal, the direct effects of adenosine receptor modulation were tested by administering the adenosine A1 receptor agonist, N(6)-cyclopentyladenosine (CPA, 0.03 and 0.1 mg/kg), the adenosine A2A agonist, CGS 21680 (0.03 and 0.1 mg/kg), the presynaptic adenosine A2A receptor antagonist, SCH 442416 (0.3, 1, and 3 mg/kg), or vehicle prior to each of six daily extinction sessions. The persistent effects of adenosine receptor modulation during extinction training were subsequently tested on reinstatement to cocaine seeking induced by cues, cocaine, and the dopamine D2 receptor agonist, quinpirole. All doses of CPA and CGS 21680 impaired initial extinction responding; however, only CPA treatment during extinction produced persistent impairment in subsequent cocaine- and quinpirole-induced seeking. Dissociating CPA treatment from extinction did not alter extinction responding or subsequent reinstatement. Administration of SCH 442416 had no direct effects on extinction responding but produced dose-dependent persistent impairment of cocaine- and quinpirole-induced seeking. These findings demonstrate that adenosine A1 or A2A receptor stimulation directly impair extinction responding. Interestingly, adenosine A1 receptor stimulation or presynaptic adenosine A2A receptor blockade during extinction produces lasting changes in relapse susceptibility.

Differential Effects Of Endocannabinoid Catabolic Inhibitors On Morphine Withdrawal In Mice Gamage TF, Ignatowska-Jankaowska BM, Muldoon PP, Cravatt BF, Damaj MI, Lichtman AH. Drug Alcohol Depend. 2015 Jan 1;146:7-16.
Inhibition of endocannabinoid catabolic enzymes fatty acid amide hydrolase (FAAH) and/or monoacylglycerol lipase (MAGL) reduces somatic morphine withdrawal signs, but its effects on aversive aspects of withdrawal are unknown. The present study investigated whether Δ9-tetrahydrocannabinol (THC), the MAGL inhibitor JZL184, the FAAH inhibitor PF-3845, or the dual FAAH/MAGL inhibitor SA-57 would reduce acquisition of morphine withdrawal-induced conditioned place avoidance (CPA) and jumping. Mice were implanted with placebo or 75mg morphine pellets, 48h later injected with naloxone or saline and placed in the conditioning apparatus, and assessed for CPA at 72h. Subjects were also observed for jumping behavior following naloxone challenge. Naloxone (0.056mg/kg) produced robust CPA in morphine-pelleted, but not placebo-pelleted, mice. Morphine pretreatment prevented the occurrence of withdrawal CPA and withdrawal jumping, while clonidine (an α2 adrenergic receptor agonist) only blocked withdrawal CPA. THC, JZL184, and SA-57 significantly reduced the percentage of mice that jumped during the conditioning session, but did not affect acquisition of withdrawal CPA. PF-3845 did not reduce morphine withdrawal CPA or jumping. Finally, neither THC nor the

endocannabinoid catabolic enzyme inhibitors in non-dependent mice elicited a conditioned place preference or aversion. These findings suggest that inhibiting endocannabinoid catabolic enzymes reduces somatic morphine withdrawal signs, but not aversive aspects as inferred in the CPA paradigm. The observation that non-dependent mice administered inhibitors of endocannabinoid degradation did not display place preferences is consistent with the idea that that endocannabinoid catabolic enzymes might be targeted therapeutically, with reduced risk of abuse.

MPDZ Expression In the Caudolateral Substantia Nigra Pars Reticulata Is Crucially Involved In Alcohol Withdrawal Kruse LC, Walter NA, Buck KJ. 188. Genes Brain Behav. 2014 Nov;13(8):769-776.

Association studies implicate the multiple PDZ domain protein (MUPP1/MPDZ) gene in risk for alcoholism in humans and alcohol withdrawal in mice. Although manipulation of the Mpdz gene by homologous recombination and bacterial artificial chromosome transgenesis has suggested that its expression affects alcohol withdrawal risk, the potential confounding effects of linked genes and developmental compensation currently limit interpretation. Here, using RNA interference (RNAi), the authors directly test the impact of Mpdz expression on alcohol withdrawal severity and provide brain regional mechanistic information. Lentiviral-mediated delivery of Mpdz short hairpin RNA (shRNA) to the caudolateral substantia nigra pars reticulata (clSNr) significantly reduces Mpdz expression and exacerbates alcohol withdrawal convulsions compared with control mice that delivered a scrambled shRNA. Neither baseline nor pentylenetetrazol-enhanced convulsions differed between Mpdz shRNA and control animals, indicating Mpdz expression in the clSNr does not generally affect seizure susceptibility. To the authors' knowledge, these represent the first in vivo Mpdz RNAi analyses, and provide the first direct evidence that Mpdz expression impacts behavior. These results confirm that Mpdz is a quantitative trait gene for alcohol withdrawal and demonstrate that its expression in the clSNr is crucially involved in risk for alcohol withdrawal.

Effects Of Environmental Enrichment On Erk1/2 Phosphorylation In The Rat Prefrontal Cortex Following Nicotine-Induced Sensitization Or Nicotine Self-Administration Gomez AM, Sun WL, Midde NM, Harrod SB, Zhu J.Eur J Neurosci. 2015 Jan;41(1):109-119.

Rats raised in an enriched condition (EC) exhibit alterations in the neurobiological and behavioral response to nicotine compared with rats reared in an impoverished condition (IC) or a standard condition (SC). The current study determined whether environmental enrichment differentially regulates extracellular signal-regulated kinase1/2 (ERK1/2) activity in the prefrontal cortex in rats following nicotine sensitization or nicotine self-administration. Under the saline control condition, EC rats displayed diminished baseline activity and greater sensitization to repeated administration of nicotine compared with IC and SC rats. After repeated saline injections, the basal levels of phosphorylated ERK1/2 (pERK1/2) were higher in EC compared with IC and SC rats, which was negatively correlated with their respective baseline activities. Repeated nicotine (0.35 mg/kg) injections induced pERK1/2 to similar levels in SC and IC rats; however, the induction of pERK1/2 in EC rats by nicotine was not significantly different from saline controls, owing to their high baseline. In the self-administration paradigm, EC rats self-administered less nicotine (0.03 mg/kg/infusion) relative to IC or SC rats on a fixed ratio-1 schedule of reinforcement. Accordingly, no differences in pERK1/2 were found between EC and IC rats self-administering saline, whereas nicotine self-administration resulted in an increase in pERK1/2 in IC rats but not in EC rats. Furthermore, the levels of pERK1/2 in EC and IC rats were positively correlated with their respective total number of nicotine infusions. Thus, these findings suggest that environmental enrichment alters the basal and nicotine-mediated pERK1/2, which may contribute to enrichment-induced behavioral alterations in response to nicotine.

Neuronal Substrates and Functional Consequences Of Prenatal Cannabis Exposure Calvigioni D, Hurd YL, Harkany T, Keimpema E. Eur Child Adolesc Psychiatry. 2014 Oct;23(10):931-941.
Cannabis remains one of the world's most widely used substance of abuse amongst pregnant women. Trends of the last 50 years show an increase in popularity in child-bearing women together with a constant increase in cannabis potency. In addition, potent herbal "legal" highs containing synthetic cannabinoids that mimic the effects of cannabis with unknown pharmacological and toxicological effects have gained rapid popularity amongst young adults. Despite the surge in cannabis use during pregnancy, little is known about the neurobiological and psychological consequences in the exposed offspring. In this review, the authors emphasize the importance of maternal programming, defined as the intrauterine presentation of maternal stimuli to the foetus, in neurodevelopment. In particular, they focus on cannabis-mediated maternal adverse effects, resulting in direct central nervous system alteration or sensitization to late-onset chronic and neuropsychiatric disorders. They compare clinical and preclinical experimental studies on the effects of foetal cannabis exposure until early adulthood, to stress the importance of animal models that permit the fine control of environmental variables and allow the dissection of cannabis-mediated molecular cascades in the developing central nervous system. In sum, the authors conclude that preclinical experimental models confirm clinical studies and that cannabis exposure evokes significant molecular modifications to neurodevelopmental programs leading to neurophysiological and behavioural abnormalities.

Genome-Scale CRISPR-Mediated Control Of Gene Repression and Activation Gilbert LA, Horlbeck MA, Adamson B, Villalta JE, Chen Y, Whitehead EH, Guimaraes C, Panning B, Ploegh HL, Bassik MC, Qi LS, Kampmann M, Weissman JS. Cell (2014): 159(3), 647-61.
While the catalog of mammalian transcripts and their expression levels in different cell types and disease states is rapidly expanding, our understanding of transcript function lags behind. The authors present a robust technology enabling systematic investigation of the cellular consequences of repressing or inducing individual transcripts. They identify rules for specific targeting of transcriptional repressors (CRISPRi), typically achieving 90%-99% knockdown with minimal off-target effects, and activators (CRISPRa) to endogenous genes via endonuclease-deficient Cas9. Together they enable modulation of gene expression over a ~1,000-fold range. Using these rules, the authors construct genome-scale CRISPRi and CRISPRa libraries, each of which we validate with two pooled screens. Growth-based screens identify essential genes, tumor suppressors, and regulators of differentiation. Screens for sensitivity to a cholera-diphtheria toxin provide broad insights into the mechanisms of pathogen entry, retrotranslocation and toxicity. These results establish CRISPRi and CRISPRa as powerful tools that provide rich and complementary information for mapping complex pathways.

Cell-Type Specific Expression Of P11 Controls Cocaine Reward Arango-Lievano M, Schwarz JT, Vernov M, Wilkinson MB, Bradbury K, Feliz A, Marongiu R, Gelfand Y, Warner-Schmidt J, Nestler EJ, Greengard P, Russo SJ, Kaplitt MG. Biol Psychiatry 2014; 76(10); 794-801.
The high rate of comorbidity between depression and cocaine addiction suggests shared molecular mechanisms and anatomical pathways. Limbic structures, such as the nucleus accumbens (NAc), play a crucial role in both disorders, yet how different cell types within these structures contribute to the pathogenesis remains elusive. Downregulation of p11 (S100A10), specifically in the NAc, elicits depressive-like behaviors in mice, but its role in drug addiction is unknown. The authors combined mouse genetics and viral strategies to determine how the titration of p11 levels within the entire NAc affects the rewarding actions of cocaine on behavior (six to eight mice per group) and molecular correlates (three experiments, five to eight mice per group). Finally, the manipulation of

p11 expression in distinct NAc dopaminoceptive neuronal subsets distinguished cell-type specific effects of p11 on cocaine reward (five to eight mice per group). The author demonstrated that p11 knockout mice have enhanced cocaine conditioned place preference, which is reproduced by the focal downregulation of p11 in the NAc of wild-type mice. In wild-type mice, cocaine reduced p11 expression in the NAc, while p11 overexpression exclusively in the NAc reduced cocaine conditioned place preference. Finally, they identified dopamine receptor-1 expressing medium spiny neurons as key mediators of the effects of p11 on cocaine reward. These data provide evidence that disruption of p11 homeostasis in the NAc, particularly in dopamine receptor-1 expressing medium spiny neurons, may underlie pathophysiological mechanisms of cocaine rewarding action. Treatments to counter maladaptation of p11 levels may provide novel therapeutic opportunities for cocaine addiction.

In vivo imaging of histone deacetylases (HDACs) in the central nervous system and major peripheral organs Wang C, Schroeder FA, Wey HY, Borra R, Wagner FF, Reis S, Kim SW, Holson EB, Haggarty SJ, Hooker JM. J Med Chem. 2014 Oct 9;57(19):7999-8009.
Epigenetic enzymes are now targeted to treat the underlying gene expression dysregulation that contribute to disease pathogenesis. Histone deacetylases (HDACs) have shown broad potential in treatments against cancer and emerging data supports their targeting in the context of cardiovascular disease and central nervous system dysfunction. Development of a molecular agent for non-invasive imaging to elucidate the distribution and functional roles of HDACs in humans will accelerate medical research and drug discovery in this domain. Herein, the authors describe the synthesis and validation of an HDAC imaging agent, [(11)C]6. Their imaging results demonstrate that this probe has high specificity, good selectivity, and appropriate kinetics and distribution for imaging HDACs in the brain, heart, kidney, pancreas, and spleen. These findings support the translational potential for [(11)C]6 for human epigenetic imaging.

Deterministic Progenitor Behavior and Unitary Production Of Neurons In the Neocortex
Gao P, Postiglione MP, Krieger TG, Hernandez L, Wang C, Han Z, Streicher C, Papusheva E, Insolera R, Chugh K, Kodish O, Huang K, Simons BD, Luo L, Hippenmeyer S, Shi SH. Cell. 2014 Nov 6;159(4):775-788.
Radial glial progenitors (RGPs) are responsible for producing nearly all neocortical neurons. To gain insight into the patterns of RGP division and neuron production, the authors quantitatively analyzed excitatory neuron genesis in the mouse neocortex using Mosaic Analysis with Double Markers, which provides single-cell resolution of progenitor division patterns and potential in vivo. They found that RGPs progress through a coherent program in which their proliferative potential diminishes in a predictable manner. Upon entry into the neurogenic phase, individual RGPs produce ~8-9 neurons distributed in both deep and superficial layers, indicating a unitary output in neuronal production. Removal of OTX1, a transcription factor transiently expressed in RGPs, results in both deep- and superficial-layer neuron loss and a reduction in neuronal unit size. Moreover, ~1/6 of neurogenic RGPs proceed to produce glia. These results suggest that progenitor behavior and histogenesis in the mammalian neocortex conform to a remarkably orderly and deterministic program.

Enzyme Clustering Accelerates Processing Of Intermediates Through Metabolic Channeling
Castellana M, Wilson MZ, Xu Y, Joshi P, Cristea IM, Rabinowitz JD, Gitai Z, Wingreen NS. Nat Biotechnol (2014): 32(10), 1011-1018.
The authors present a quantitative model to demonstrate that coclustering multiple enzymes into compact agglomerates accelerates the processing of intermediates, yielding the same efficiency

benefits as direct channeling, a well-known mechanism in which enzymes are funneled between enzyme active sites through a physical tunnel. The model predicts the separation and size of coclusters that maximize metabolic efficiency, and this prediction is in agreement with previously reported spacings between coclusters in mammalian cells. For direct validation, the authors study a metabolic branch point in Escherichia coli and experimentally confirm the model prediction that enzyme agglomerates can accelerate the processing of a shared intermediate by one branch, and thus regulate steady-state flux division. These studies establish a quantitative framework to understand coclustering-mediated metabolic channeling and its application to both efficiency improvement and metabolic regulation.

A Critical Time Window For Dopamine Actions On The Structural Plasticity Of Dendritic Spines Yagishita S, Hayashi-Takagi A, Ellis-Davies GCR, Urakubo H, Ishii S, Kasai H. Science (2014): 345(6204), 1616-1620.
Animal behaviors are reinforced by subsequent rewards following within a narrow time window. Such reward signals are primarily coded by dopamine, which modulates the synaptic connections of medium spiny neurons in the striatum. The mechanisms of the narrow timing detection, however, remain unknown. Here, the authors optically stimulated dopaminergic and glutamatergic inputs separately and found that dopamine promoted spine enlargement only during a narrow time window (0.3 to 2 seconds) after the glutamatergic inputs. The temporal contingency was detected by rapid regulation of adenosine 3',5'-cyclic monophosphate in thin distal dendrites, in which protein-kinase A was activated only within the time window because of a high phosphodiesterase activity. Thus, they describe a molecular basis of reinforcement plasticity at the level of single dendritic spines.

Neural Correlates Of Strategic Reasoning During Competitive Games Seo H, Cai X, Donahue CH, Lee D. Science 2014; 346(6207): 340-343.
Although human and animal behaviors are largely shaped by reinforcement and punishment, choices in social settings are also influenced by information about the knowledge and experience of other decision-makers. During competitive games, monkeys increased their payoffs by systematically deviating from a simple heuristic learning algorithm and thereby countering the predictable exploitation by their computer opponent. Neurons in the dorsomedial prefrontal cortex (dmPFC) signaled the animal's recent choice and reward history that reflected the computer's exploitative strategy. The strength of switching signals in the dmPFC also correlated with the animal's tendency to deviate from the heuristic learning algorithm. Therefore, the dmPFC might provide control signals for overriding simple heuristic learning algorithms based on the inferred strategies of the opponent.

Conserved Higher-Order Chromatin Regulates NMDA Receptor Gene Expression and Cognition Bharadwaj R, Peter CJ, Jiang Y, Roussos P, Vogel-Ciernia A, Shen EY, Mitchell AC, Mao W, Whittle C, Dincer A, Jakovcevski M, Pothula V, Rasmussen TP, Giakoumaki SG, Bitsios P, Sherif A, Gardner PD, Ernst P, Ghose S, Sklar P, Haroutunian V, Tamminga C, Myers RH, Futai K, Wood MA, Akbarian S. Neuron (2014): 84(5), 997-1008.
Three-dimensional chromosomal conformations regulate transcription by moving enhancers and regulatory elements into spatial proximity with target genes. Here the authors describe activity-regulated long-range loopings bypassing up to 0.5 Mb of linear genome to modulate NMDA glutamate receptor GRIN2B expression in human and mouse prefrontal cortex. Distal intronic and 3' intergenic loop formations competed with repressor elements to access promoter-proximal sequences, and facilitated expression via a "cargo" of AP-1 and NRF-1 transcription factors and TALE-based transcriptional activators. Neuronal deletion or overexpression of Kmt2a/Mll1 H3K4-

and Kmt1e/Setdb1 H3K9-methyltransferase was associated with higher-order chromatin changes at distal regulatory Grin2b sequences and impairments in working memory. Genetic polymorphisms and isogenic deletions of loop-bound sequences conferred liability for cognitive performance and decreased GRIN2B expression. Dynamic regulation of chromosomal conformations emerges as a novel layer for transcriptional mechanisms impacting neuronal signaling and cognition.

SDCCAG8 Regulates Pericentriolar Material Recruitment And Neuronal Migration In The Developing Cortex Insolera R, Shao W, Airik R, Hildebrandt F, Shi S-H. Neuron (2014): 83(4), 805-822.
Mutations of SDCCAG8 are associated with nephronophthisis and Bardet-Biedl syndrome, as well as schizophrenia; however, the function of SDCCAG8 remains largely unknown. Here, the authors show that SDCCAG8 regulates centrosomal accumulation of pericentriolar material and neuronal polarization and migration in the developing mouse cortex. Sdccag8 expression is selectively elevated in newborn neurons prior to their commencement of radial locomotion, and suppression of this expression by short-hairpin RNAs or a loss-of-function allele impairs centrosomal recruitment of γ-tubulin and pericentrin, interferes with microtubule organization, decouples the centrosome and the nucleus, and disrupts neuronal migration. Moreover, SDCCAG8 interacts and cotraffics with pericentriolar material 1 (PCM1), a centriolar satellite protein crucial for targeting proteins to the centrosome. Expression of SDCCAG8 carrying a human mutation causes neuronal migration defects. These results reveal a critical role for SDCCAG8 in controlling centrosomal properties and function, and provide insights into the basis of neurological defects linked to SDCCAG8 mutations.

Direct Reactivation Of A Coherent Neocortical Memory Of Contex Cowansage KK, Shuman T, Dillingham BC, Chang A, Golshani P, Mayford M. Neuron 2014; 84(2): 432-441.
Declarative memories are thought to be stored within anatomically distributed neuronal networks requiring the hippocampus; however, it is unclear how neocortical areas participate in memory at the time of encoding. Here, the authors use a c-fos-based genetic tagging system to selectively express the channelrhodopsin variant, ChEF, and optogenetically reactivate a specific neural ensemble in retrosplenial cortex (RSC) engaged by context fear conditioning. Artificial stimulation of RSC was sufficient to produce both context-specific behavior and downstream cellular activity commensurate with natural experience. Moreover, optogenetically but not contextually elicited responses were insensitive to hippocampal inactivation, suggesting that although the hippocampus is needed to coordinate activation by sensory cues, a higher-order cortical framework can independently subserve learned behavior, even shortly after learning.

Neural Control and Modulation Of Swimming Speed In the Larval Zebrafish Severi KE, Portugues R, Marques JC, O'Malley DM, Orger MB, Engert F. Neuron 2014; 83(3): 692-707.
Vertebrate locomotion at different speeds is driven by descending excitatory connections to central pattern generators in the spinal cord. To investigate how these inputs determine locomotor kinematics, the authors used whole-field visual motion to drive zebrafish to swim at different speeds. Larvae match the stimulus speed by utilizing more locomotor events, or modifying kinematic parameters such as the duration and speed of swimming bouts, the tail-beat frequency, and the choice of gait. They used laser ablations, electrical stimulation, and activity recordings in descending neurons of the nucleus of the medial longitudinal fasciculus (nMLF) to dissect their contribution to controlling forward movement. They found that the activity of single identified neurons within the nMLF is correlated with locomotor kinematics, and modulates both the duration and oscillation frequency of tail movements. By identifying the contribution of individual

supraspinal circuit elements to locomotion kinematics, the authors build a better understanding of how the brain controls movement.

Pupil Fluctuations Track Fast Switching of Cortical States during Quiet Wakefulness Reimer J, Froudarakis E, Cadwell CR, Yatsenko D, Denfield GH, Tolias AS. Neuron 2014; 84(2): 355-362.
Neural responses are modulated by brain state, which varies with arousal, attention, and behavior. In mice, running and whisking desynchronize the cortex and enhance sensory responses, but the quiescent periods between bouts of exploratory behaviors have not been well studied. The authors found that these periods of "quiet wakefulness" were characterized by state fluctuations on a timescale of 1-2 s. Small fluctuations in pupil diameter tracked these state transitions in multiple cortical areas. During dilation, the intracellular membrane potential was desynchronized, sensory responses were enhanced, and population activity was less correlated. In contrast, constriction was characterized by increased low-frequency oscillations and higher ensemble correlations. Specific subtypes of cortical interneurons were differentially activated during dilation and constriction, consistent with their participation in the observed state changes. Pupillometry has been used to index attention and mental effort in humans, but the intracellular dynamics and differences in population activity underlying this phenomenon were previously unknown.

The Circuit Architecture Of Whole Brains At The Mesoscopic Scale Mitra, PP. Neuron 2014; 83(6): 1273-1283.
Vertebrate brains of even moderate size are composed of astronomically large numbers of neurons and show a great degree of individual variability at the microscopic scale. This variation is presumably the result of phenotypic plasticity and individual experience. At a larger scale, however, relatively stable species-typical spatial patterns are observed in neuronal architecture, e.g., the spatial distributions of somata and axonal projection patterns, probably the result of a genetically encoded developmental program. The mesoscopic scale of analysis of brain architecture is the transitional point between a microscopic scale where individual variation is prominent and the macroscopic level where a stable, species-typical neural architecture is observed. The empirical existence of this scale, implicit in neuroanatomical atlases, combined with advances in computational resources, makes studying the circuit architecture of entire brains a practical task. A methodology has previously been proposed that employs a shotgun-like grid-based approach to systematically cover entire brain volumes with injections of neuronal tracers. This methodology is being employed to obtain mesoscale circuit maps in mouse and should be applicable to other vertebrate taxa. The resulting large data sets raise issues of data representation, analysis, and interpretation, which must be resolved. Even for data representation the challenges are nontrivial: the conventional approach using regional connectivity matrices fails to capture the collateral branching patterns of projection neurons. Future success of this promising research enterprise depends on the integration of previous neuroanatomical knowledge, partly through the development of suitable computational tools that encapsulate such expertise.

Loss Of mTOR-Dependent Macroautophagy Causes Autistic-Like Synaptic Pruning Deficits Tang G, Gudsnuk K, Kuo S-H, Cotrina ML, Rosoklija G, Sosunov A, Sonders MS, Kanter E, Castagna C, Yamamoto A, Yue Z, Arancio O, Peterson BS, Champagne F, Dwork AJ, Goldman J, Sulzer D. Neuron 2014; 83(5): 1131-1143.
Developmental alterations of excitatory synapses are implicated in autism spectrum disorders (ASDs). Here, the authors report increased dendritic spine density with reduced developmental spine pruning in layer V pyramidal neurons in postmortem ASD temporal lobe. These spine deficits correlate with hyperactivated mTOR and impaired autophagy. In Tsc2 ± ASD mice where mTOR is

constitutively overactive, the authors observed postnatal spine pruning defects, blockade of autophagy, and ASD-like social behaviors. The mTOR inhibitor rapamycin corrected ASD-like behaviors and spine pruning defects in Tsc2 ± mice, but not in Atg7(CKO) neuronal autophagy-deficient mice or Tsc2 ± :Atg7(CKO) double mutants. Neuronal autophagy furthermore enabled spine elimination with no effects on spine formation. These findings suggest that mTOR-regulated autophagy is required for developmental spine pruning, and activation of neuronal autophagy corrects synaptic pathology and social behavior deficits in ASD models with hyperactivated mTOR.

Sensory-Related Neural Activity Regulates The Structure Of Vascular Networks In The Cerebral Cortex Lacoste B, Comin CH, Ben-Zvi A, Kaeser PS, Xu X, Costa L da F, Gu C. Neuron 2014; 83(5): 1117-1130.
Neurovascular interactions are essential for proper brain function. While the effect of neural activity on cerebral blood flow has been extensively studied, whether or not neural activity influences vascular patterning remains elusive. Here, the authors demonstrate that neural activity promotes the formation of vascular networks in the early postnatal mouse barrel cortex. Using a combination of genetics, imaging, and computational tools to allow simultaneous analysis of neuronal and vascular components, we found that vascular density and branching were decreased in the barrel cortex when sensory input was reduced by either a complete deafferentation, a genetic impairment of neurotransmitter release at thalamocortical synapses, or a selective reduction of sensory-related neural activity by whisker plucking. In contrast, enhancement of neural activity by whisker stimulation led to an increase in vascular density and branching. The finding that neural activity is necessary and sufficient to trigger alterations of vascular networks reveals an important feature of neurovascular interactions.

Phasic Dopamine Release Drives Rapid Activation Of Striatal D2-Receptors Marcott PF, Mamaligas AA, Ford CP. Neuron 2014; 84(1): 164-176.
Striatal dopamine transmission underlies numerous goal-directed behaviors. Medium spiny neurons (MSNs) are a major target of dopamine in the striatum. However, as dopamine does not directly evoke a synaptic event in MSNs, the time course of dopamine signaling in these cells remains unclear. To examine how dopamine release activates D2-receptors on MSNs, G protein activated inwardly rectifying potassium (GIRK2; Kir 3.2) channels were virally overexpressed in the striatum, and the resulting outward currents were used as a sensor of D2-receptor activation. Electrical and optogenetic stimulation of dopamine terminals evoked robust D2-receptor inhibitory postsynaptic currents (IPSCs) in GIRK2-expressing MSNs that occurred in under a second. Evoked D2-IPSCs could be driven by repetitive stimulation and were not occluded by background dopamine tone. Together, the results indicate that D2-receptors on MSNs exhibit functional low affinity and suggest that striatal D2-receptors can encode both tonic and phasic dopamine signals.

Analytical Tools and Current Challenges In the Modern Era Of Neuroepigenomics Maze I, Shen L, Zhang B, Garcia BA, Shao N, Mitchell A, Sun HS, Akbarian S, Allis CD, Nestler EJ. Nat Neurosci 2014; 17(11): 1476-1490.
Over the past decade, rapid advances in epigenomics research have extensively characterized critical roles for chromatin regulatory events during normal periods of eukaryotic cell development and plasticity, as well as part of aberrant processes implicated in human disease. Application of such approaches to studies of the CNS, however, is more recent. Here the authors provide a comprehensive overview of available tools for analyzing neuroepigenomics data, as well as a discussion of pending challenges specific to the field of neuroscience. Integration of numerous unbiased genome-wide and proteomic approaches will be necessary to fully understand the

neuroepigenome and the extraordinarily complex nature of the human brain. This will be critical to the development of future diagnostic and therapeutic strategies aimed at alleviating the vast array of heterogeneous and genetically distinct disorders of the CNS.

VTA CRF Neurons Mediate The Aversive Effects Of Nicotine Withdrawal And Promote Intake Escalation Grieder TE, Herman MA, Contet C, Tan LA, Vargas-Perez H, Cohen A, Chwalek M, Maal-Bared G, Freiling J, Schlosburg JE, Clarke L, Crawford E, Koebel P. Repunte-Canonigo V, P Sanna P, Tapper AR, Roberto M, Kieffer BL, Sawchenko PE, Koob GF, van der Kooy D, George O. Nat Neurosci 2014; 17(12): 1751-1758.
Dopaminergic neurons in the ventral tegmental area (VTA) are well known for mediating the positive reinforcing effects of drugs of abuse. Here the authors identify in rodents and humans a population of VTA dopaminergic neurons expressing corticotropin-releasing factor (CRF). They provide further evidence in rodents that chronic nicotine exposure upregulates Crh mRNA (encoding CRF) in dopaminergic neurons of the posterior VTA, activates local CRF1 receptors and blocks nicotine-induced activation of transient GABAergic input to dopaminergic neurons. Local downregulation of Crh mRNA and specific pharmacological blockade of CRF1 receptors in the VTA reversed the effect of nicotine on GABAergic input to dopaminergic neurons, prevented the aversive effects of nicotine withdrawal and limited the escalation of nicotine intake. These results link the brain reward and stress systems in the same brain region to signaling of the negative motivational effects of nicotine withdrawal.

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

Reward and Motivation In Pain and Pain Relief Navratilova E, Porreca F. Nat Neurosci 2014; 17(10): 1304-1312.
Pain is fundamentally unpleasant, a feature that protects the organism by promoting motivation and learning. Relief of aversive states, including pain, is rewarding. The aversiveness of pain, as well as the reward from relief of pain, is encoded by brain reward/motivational mesocorticolimbic circuitry. In this Review, the authors describe current knowledge of the impact of acute and chronic pain on reward/motivation circuits gained from preclinical models and from human neuroimaging. They highlight emerging clinical evidence suggesting that anatomical and functional changes in these circuits contribute to the transition from acute to chronic pain. They propose that assessing activity in these conserved circuits can offer new outcome measures for preclinical evaluation of analgesic efficacy to improve translation and speed drug discovery. They further suggest that targeting reward/motivation circuits may provide a path for normalizing the consequences of chronic pain to the brain, surpassing symptomatic management to promote recovery from chronic pain.

Acid-Sensing Ion Channels Contribute To Synaptic Transmission And Inhibit Cocaine-Evoked Plasticity Kreple CJ, Lu Y, Taugher RJ, Schwager-Gutman AL, Du J, Stump M, Wang Y, Ghobbeh A, Fan R, Cosme CV, Sowers LP, Welsh MJ, Radley JJ, LaLumiere RT, Wemmie JA. Nat Neurosci 2014; 17(8): 1083-1091.
Acid-sensing ion channel 1A (ASIC1A) is abundant in the nucleus accumbens (NAc), a region known for its role in addiction. Because ASIC1A has been suggested to promote associative learning, we hypothesized that disrupting ASIC1A in the NAc would reduce drug-associated learning and memory. However, contrary to this hypothesis, the authors found that disrupting ASIC1A in the mouse NAc increased cocaine-conditioned place preference, suggesting an unexpected role for ASIC1A in addiction-related behavior. Moreover, overexpressing ASIC1A in rat NAc reduced cocaine self-administration. Investigating the underlying mechanisms, the authors identified a previously unknown postsynaptic current during neurotransmission that was mediated by ASIC1A and ASIC2 and thus well positioned to regulate synapse structure and function. Consistent with this possibility, disrupting ASIC1A altered dendritic spine density and glutamate receptor function, and increased cocaine-evoked plasticity, which resemble changes previously associated with cocaine-induced behavior. Together, these data suggest that ASIC1A inhibits the plasticity underlying addiction-related behavior and raise the possibility of developing therapies for drug addiction by targeting ASIC-dependent neurotransmission.

The GABAergic Parafacial Zone Is A Medullary Slow Wave Sleep-Promoting Center Anaclet C, Ferrari L, Arrigoni E, Bass CE, Saper CB, Lu J, Fuller PM. Nat Neurosci 2014; 17(9): 1217-1224.
Work in animals and humans has suggested the existence of a slow wave sleep (SWS)-promoting/electroencephalogram (EEG)-synchronizing center in the mammalian lower brainstem. Although sleep-active GABAergic neurons in the medullary parafacial zone (PZ) are needed for normal SWS, it remains unclear whether these neurons can initiate and maintain SWS or EEG slow-wave activity (SWA) in behaving mice. The authors used genetically targeted activation and optogenetically based mapping to examine the downstream circuitry engaged by SWS-promoting PZ neurons, and we found that this circuit uniquely and potently initiated SWS and EEG SWA, regardless of the time of day. PZ neurons monosynaptically innervated and released synaptic GABA onto parabrachial neurons, which in turn projected to and released synaptic glutamate onto cortically projecting neurons of the magnocellular basal forebrain; thus, there is a circuit substrate through which GABAergic PZ neurons can potently trigger SWS and modulate the cortical EEG.

Noninvasive Optical Inhibition With A Red-Shifted Microbial Rhodopsin Chuong AS, Miri ML, Busskamp V, Matthews GAC, Acker LC, Sorensen AT, Young A, Klapoetke NC, Henninger M, Kodandaramaiah SB, Ogawa M, Ramanlal SB, Bandler RC, Allen BD, Forest CR, Chow BY, Han X, Lin Y, Tye KM, Roska B, Cardin JA, Boyden ES. Nat Neurosci 2014; 17(8): 1123-1129.
Optogenetic inhibition of the electrical activity of neurons enables the causal assessment of their contributions to brain functions. Red light penetrates deeper into tissue than other visible wavelengths. The authors present a red-shifted cruxhalorhodopsin, Jaws, derived from Haloarcula (Halobacterium) salinarum (strain Shark) and engineered to result in red light-induced photocurrents three times those of earlier silencers. Jaws exhibits robust inhibition of sensory-evoked neural activity in the cortex and results in strong light responses when used in retinas of retinitis pigmentosa model mice. They also demonstrate that Jaws can noninvasively mediate transcranial optical inhibition of neurons deep in the brains of awake mice. The noninvasive optogenetic inhibition opened up by Jaws enables a variety of important neuroscience experiments and offers a powerful general-use chloride pump for basic and applied neuroscience.

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

Anxiety, Depression, and Cigarette Smoking: A Transdiagnostic Vulnerability Framework to Understanding Emotion-Smoking Comorbidity Leventhal AM, Zvolensky MJ. Psychol Bull 2014 [epub ahead of print].
Research into the comorbidity between emotional psychopathology and cigarette smoking has often focused upon anxiety and depression's manifest symptoms and syndromes, with limited theoretical and clinical advancement. This article presents a novel framework to understanding emotion-smoking comorbidity. The authors propose that transdiagnostic emotional vulnerabilities-core biobehavioral traits reflecting maladaptive responses to emotional states that underpin multiple types of emotional psychopathology-link various anxiety and depressive psychopathologies to smoking. This framework is applied in a review and synthesis of the empirical literature on 3 transdiagnostic emotional vulnerabilities implicated in smoking: (a) anhedonia (Anh; diminished pleasure/interest in response to rewards), (b) anxiety sensitivity (AS; fear of anxiety-related sensations), and (c) distress tolerance (DT; ability to withstand distressing states). The authors conclude that Anh, AS, and DT collectively (a) underpin multiple emotional psychopathologies, (b) amplify smoking's anticipated and actual affect-enhancing properties and other mechanisms underlying smoking, (c) promote progression across the smoking trajectory (i.e., initiation, escalation/progression, maintenance, cessation/relapse), and (d) are promising targets for smoking intervention. After existing gaps are identified, an integrative model of transdiagnostic processes linking emotional psychopathology to smoking is proposed. The model's key premise is that Anh amplifies smoking's anticipated and actual pleasure-enhancing effects, AS amplifies smoking's anxiolytic effects, and poor DT amplifies smoking's distress terminating effects. Collectively, these processes augment the reinforcing properties of smoking for individuals with emotional psychopathology to heighten risk of smoking initiation, progression, maintenance, cessation avoidance, and relapse. The authors conclude by drawing clinical and scientific implications from this framework that may generalize to other comorbidities.

Childhood Maltreatment, Altered Limbic Neurobiology, And Substance Use Relapse Severity Via Trauma-Specific Reductions In Limbic Gray Matter Volume Van Dam NT, Rando K, Potenza MN, Tuit K, Sinha R. JAMA Psychiatry 2014; 71(8): 917-925.
Substance use disorders (SUDs) are among the most common sequelae of childhood maltreatment, yet the independent contributions of SUDs and childhood maltreatment to neurobiological changes and the effect of the latter on relapse risk (a critical variable in addiction treatment) are relatively unknown. The objectives of this study were to identify structural neural characteristics independently associated with childhood maltreatment (CM; a common type of childhood adversity), comparing a sample with SUD with a demographically comparable control sample, and to examine the relationship between CM-related structural brain changes and subsequent relapse. Structural magnetic resonance imaging study comparing 79 treatment-engaged participants with SUD in acute remission in inpatient treatment at a community mental health center vs 98 healthy

control participants at an outpatient research center at an academic medical center. Both groups included individuals with a range of CM experiences. Participants with SUD were followed up prospectively for 90 days to assess relapse and relapse severity. The study intervention was a standard 12-step, recovery-based, inpatient addiction treatment for all participants with SUD. Main outcomes and measures were gray matter volume (GMV), subsequent substance use relapse, days to relapse, and severity of relapse. Controlling for SUD and psychiatric comorbidity, CM (dichotomously classified) was uniquely associated with lower GMV across all participants in the left hippocampus (cornu ammonis 1-3, dentate gyrus), parahippocampus (presubiculum, parasubiculum, prosubiculum, subiculum, and entorhinal cortex), and anterior fusiform gyrus (corrected P<.05; uncorrected P=.001). Among the sample with SUD, CM prospectively predicted a shorter relapse to use of any drug (P=.048), while CM-related GMV reductions predicted severity of substance use relapse (P=.04). Findings indicate that CM was related to decreased GMV in limbic regions, which in turn predicted increased risk of relapse in SUD. These results suggest that CM may significantly affect the course of SUD treatment outcomes and that SUD treatment planning may benefit from identifying and addressing CM.

The Contribution Of Rare and Common Variants In 30 Genes To Risk Nicotine Dependence
Yang J, Wang S, Yang Z, Hodgkinson CA, Iarikova P, Ma JZ, Payne TJ, Goldman D, Li MD. Mol Psychiatry 2014 [epub ahead of print].
Genetic and functional studies have revealed that both common and rare variants of several nicotinic acetylcholine receptor subunits are associated with nicotine dependence (ND). In this study, the authors identified variants in 30 candidate genes including nicotinic receptors in 200 sib pairs selected from the Mid-South Tobacco Family population with equal numbers of African Americans (AAs) and European Americans (EAs). They selected 135 of the rare and common variants and genotyped them in the Mid-South Tobacco Case-Control (MSTCC) population, which consists of 3088 AAs and 1430 EAs. None of the genotyped common variants showed significant association with smoking status (smokers vs non-smokers), Fagerström Test for ND scores or indexed cigarettes per day after Bonferroni correction. Rare variants in NRXN1, CHRNA9, CHRNA2, NTRK2, GABBR2, GRIN3A, DNM1, NRXN2, NRXN3 and ARRB2 were significantly associated with smoking status in the MSTCC AA sample, with weighted sum statistic (WSS) P-values ranging from 2.42 × 10-3 to 1.31 × 10-4 after 106 phenotype rearrangements. The authors also observed a significant excess of rare nonsynonymous variants exclusive to EA smokers in NRXN1, CHRNA9, TAS2R38, GRIN3A, DBH, ANKK1/DRD2, NRXN3 and CDH13 with WSS P-values between 3.5 × 10-5 and 1 × 10-6. Variants rs142807401 (A432T) and rs139982841 (A452V) in CHRNA9 and variants V132L, V389L, rs34755188 (R480H) and rs75981117 (N549S) in GRIN3A are of particular interest because they are found in both the AA and EA samples. A significant aggregate contribution of rare and common coding variants in CHRNA9 to the risk for ND (SKAT-C: P=0.0012) was detected by applying the combined sum test in MSTCC EAs. Together, these results indicate that rare variants alone or combined with common variants in a subset of 30 biological candidate genes contribute substantially to the risk of ND.

Genetic Predisposition To Schizophrenia Associated With Increased Use Of Cannabis Power RA, Verweij KJH, Zuhair M, Montgomery GW, Henders AK, Heath AC, Madden PAF, Medland SE, Wray NR, Martin NG. Mol Psychiatry 2014; 19(11): 1201-1204.
Cannabis is the most commonly used illicit drug worldwide. With debate surrounding the legalization and control of use, investigating its health risks has become a pressing area of research. One established association is that between cannabis use and schizophrenia, a debilitating psychiatric disorder affecting ~1% of the population over their lifetime. Although considerable

evidence implicates cannabis use as a component cause of schizophrenia, it remains unclear whether this is entirely due to cannabis directly raising risk of psychosis, or whether the same genes that increases psychosis risk may also increase risk of cannabis use. In a sample of 2082 healthy individuals, we show an association between an individual's burden of schizophrenia risk alleles and use of cannabis. This was significant both for comparing those who have ever versus never used cannabis (P=2.6 × 10(-4)), and for quantity of use within users (P=3.0 × 10(-3)). Although directly predicting only a small amount of the variance in cannabis use, these findings suggest that part of the association between schizophrenia and cannabis is due to a shared genetic aetiology. This form of gene-environment correlation is an important consideration when calculating the impact of environmental risk factors, including cannabis use.

Dietary Triglycerides Act On Mesolimbic Structures To Regulate the Rewarding and Motivational Aspects Of Feeding Cansell C, Castel J, Denis RGP, Rouch C, Delbes A-S, Martinez S, Mestivier D, Finan B, Maldonado-Aviles JG, Rijnsburger M, Tschop MH, DiLeone RJ, Eckel RH, la Fleur SE, Magnan C, Hnasko TS, Luquet S. Mol Psychiatry 2014; 19(10): 1095-1105.
Circulating triglycerides (TGs) normally increase after a meal but are altered in pathophysiological conditions, such as obesity. Although TG metabolism in the brain remains poorly understood, several brain structures express enzymes that process TG-enriched particles, including mesolimbic structures. For this reason, and because consumption of high-fat diet alters dopamine signaling, the authors tested the hypothesis that TG might directly target mesolimbic reward circuits to control reward-seeking behaviors. They found that the delivery of small amounts of TG to the brain through the carotid artery rapidly reduced both spontaneous and amphetamine-induced locomotion, abolished preference for palatable food and reduced the motivation to engage in food-seeking behavior. Conversely, targeted disruption of the TG-hydrolyzing enzyme lipoprotein lipase specifically in the nucleus accumbens increased palatable food preference and food-seeking behavior. Finally, prolonged TG perfusion resulted in a return to normal palatable food preference despite continued locomotor suppression, suggesting that adaptive mechanisms occur. These findings reveal new mechanisms by which dietary fat may alter mesolimbic circuit function and reward seeking.

Epigenetic Reprogramming Of Cortical Neurons Through Alteration Of Dopaminergic Circuits Brami-Cherrier K, Anzalone A, Ramos M, Forne I, Macciardi F, Imhof A, Borrelli E. Mol Psychiatry 2014; 19(11): 1193-1200.
Alterations of the dopaminergic system are associated with the cognitive and functional dysfunctions that characterize complex neuropsychiatric disorders. The authors modeled a dysfunctional dopaminergic system using mice with targeted ablation of dopamine (DA) D2 autoreceptors in mesencephalic dopaminergic neurons. Loss of D2 autoreceptors abolishes D2-mediated control of DA synthesis and release. Here, they show that this mutation leads to a profound alteration of the genomic landscape of neurons receiving dopaminergic afferents at distal sites, specifically in the prefrontal cortex. Indeed, they observed a remarkable downregulation of gene expression in this area of ~2000 genes, which involves a widespread increase in the histone repressive mark H3K9me2/3. This reprogramming process is coupled to psychotic-like behaviors in the mutant mice. Importantly, chronic treatment with a DA agonist can revert the genomic phenotype. Thus, cortical neurons undergo a profound epigenetic reprogramming in response to dysfunctional D2 autoreceptor signaling leading to altered DA levels, a process that may underlie a number of neuropsychiatric disorders.

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

A New Mechanism Of Allostery In A G Protein-Coupled Receptor Dimer Lane JR, Donthamsetti P, Shonberg J, Draper-Joyce CJ, Dentry S, Michino M, Shi L, Lopez L, Scammells PJ, Capuano B, Sexton PM, Javitch JA, Christopoulos A. Nat Chem Biol 2014; 10(9): 745-752.
SB269652 is to the authors' knowledge the first drug-like allosteric modulator of the dopamine D2 receptor (D2R), but it contains structural features associated with orthosteric D2R antagonists. Using a functional complementation system to control the identity of individual protomers within a dimeric D2R complex, the authors converted the pharmacology of the interaction between SB269652 and dopamine from allosteric to competitive by impairing ligand binding to one of the protomers, indicating that the allostery requires D2R dimers. Additional experiments identified a 'bitopic' pose for SB269652 extending from the orthosteric site into a secondary pocket at the extracellular end of the transmembrane (TM) domain, involving TM2 and TM7. Engagement of this secondary pocket was a requirement for the allosteric pharmacology of SB269652. This suggests a new mechanism whereby a bitopic ligand binds in an extended pose on one G protein-coupled receptor protomer to allosterically modulate the binding of a ligand to the orthosteric site of a second protomer.

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

A Gene-Specific Role For the Ssu72 RNAPII CTD Phosphatase In HIV-1 Tat Transactivation
Chen Y, Zhang L, Estaras C, Choi SH, Moreno Jr L, Karn J, Moresco JJ, Yates 3rd JR, Jones KA. Genes Dev 2014; 28(20): 2261-2275.
HIV-1 Tat stimulates transcription elongation by recruiting the P-TEFb (positive transcription elongation factor-b) (CycT1:CDK9) C-terminal domain (CTD) kinase to the HIV-1 promoter. Here the authors show that Tat transactivation also requires the Ssu72 CTD Ser5P (S5P)-specific phosphatase, which mediates transcription termination and intragenic looping at eukaryotic genes. Importantly, HIV-1 Tat interacts directly with Ssu72 and strongly stimulates its CTD phosphatase activity. They found that Ssu72 is essential for Tat:P-TEFb-mediated phosphorylation of the S5P-CTD in vitro. Interestingly, Ssu72 also stimulates nascent HIV-1 transcription in a phosphatase-dependent manner in vivo. Chromatin immunoprecipitation (ChIP) experiments reveal that Ssu72, like P-TEFb and AFF4, is recruited by Tat to the integrated HIV-1 proviral promoter in TNF-α signaling 2D10 T cells and leaves the elongation complex prior to the termination site. ChIP-seq (ChIP combined with deep sequencing) and GRO-seq (genome-wide nuclear run-on [GRO] combined with deep sequencing) analysis further reveals that Ssu72 predominantly colocalizes with S5P-RNAPII (RNA polymerase II) at promoters in human embryonic stem cells, with a minor peak in the terminator region. A few genes, like NANOG, also have high Ssu72 at the terminator. Ssu72 is not required for transcription at most cellular genes but has a modest effect on cotranscriptional termination. The authors conclude that Tat alters the cellular function of Ssu72 to stimulate viral gene expression and facilitate the early S5P-S2P transition at the integrated HIV-1 promoter.

Functionalized Anodic Aluminum Oxide Membrane-Electrode System For Enzyme Immobilization Chen Z, Zhang J, Singh S, Peltier-Pain P, Thorson JS, Hinds BJ. ACS Nano 2014; 8(8): 8104-8112.
A nanoporous membrane system with directed flow carrying reagents to sequentially attached enzymes to mimic nature's enzyme complex system was demonstrated. Genetically modified glycosylation enzyme, OleD Loki variant, was immobilized onto nanometer-scale electrodes at the pore entrances/exits of anodic aluminum oxide membranes through His6-tag affinity binding. The enzyme activity was assessed in two reactions—a one-step "reverse" sugar nucleotide formation reaction (UDP-Glc) and a two-step sequential sugar nucleotide formation and sugar nucleotide-based glycosylation reaction. For the one-step reaction, enzyme specific activity of 6–20 min(–1) on membrane supports was seen to be comparable to solution enzyme specific activity of 10 min(–1). UDP-Glc production efficiencies as high as 98% were observed at a flow rate of 0.5 mL/min, at which the substrate residence time over the electrode length down pore entrances was matched to the enzyme activity rate. This flow geometry also prevented an unwanted secondary product hydrolysis reaction, as observed in the test homogeneous solution. Enzyme utilization increased by a factor of 280 compared to test homogeneous conditions due to the continuous flow of fresh substrate over the enzyme. To mimic enzyme complex systems, a two-step sequential reaction using OleD Loki enzyme was performed at membrane pore entrances then exits. After UDP-Glc formation at the entrance electrode, aglycon 4-methylumbelliferone was supplied at the exit face of the reactor, affording overall 80% glycosylation efficiency. The membrane platform showed the ability to be regenerated with purified enzyme as well as directly from expression crude, thus demonstrating a single-step immobilization and purification process.

Screen-Based Analysis Of Magnetic Nanoparticle Libraries Formed Using Peptidic Iron Oxide Ligands Barch M, Okada S, Bartelle BB, Jasanoff A. J Am Chem Soc 2014; 136(36): 12516-12519.

The identification of effective polypeptide ligands for magnetic iron oxide nanoparticles (IONPs) could considerably accelerate the high-throughput analysis of IONP-based reagents for imaging and cell labeling. The authors developed a procedure for screening IONP ligands and applied it to compare candidate peptides that incorporated carboxylic acid side chains, catechols, and sequences derived from phage display selection. They found that only l-3,4-dihydroxyphenylalanine (DOPA)-containing peptides were sufficient to maintain particles in solution. They used a DOPA-containing sequence motif as the starting point for generation of a further library of over 30 peptides, each of which was complexed with IONPs and evaluated for colloidal stability and magnetic resonance imaging (MRI) contrast properties. Optimal properties were conferred by sequences within a narrow range of biophysical parameters, suggesting that these sequences could serve as generalizable anchors for formation of polypeptide-IONP complexes. Differences in the amino acid sequence affected T1- and T2-weighted MRI contrast without substantially altering particle size, indicating that the microstructure of peptide-based IONP coatings exerts a substantial influence and could be manipulated to tune properties of targeted or responsive contrast agents. A representative peptide-IONP complex displayed stability in biological buffer and induced persistent MRI contrast in mice, indicating suitability of these species for in vivo molecular imaging applications.

Neuroendocrine Control Of Seasonal Plasticity In The Auditory and Vocal Systems Of Fish Forlano PM, Sisneros JA, Rohmann KN, Bass AH. Front Neuroendocrinol 2014 [epub ahead of print].

Seasonal changes in reproductive-related vocal behavior are widespread among fishes. This review highlights recent studies of the vocal plainfin midshipman fish, Porichthys notatus, a neuroethological model system used for the past two decades to explore neural and endocrine mechanisms of vocal-acoustic social behaviors shared with tetrapods. Integrative approaches combining behavior, neurophysiology, neuropharmacology, neuroanatomy, and gene expression methodologies have taken advantage of simple, stereotyped and easily quantifiable behaviors controlled by discrete neural networks in this model system to enable discoveries such as the first demonstration of adaptive seasonal plasticity in the auditory periphery of a vertebrate as well as rapid steroid and neuropeptide effects on vocal physiology and behavior. This simple model system has now revealed cellular and molecular mechanisms underlying seasonal and steroid-driven auditory and vocal plasticity in the vertebrate brain.

Developmental and Activity-Dependent Expression Of Lancl1 Confers Antioxidant Activity Required For Neuronal Survival Huang C, Chen M, Pang D, Bi D, Zou Y, Xia X, Yang W, Luo L, Deng R, Tan H, Zhou L, Yu S, Guo L, Du X, Cui Y, Hu J, Mao Q, Worley PF, Xiao B. Dev Cell 2014; 30(4): 479-487.

Production of reactive oxygen species (ROS) increases with neuronal activity that accompanies synaptic development and function. Transcription-related factors and metabolic enzymes that are expressed in all tissues have been described to counteract neuronal ROS to prevent oxidative damage. Here, the authors describe the antioxidant gene LanCL1 that is prominently enriched in brain neurons. Its expression is developmentally regulated and induced by neuronal activity, neurotrophic factors implicated in neuronal plasticity and survival, and oxidative stress. Genetic deletion of LanCL1 causes enhanced accumulation of ROS in brain, as well as development-related lipid, protein, and DNA damage; mitochondrial dysfunction; and apoptotic neurodegeneration. LanCL1 transgene protects neurons from ROS. LanCL1 protein purified from eukaryotic cells

catalyzes the formation of thioether products similar to glutathione S-transferase. These studies reveal a neuron-specific glutathione defense mechanism that is essential for neuronal function and survival.

Neuronal BC Rnas Cooperate With Eif4b To Mediate Activity-Dependent Translational Control Eom T, Muslimov IA, Tsokas P, Berardi V, Zhong J, Sacktor TC, Tiedge H. J Cell Biol 2014; 207(2): 237-252.

In neurons, translational regulation of gene expression has been implicated in the activity-dependent management of synapto-dendritic protein repertoires. However, the fundamentals of stimulus-modulated translational control in neurons remain poorly understood. Here the authors describe a mechanism in which regulatory brain cytoplasmic (BC) RNAs cooperate with eukaryotic initiation factor 4B (eIF4B) to control translation in a manner that is responsive to neuronal activity. eIF4B is required for the translation of mRNAs with structured 5' untranslated regions (UTRs), exemplified here by neuronal protein kinase Mζ (PKMζ) mRNA. Upon neuronal stimulation, synapto-dendritic eIF4B is dephosphorylated at serine 406 in a rapid process that is mediated by protein phosphatase 2A. Such dephosphorylation causes a significant decrease in the binding affinity between eIF4B and BC RNA translational repressors, enabling the factor to engage the 40S small ribosomal subunit for translation initiation. BC RNA translational control, mediated via eIF4B phosphorylation status, couples neuronal activity to translational output, and thus provides a mechanistic basis for long-term plastic changes in nerve cells.

Low-Frequency Calcium Oscillations Accompany Deoxyhemoglobin Oscillations In Rat Somatosensory Cortex Du C, Volkow ND, Koretsky AP, Pan Y. Proc Natl Acad Sci U S A 2014; 111(43): E4677-4686.

Spontaneous low-frequency oscillations (LFOs) of blood-oxygen-level-dependent (BOLD) signals are used to map brain functional connectivity with functional MRI, but their source is not well understood. Here the authors used optical imaging to assess whether LFOs from vascular signals covary with oscillatory intracellular calcium (Ca(2+)i) and with local field potentials in the rat's somatosensory cortex. They observed that the frequency of Ca(2+)i oscillations in tissue (~0.07 Hz) was similar to the LFOs of deoxyhemoglobin (HbR) and oxyhemoglobin (HbO2) in both large blood vessels and capillaries. The HbR and HbO2 fluctuations within tissue correlated with Ca(2+)i oscillations with a lag time of ~5-6 s. The Ca(2+)i and hemoglobin oscillations were insensitive to hypercapnia. In contrast, cerebral-blood-flow velocity (CBFv) in arteries and veins fluctuated at a higher frequency (~0.12 Hz) and was sensitive to hypercapnia. However, in parenchymal tissue, CBFv oscillated with peaks at both ~0.06 Hz and ~0.12 Hz. Although the higher-frequency CBFv oscillation (~0.12 Hz) was decreased by hypercapnia, its lower-frequency component (~0.06 Hz) was not. The sensitivity of the higher CBFV oscillations to hypercapnia, which triggers blood vessel vasodilation, suggests its dependence on vascular effects that are distinct from the LFOs detected in HbR, HbO2, Ca(2+)i, and the lower-frequency tissue CBFv, which were insensitive to hypercapnia. Hemodynamic LFOs correlated both with Ca(2+)i and neuronal firing (local field potentials), indicating that they directly reflect neuronal activity (perhaps also glial). These findings show that HbR fluctuations (basis of BOLD oscillations) are linked to oscillatory cellular activity and detectable throughout the vascular tree (arteries, capillaries, and veins).

The Two-Pore Channel (TPC) Interactome Unmasks Isoform-Specific Roles For TPCs In Endolysosomal Morphology and Cell Pigmentation Lin-Moshier Y, Keebler MV, Hooper R, Boulware MJ, Liu X, Churamani D, Abood ME, Walseth TF, Brailoiu E, Patel S, Marchant JS. Proc Natl Acad Sci U S A 2014; 111(36): 13087-13092.

The two-pore channels (TPC1 and TPC2) belong to an ancient family of intracellular ion channels expressed in the endolysosomal system. Little is known about how regulatory inputs converge to modulate TPC activity, and proposed activation mechanisms are controversial. Here, the authors compiled a proteomic characterization of the human TPC interactome, which revealed that TPCs complex with many proteins involved in Ca(2+) homeostasis, trafficking, and membrane organization. Among these interactors, TPCs were resolved to scaffold Rab GTPases and regulate endomembrane dynamics in an isoform-specific manner. TPC2, but not TPC1, caused a proliferation of endolysosomal structures, dysregulating intracellular trafficking, and cellular pigmentation. These outcomes required both TPC2 and Rab activity, as well as their interactivity, because TPC2 mutants that were inactive, or rerouted away from their endogenous expression locale, or deficient in Rab binding, failed to replicate these outcomes. Nicotinic acid adenine dinucleotide phosphate (NAADP)-evoked Ca(2+) release was also impaired using either a Rab binding-defective TPC2 mutant or a Rab inhibitor. These data suggest a fundamental role for the ancient TPC complex in trafficking that holds relevance for lysosomal proliferative scenarios observed in disease.

Economic Demand Predicts Addiction-Like Behavior and Therapeutic Efficacy Of Oxytocin In the Rat Bentzley BS, Jhou TC, Aston-Jones G. Proc Natl Acad Sci U S A 2014; 111(32): 11822-11827.

The two-pore channels (TPC1 and TPC2) belong to an ancient family of intracellular ion channels expressed in the endolysosomal system. Little is known about how regulatory inputs converge to modulate TPC activity, and proposed activation mechanisms are controversial. Here, the authors compiled a proteomic characterization of the human TPC interactome, which revealed that TPCs complex with many proteins involved in Ca(2+) homeostasis, trafficking, and membrane organization. Among these interactors, TPCs were resolved to scaffold Rab GTPases and regulate endomembrane dynamics in an isoform-specific manner. TPC2, but not TPC1, caused a proliferation of endolysosomal structures, dysregulating intracellular trafficking, and cellular pigmentation. These outcomes required both TPC2 and Rab activity, as well as their interactivity, because TPC2 mutants that were inactive, or rerouted away from their endogenous expression locale, or deficient in Rab binding, failed to replicate these outcomes. Nicotinic acid adenine dinucleotide phosphate (NAADP)-evoked Ca(2+) release was also impaired using either a Rab binding-defective TPC2 mutant or a Rab inhibitor. These data suggest a fundamental role for the ancient TPC complex in trafficking that holds relevance for lysosomal proliferative scenarios observed in disease.

IL-6/STAT3 Promotes Regeneration Of Airway Ciliated Cells From Basal Stem Cells Tadokoro T, Wang Y, Barak LS, Bai Y, Randell SH, Hogan BLM. Proc Natl Acad Sci U S A 2014; 111(35): E3641-3649.

The pseudostratified airway epithelium of the lung contains a balanced proportion of multiciliated and secretory luminal cells that are maintained and regenerated by a population of basal stem cells. However, little is known about how these processes are modulated in vivo, and about the potential role of cytokine signaling between stem and progenitor cells and their niche. Using a clonal 3D organoid assay, the authors found that IL-6 stimulated, and Stat3 inhibitors reduced, the generation of ciliated vs. secretory cells from basal cells. Gain-of-function and loss-of-function studies with

cultured mouse and human basal cells suggest that IL-6/Stat3 signaling promotes ciliogenesis at multiple levels, including increases in multicilin gene and forkhead box protein J1 expression and inhibition of the Notch pathway. To test the role of IL-6 in vivo genetically, the authors followed the regeneration of mouse tracheal epithelium after ablation of luminal cells by inhaled SO2. Stat3 is activated in basal cells and their daughters early in the repair process, correlating with an increase in Il-6 expression in platelet-derived growth factor receptor alpha(+) mesenchymal cells in the stroma. Conditional deletion in basal cells of suppressor of cytokine signaling 3, encoding a negative regulator of the Stat3 pathway, results in an increase in multiciliated cells at the expense of secretory and basal cells. By contrast, Il-6 null mice regenerate fewer ciliated cells and an increased number of secretory cells after injury. The results support a model in which IL-6, produced in the reparative niche, functions to enhance the differentiation of basal cells, and thereby acts as a "friend" to promote airway repair rather than a "foe."

Angiotensin II Signaling Via Protein Kinase C Phosphorylates Kelch-Like 3, Preventing WNK4 Degradation Shibata S, Arroyo JP, Castaneda-Bueno M, Puthumana J, Zhang J, Uchida S, Stone KL, Lam TT, Lifton RP. Proc Natl Acad Sci U S A 2014; 111(43): 15556-15561.
Hypertension contributes to the global burden of cardiovascular disease. Increased dietary K(+) reduces blood pressure; however, the mechanism has been obscure. Human genetic studies have suggested that the mechanism is an obligatory inverse relationship between renal salt reabsorption and K(+) secretion. Mutations in the kinases with-no-lysine 4 (WNK4) or WNK1, or in either Cullin 3 (CUL3) or Kelch-like 3 (KLHL3)--components of an E3 ubiquitin ligase complex that targets WNKs for degradation--cause constitutively increased renal salt reabsorption and impaired K(+) secretion, resulting in hypertension and hyperkalemia. The normal mechanisms that regulate the activity of this ubiquitin ligase and levels of WNKs have been unknown. The authors posited that missense mutations in KLHL3 that impair binding of WNK4 might represent a phenocopy of the normal physiologic response to volume depletion in which salt reabsorption is maximized. They show that KLHL3 is phosphorylated at serine 433 in the Kelch domain (a site frequently mutated in hypertension with hyperkalemia) by protein kinase C in cultured cells and that this phosphorylation prevents WNK4 binding and degradation. This phosphorylation can be induced by angiotensin II (AII) signaling. Consistent with these in vitro observations, AII administration to mice, even in the absence of volume depletion, induces renal KLHL3(S433) phosphorylation and increased levels of both WNK4 and the NaCl cotransporter. Thus, AII, which is selectively induced in volume depletion, provides the signal that prevents CUL3/KLHL3-mediated degradation of WNK4, directing the kidney to maximize renal salt reabsorption while inhibiting K(+) secretion in the setting of volume depletion.

Nicotinic and Muscarinic Agonists and Acetylcholinesterase Inhibitors Stimulate A Common Pathway To Enhance Glun2b-NMDAR Responses Ishibashi M, Yamazaki Y, Miledi R, Sumikawa K. Proc Natl Acad Sci U S A 2014; 111(34): 12538-12543.
Nicotinic and muscarinic ACh receptor agonists and acetylcholinesterase inhibitors (AChEIs) can enhance cognitive function. However, it is unknown whether a common signaling pathway is involved in the effect. Here, the authors show that in vivo administration of nicotine, AChEIs, and an m1 muscarinic (m1) agonist increase glutamate receptor, ionotropic, N-methyl D-aspartate 2B (GluN2B)-containing NMDA receptor (NR2B-NMDAR) responses, a necessary component in memory formation, in hippocampal CA1 pyramidal cells, and that coadministration of the m1 antagonist pirenzepine prevents the effect of cholinergic drugs. These observations suggest that the effect of nicotine is secondary to increased release of ACh via the activation of nicotinic ACh receptors (nAChRs) and involves m1 receptor activation through ACh. In vitro activation of m1

receptors causes the selective enhancement of NR2B-NMDAR responses in CA1 pyramidal cells, and in vivo exposure to cholinergic drugs occludes the in vitro effect. Furthermore, in vivo exposure to cholinergic drugs suppresses the potentiating effect of Src on NMDAR responses in vitro. These results suggest that exposure to cholinergic drugs maximally stimulates the m1/guanine nucleotide-binding protein subunit alpha q/PKC/proline-rich tyrosine kinase 2/Src signaling pathway for the potentiation of NMDAR responses in vivo, occluding the in vitro effects of m1 activation and Src. Thus, our results indicate not only that nAChRs, ACh, and m1 receptors are on the same pathway involving Src signaling but also that NR2B-NMDARs are a point of convergence of cholinergic and glutamatergic pathways involved in learning and memory.

Temporally Defined Neocortical Translation and Polysome Assembly Are Determined By the RNA-Binding Protein Hu Antigen R Kraushar ML, Thompson K, Wijeratne HRS, Viljetic B, Sakers K, Marson JW, Kontoyiannis DL, Buyske S, Hart RP, Rasin M-R. Proc Natl Acad Sci U S A 2014); 111(36): E3815-3824.

Precise spatiotemporal control of mRNA translation machinery is essential to the development of highly complex systems like the neocortex. However, spatiotemporal regulation of translation machinery in the developing neocortex remains poorly understood. Here, the authors show that an RNA-binding protein, Hu antigen R (HuR), regulates both neocorticogenesis and specificity of neocortical translation machinery in a developmental stage-dependent manner in mice. Neocortical absence of HuR alters the phosphorylation states of initiation and elongation factors in the core translation machinery. In addition, HuR regulates the temporally specific positioning of functionally related mRNAs into the active translation sites, the polysomes. HuR also determines the specificity of neocortical polysomes by defining their combinatorial composition of ribosomal proteins and initiation and elongation factors. For some HuR-dependent proteins, the association with polysomes likewise depends on the eukaryotic initiation factor 2 alpha kinase 4, which associates with HuR in prenatal developing neocortices. Finally, the authors found that deletion of HuR before embryonic day 10 disrupts both neocortical lamination and formation of the main neocortical commissure, the corpus callosum. This study identifies a crucial role for HuR in neocortical development as a translational gatekeeper for functionally related mRNA subgroups and polysomal protein specificity.

FGF2 Is A Target and A Trigger Of Epigenetic Mechanisms Associated With Differences In Emotionality: Partnership With H3k9me3 Chaudhury S, Aurbach EL, Sharma V, Blandino Jr P, Turner CA, Watson SJ, Akil H. Proc Natl Acad Sci U S A 2014; 111(32): 11834-11839.

Posttranslational modifications of histone tails in chromatin template can result from environmental experiences such as stress and substance abuse. However, the role of epigenetic modifications as potential predisposing factors in affective behavior is less well established. To address this question, the authors used their selectively bred lines of high responder (bHR) and low responder (bLR) rats that show profound and stable differences in affective responses, with bLRs being prone to anxiety- and depression-like behavior and bHRs prone to addictive behavior. They first asked whether these phenotypes are associated with basal differences in epigenetic profiles. Their results reveal broad between-group differences in basal levels of trimethylated histone protein H3 at lysine 9 (H3K9me3) in hippocampus (HC), amygdala, and nucleus accumbens. Moreover, levels of association of H3K9me3 at Glucocorticoid Receptor (GR) and Fibroblast growth Factor 2 (FGF2) promoters differ reciprocally between bHRs and bLRs in these regions, consistent with these genes' opposing levels of expression and roles in modulating anxiety behavior. Importantly, this basal epigenetic pattern is modifiable by FGF2, a factor that modulates anxiety behavior. Thus, early-life FGF2, which decreases anxiety, altered the levels of H3K9me3 and its binding at FGF2 and GR

promoters of bLRs rendering them more similar to bHRs. Conversely, knockdown of HC FGF2 altered both anxiety behavior and levels of H3K9me3 in bHRs, rendering them more bLR-like. These findings implicate FGF2 as a modifier of epigenetic mechanisms associated with emotional responsiveness, and point to H3K9me3 as a key player in the regulation of affective vulnerability.

The Hereditary Spastic Paraplegia-Related Enzyme DDHD2 Is A Principal Brain Triglyceride Lipase Inloes JM, Hsu K-L, Dix MM, Viader A, Masuda K, Takei T, Wood MR, Cravatt BF. Proc Natl Acad Sci U S A 2014; 111(41): 14924-14929.
Complex hereditary spastic paraplegia (HSP) is a genetic disorder that causes lower limb spasticity and weakness and intellectual disability. Deleterious mutations in the poorly characterized serine hydrolase DDHD2 are a causative basis for recessive complex HSP. DDHD2 exhibits phospholipase activity in vitro, but its endogenous substrates and biochemical functions remain unknown. Here, the authors report the development of DDHD2(-/-) mice and a selective, in vivo-active DDHD2 inhibitor and their use in combination with mass spectrometry-based lipidomics to discover that DDHD2 regulates brain triglycerides (triacylglycerols, or TAGs). DDHD2(-/-) mice show age-dependent TAG elevations in the central nervous system, but not in several peripheral tissues. Large lipid droplets accumulated in DDHD2(-/-) brains and were localized primarily to the intracellular compartments of neurons. These metabolic changes were accompanied by impairments in motor and cognitive function. Recombinant DDHD2 displays TAG hydrolase activity, and TAGs accumulated in the brains of wild-type mice treated subchronically with a selective DDHD2 inhibitor. These findings, taken together, indicate that the central nervous system possesses a specialized pathway for metabolizing TAGs, disruption of which leads to massive lipid accumulation in neurons and complex HSP syndrome.

Neurod1 Modulates Opioid Antinociceptive Tolerance Via Two Distinct Mechanisms Li W, He S, Zhou Y, Li Y, Hao J, Zhou X, Wang F, Zhang Y, Huang Z, Li Z, Loh HH, Law P-Y, Zheng H. Biol Psychiatry 2014; 76(10):775-784.
The activity of neurogenic differentiation 1 (Neurod1) decreases after morphine administration, which leads to impairments of the stability of dendritic spines in primary hippocampal neurons, adult neurogenesis in mouse hippocampi, and drug-associated contextual memory. The current study examined whether Neurod1 could affect the development of opioid tolerance. Lentivirus encoding Neurod1, microRNA-190 (miR-190), or short hairpin RNA against Neurod1 was injected into mouse hippocampi separately or combined (more than eight mice for each treatment) to modulate NeuroD1 activity. The antinociceptive median effective dose values of morphine and fentanyl were determined with tail-flick assay and used to calculate development of tolerance. Contextual learning and memory were assayed using the Morris water maze. Decrease in NeuroD1 activity increased the initial antinociceptive median effective dose values of both morphine and fentanyl, which was reversed by restoring NeuroD1 activity. In contrast, decrease in NeuroD1 activity inhibited development of tolerance in a time-dependent manner, paralleling its effects on the acquisition and extinction of contextual memory. In addition, only development of tolerance, but not antinociceptive median effective dose values, was modulated by the expression of miR-190 and Neurod1 driven by Nestin promoter. Neurod1 regulates the developments of opioid tolerance via a time-dependent pathway through contextual learning and a short-response pathway through antinociception.

Loss Of Morphine Reward And Dependence In Mice Lacking G Protein-Coupled Receptor Kinase 5 Gluck L, Loktev A, Mouledous L, Mollereau C, Law P-Y, Schulz S. Biol Psychiatry 2014; 76(10): 767-774.

The clinical benefits of opioid drugs are counteracted by the development of tolerance and addiction. The authors provide in vivo evidence for the involvement of G protein-coupled receptor kinases (GRKs) in opioid dependence in addition to their roles in agonist-selective mu-opioid receptor (MOR) phosphorylation. In vivo MOR phosphorylation was examined by immunoprecipitation and nanoflow liquid chromatography-tandem mass spectrometry analysis. Using the hot-plate and conditioned place preference test, we investigated opioid-related antinociception and reward effects in mice lacking GRK3 or GRK5. Etonitazene and fentanyl stimulated the in vivo phosphorylation of multiple carboxyl-terminal phosphate acceptor sites, including threonine 370, serine 375, and threonine 379, which was predominantly mediated by GRK3. By contrast, morphine promoted a selective phosphorylation of serine 375 that was predominantly mediated by GRK5. In contrast to GRK3 knockout mice, GRK5 knockout mice exhibited reduced antinociceptive responses after morphine administration and developed morphine tolerance similar to wild-type mice but fewer signs of physical dependence. Also, morphine was ineffective in inducing conditioned place preference in GRK5 knockout mice, whereas cocaine conditioned place preference was retained. However, the reward properties of morphine were evident in knock-in mice expressing a phosphorylation-deficient S375A mutation of the MOR. These findings show for the first time that MOR phosphorylation is regulated by agonist-selective recruitment of distinct GRK isoforms that influence different opioid-related behaviors. Modulation of GRK5 function could serve as a new approach for preventing addiction to opioids, while maintaining the analgesic properties of opioid drugs at an effective level.

Interneurons Are Necessary for Coordinated Activity During Reversal Learning in Orbitofrontal Cortex Bissonette GB, Schoenbaum G, Roesch MR, Powell EM. Biol Psychiatry 2014) [epub ahead of print].

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

Poststress Block Of Kappa Opioid Receptors Rescues Long-Term Potentiation Of Inhibitory Synapses And Prevents Reinstatement Of Cocaine Seeking Polter AM, Bishop RA, Briand LA, Graziane NM, Pierce RC, Kauer JA. Biol Psychiatry 2014; 76(10): 785-793.
Dopaminergic neurons in the ventral tegmental area of the brain are an important site of convergence of drugs and stress. The authors previously identified a form of long-term potentiation of gamma-aminobutyric acid (GABA)ergic synapses on these neurons (LTPGABA). Their studies have shown that exposure to acute stress blocks this LTP and that reversal of the block of LTPGABA is correlated with prevention of stress-induced reinstatement of cocaine-seeking behavior. Sprague-Dawley rats were subjected to cold-water swim stress. Midbrain slices were prepared following stress, and whole-cell patch clamp recordings of inhibitory postsynaptic currents were performed from ventral tegmental area dopamine neurons. Antagonists of glucocorticoid receptors and kappa opioid receptors (κORs) were administered at varying time points after stress. Additionally, the ability of a kappa antagonist administered following stress to block forced swim stress-induced reinstatement of cocaine self-administration was tested. The authors found that an acute stressor blocks LTPGABA for 5 days after stress through a transient activation of glucocorticoid receptors and more lasting contribution of κORs. Even pharmacological block of κORs beginning 4 days after stress has occurred reversed the block of LTPGABA. Administration of a κORs antagonist following stress prevents reinstatement of cocaine-seeking behavior. A brief stressor produces changes in the reward circuitry lasting several days. These findings reveal roles for glucocorticoid receptors and κORs as mediators of the lasting effects of stress on synaptic plasticity. κORs antagonists reverse the neuroadaptations underlying stress-induced drug-seeking behavior and may be useful in the treatment of cocaine addiction.

Aversive Stimuli Drive Drug Seeking In A State Of Low Dopamine Tone Twining RC, Wheeler DS, Ebben AL, Jacobsen AJ, Robble MA, Mantsch JR, Wheeler RA. Biol Psychiatry 2014 [epub ahead of print].
Stressors negatively impact emotional state and drive drug seeking, in part, by modulating the activity of the mesolimbic dopamine system. Unfortunately, the rapid regulation of dopamine signaling by the aversive stimuli that cause drug seeking is not well characterized. In a series of experiments, the authors scrutinized the subsecond regulation of dopamine signaling by the aversive stimulus, quinine, and tested its ability to cause cocaine seeking. Additionally, they examined the midbrain regulation of both dopamine signaling and cocaine seeking by the stress-sensitive peptide, corticotropin releasing factor (CRF). Combining fast-scan cyclic voltammetry with behavioral pharmacology, the authors examined the effect of intraoral quinine administration on nucleus accumbens dopamine signaling and hedonic expression in 21 male Sprague-Dawley rats. They tested the role of CRF in modulating aversion-induced changes in dopamine concentration and cocaine seeking by bilaterally infusing the CRF antagonist, CP-376395, into the ventral tegmental area (VTA). The authors found that quinine rapidly reduced dopamine signaling on two distinct time scales. They determined that CRF acted in the VTA to mediate this reduction on only one of these time scales. Further, they found that the reduction of dopamine tone and quinine-induced cocaine seeking were eliminated by blocking the actions of CRF in the VTA during the experience of the aversive stimulus. These data demonstrate that stress-induced drug seeking can occur in a terminal environment of low dopamine tone that is dependent on a CRF-induced decrease in midbrain dopamine activity.

A Shift In the Role Of Glutamatergic Signaling In the Nucleus Accumbens Core With the Development Of An Addicted Phenotype Doyle SE, Ramoa C, Garber G, Newman J, Toor Z, Lynch WJ. Biol Psychiatry 2014; 76(10): 810-815.

While dopamine signaling in the nucleus accumbens (NAc) plays a well-established role in motivating cocaine use in early nonaddicted stages, recent evidence suggests that other signaling pathways may be critical once addiction has developed. Given the importance of glutamatergic signaling in the NAc for drug seeking and relapse, here the authors examined its role in motivating cocaine self-administration under conditions known to produce either a nonaddicted or an addicted phenotype. Following acquisition, male and female Sprague Dawley rats were given either short access (three fixed-ratio 1 sessions, 20 infusions/day) or extended 24-hour access (10 days; 4 trials/hour; up to 96 infusions/day) to cocaine. Following a 14-day abstinence period, motivation for cocaine was assessed under a progressive-ratio schedule, and once stable, the effects of intra-NAc infusions of the glutamate alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate/kainate receptor antagonist CNQX (0, .01, .03, .1 μg/side) were determined. As an additional measure for the development of an addicted phenotype, separate groups of rats were screened under an extinction/cue-induced reinstatement procedure following abstinence from short-access versus extended-access self-administration. Motivation for cocaine and levels of extinction and reinstatement responding were markedly higher following extended-access versus short-access self-administration, confirming the development of an addicted phenotype in the extended-access group. CNQX dose-dependently reduced motivation for cocaine in the extended-access group but was without effect in the short-access group. These results suggest that the role of glutamatergic signaling in the NAc, though not essential for motivating cocaine use in nonaddicted stages, becomes critical once addiction has developed.

Methylphenidate Exerts Dose-Dependent Effects On Glutamate Receptors and Behaviors Cheng J, Xiong Z, Duffney LJ, Wei J, Liu A, Liu S, Chen G-J, Yan Z. Biol Psychiatry 2014; 76(12): 953-962.

Methylphenidate (MPH), a psychostimulant drug used to treat attention-deficit/hyperactivity disorder, produces the effects of increasing alertness and improving attention. However, misuse of MPH has been associated with an increased risk of aggression and psychosis. The authors sought to determine the molecular mechanism underlying the complex actions of MPH. Adolescent (4-week-old) rats were given one injection of MPH at different doses. The impact of MPH on glutamatergic signaling in pyramidal neurons of prefrontal cortex was measured. Behavioral changes induced by MPH were also examined in parallel. Administration of low-dose (.5 mg/kg) MPH selectively potentiated N-methyl-D-aspartate receptor (NMDAR)-mediated excitatory postsynaptic currents (EPSCs) via adrenergic receptor activation, whereas high-dose (10 mg/kg) MPH suppressed both NMDAR-mediated and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor-mediated EPSCs. The dual effects of MPH on EPSCs were associated with bidirectional changes in the surface level of glutamate receptor subunits. Behavioral tests also indicated that low-dose MPH facilitated prefrontal cortex-mediated temporal order recognition memory and attention. Animals injected with high-dose MPH exhibited significantly elevated locomotive activity. Inhibiting the function of synaptosomal-associated protein 25, a key SNARE protein involved in NMDAR exocytosis, blocked the increase of NMDAR-mediated EPSCs by low-dose MPH. In animals exposed to repeated stress, administration of low-dose MPH effectively restored NMDAR function and temporal order recognition memory via a mechanism dependent on synaptosomal-associated protein 25. These results provide a potential mechanism underlying the cognitive-enhancing effects of low-dose MPH as well as the psychosis-inducing effects of high-dose MPH.

The Role Of Brain Interleukin-1 In Stress-Enhanced Fear Learning Jones ME, Lebonville CL, Barrus D, Lysle DT. Neuropsychopharmacology 2014 [epub ahead of print].
Post-Traumatic Stress Disorder (PTSD) has been shown to be associated with pro-inflammatory markers, including elevated plasma levels of interleukin-1β (IL-1β). However, the precise role of neuroinflammation and central immune signaling on the development of this debilitating psychological disorder is not known. Here, the authors employed stress-enhanced fear learning, an animal model of the disorder, to examine the role of central IL-1β in PTSD. The results show that the severe stressor in SEFL induces a time-dependent increase in IL-1β immunoreactivity and mRNA expression within the dentate gyrus of the dorsal hippocampus. There was no increase in IL-1β in the basolateral amygdala or the perirhinal cortex. Moreover, blocking the action of IL-1β following the severe stressor with IL-1 receptor antagonist (10μg, i.c.v., 24 and 48 h after the stressor) prevented the development of SEFL. To provide further support for the role of IL-1β in the development of SEFL, the authors show that systemic morphine, a treatment which is known to reduce both PTSD and SEFL, also reduces IL-1β expression in the dorsal hippocampus induced by the severe stressor. These studies provide the first evidence that IL-1 is involved SEFL, and suggest that IL-1 signaling in the brain may play a critical role in the development of PTSD.

Contribution Of Adenylyl Cyclase Modulation Of Pre- and Postsynaptic GABA Neurotransmission To Morphine Antinociception and Tolerance Bobeck EN, Chen Q, Morgan MM, Ingram SL. Neuropsychopharmacology 2014; 39(9): 2142-2152.
Opioid inhibition of presynaptic GABA release in the ventrolateral periaqueductal gray (vlPAG) activates the descending antinociception pathway. Tolerance to repeated opioid administration is associated with upregulation of adenylyl cyclase activity. The objective of these studies was to test the hypothesis that adenylyl cyclase contributes to opioid tolerance by modulating GABA neurotransmission. Repeated microinjections of morphine or the adenylyl cyclase activator NKH477 into the vlPAG decreased morphine antinociception as would be expected with the development of tolerance. Conversely, microinjection of the adenylyl cyclase inhibitor SQ22536 reversed both the development and expression of morphine tolerance. These behavioral results indicate that morphine tolerance is dependent on adenylyl cyclase activation. Electrophysiological experiments revealed that acute activation of adenylyl cyclase with forskolin increased the frequency of presynaptic GABA release. However, recordings from rats treated with repeated morphine administration did not exhibit increased basal miniature inhibitory postsynaptic current (mIPSC) frequency but showed a decrease in mean amplitude of mIPSCs indicating that repeated morphine administration modulates postsynaptic GABAA receptors without affecting the probability of presynaptic GABA release. SQ22536 reversed this change in mIPSC amplitude and inhibited mIPSC frequency selectively in morphine tolerant rats. Repeated morphine or NKH477 administration also decreased antinociception induced by microinjection of the GABAA receptor antagonist bicuculline, further demonstrating changes in GABA neurotransmission with morphine tolerance. These results show that the upregulation of adenylyl cyclase caused by repeated vlPAG morphine administration produces antinociceptive tolerance by modulating both pre- and postsynaptic GABA neurotransmission.

Selective Deletion Of GRK2 Alters Psychostimulant-Induced Behaviors and Dopamine Neurotransmission Daigle TL, Ferris MJ, Gainetdinov RR, Sotnikova TD, Urs NM, Jones SR, Caron MG. Neuropsychopharmacology 2014; 39(10): 2450-2462.
GRK2 is a G protein-coupled receptor kinase (GRK) that is broadly expressed and is known to regulate diverse types of receptors. GRK2 null animals exhibit embryonic lethality due to a severe developmental heart defect, which has precluded the study of this kinase in the adult brain. To

elucidate the specific role of GRK2 in the brain dopamine (DA) system, the authors used a conditional gene knockout approach to selectively delete GRK2 in DA D1 receptor (D1R)-, DA D2 receptor (D2R)-, adenosine 2A receptor (A2AR)-, or DA transporter (DAT)-expressing neurons. Here the authors show that select GRK2-deficient mice display hyperactivity, hyposensitivity, or hypersensitivity to the psychomotor effects of cocaine, altered striatal signaling, and DA release and uptake. Mice with GRK2 deficiency in D2R-expressing neurons also exhibited increased D2 autoreceptor activity. These findings reveal a cell-type-specific role for GRK2 in the regulation of normal motor behavior, sensitivity to psychostimulants, dopamine neurotransmission, and D2 autoreceptor function.

A Molecular Profile Of Cocaine Abuse Includes the Differential Expression Of Genes That Regulate Transcription, Chromatin, and Dopamine Cell Phenotype Bannon MJ, Johnson MM, Michelhaugh SK, Hartley ZJ, Halter SD, David JA, Kapatos G, Schmidt CJ. Neuropsychopharmacology 2014; 39(9): 2191-2199.
Chronic drug abuse, craving, and relapse are thought to be linked to long-lasting changes in neural gene expression arising through transcriptional and chromatin-related mechanisms. The key contributions of midbrain dopamine (DA)-synthesizing neurons throughout the addiction process provide a compelling rationale for determining the drug-induced molecular changes that occur in these cells. Yet our understanding of these processes remains rudimentary. The postmortem human brain constitutes a unique resource that can be exploited to gain insights into the pathophysiology of complex disorders such as drug addiction. In this study, the authors analyzed the profiles of midbrain gene expression in chronic cocaine abusers and well-matched drug-free control subjects using microarray and quantitative PCR. A small number of genes exhibited robust differential expression; many of these are involved in the regulation of transcription, chromatin, or DA cell phenotype. Transcript abundances for approximately half of these differentially expressed genes were diagnostic for assigning subjects to the cocaine-abusing vs control cohort. Identification of a molecular signature associated with pathophysiological changes occurring in cocaine abusers' midbrains should contribute to the development of biomarkers and novel therapeutic targets for drug addiction.

Persistent Pain Facilitates Response To Morphine Reward By Downregulation Of Central Amygdala Gabaergic Function Zhang Z, Tao W, Hou Y-Y, Wang W, Lu Y-G, Pan, Zhizhong Z. Neuropsychopharmacology 2014; 39(9): 2263-2271.
Opioid-based analgesics are widely used for treating chronic pain, but opioids are highly addictive when repeatedly used because of their strong rewarding effects. In recent years, abuse of prescription opioids has dramatically increased, including incidences of misuse of opioid drugs prescribed for pain control. Despite this issue in current clinical pain management, it remains unknown how pain influences the abuse liability of prescription opioids. Pain as aversive experience may affect opioid reward of positive emotion through common brain sites involved in emotion processing. In this study, on a rat model of chronic pain, the authors determined how persistent pain altered behavioral responses to morphine reward measured by the paradigm of unbiased conditioned place preference (CPP), focusing on GABAergic synaptic activity in neurons of the central nucleus of the amygdala (CeA), an important brain region for emotional processing of both pain and reward. They found that pain reduced the minimum number of morphine-conditioning sessions required for inducing CPP behavior. Both pain and morphine conditioning that elicited CPP inhibited GABA synaptic transmission in CeA neurons. Pharmacological activation of CeA GABAA receptors reduced the pain and inhibited CPP induced both by an effective dose of morphine and by a sub-threshold dose of morphine under pain condition.

Furthermore, inhibition of CeA GABAA receptors mimicked the pain effect, rendering the sub-threshold dose of morphine effective in CPP induction. These findings suggest that pain facilitates behavioral responses to morphine reward by predisposing the inhibitory GABA function in the CeA circuitry involved in the behavior of opioid reward.

Brief Intermittent Cocaine Self-Administration and Abstinence Sensitizes Cocaine Effects on the Dopamine Transporter and Increases Drug Seeking Calipari ES, Siciliano CA, Zimmer BA, Jones SR. Neuropsychopharmacology 2014 [epub ahead of print].

Although traditional sensitization paradigms, which result in an augmentation of cocaine-induced locomotor behavior and dopamine (DA) overflow following repeated experimenter-delivered cocaine injections, are often used as a model to study drug addiction, similar effects have been difficult to demonstrate following cocaine self-administration. The authors have recently shown that intermittent access (IntA) to cocaine can result in increased cocaine potency at the DA transporter (DAT); however, traditional sensitization paradigms often show enhanced effects following withdrawal/abstinence periods. Therefore, they determined a time course of IntA-induced sensitization by examining the effects of 1 or 3 days of IntA, as well as a 7-day abstinence period on DA function, cocaine potency, and reinforcement. Here the authors show that cocaine potency is increased following as little as 3 days of IntA and further augmented following an abstinence period. In addition, IntA plus abstinence produced greater evoked DA release in the presence of cocaine as compared with all other groups, demonstrating that following abstinence, both cocaine's ability to increase DA release and inhibit uptake at the DAT, two separate mechanisms for increasing DA levels, are enhanced. Finally, the authors found that IntA-induced sensitization of the DA system resulted in an increased reinforcing efficacy of cocaine, an effect that was augmented after the 7-day abstinence period. These results suggest that sensitization of the DA system may have an important role in the early stages of drug abuse and may drive the increased drug seeking and taking that characterize the transition to uncontrolled drug use. Human data suggest that intermittency, sensitization, and periods of abstinence have an integral role in the process of addiction, highlighting the importance of utilizing pre-clinical models that integrate these phenomena, and suggesting that IntA paradigms may serve as novel models of human addiction

Effects Of the Trace Amine-Associated Receptor 1 Agonist RO5263397 On Abuse-Related Effects Of Cocaine In Rats Thorn DA, Jing L, Qiu Y, Gancarz-Kausch AM, Galuska CM, Dietz DM, Zhang Y, Li J-X. Neuropsychopharmacology 2014; 39(10); 2309-2316.

Animal knockout studies suggest that trace amine-associated receptor (TAAR) 1 is involved in behavioral effects of psychostimulants such as cocaine. Recently, several highly selective TAAR 1 agonists have been discovered. However, little is known of the impact of TAAR 1 agonists on abuse-related effects of cocaine. Here, the authors report the effects of a TAAR 1 agonist RO5263397 on several abuse-related behavioral effects of cocaine in rats. RO5263397 was evaluated for its effects on cocaine-induced behavioral sensitization, conditioned place preference (CPP), cue- and cocaine prime-induced reinstatement of cocaine-seeking behavior, and cocaine self-administration using behavioral economic analysis. RO5263397 reduced the expression of cocaine behavioral sensitization, cue- and cocaine prime-induced reinstatement of cocaine seeking, and expression but not development of cocaine CPP. Behavioral economic analysis showed that RO5263397 increased the elasticity of the cocaine demand curve, but did not change cocaine consumption at minimal prices. Taken together, this is the first systematic assessment of a TAAR 1 agonist on a range of behavioral effects of cocaine, showing that RO5263397 was efficacious in reducing cocaine-mediated behaviors. Collectively, these data uncover essential neuromodulatory

roles of TAAR 1 on cocaine abuse, and suggest that TAAR 1 may represent a novel drug target for the treatment of cocaine addiction.

BEHAVIORAL AND BRAIN DEVELOPMENT RESEARCH

In Search of Rare Variants: Preliminary Results from Whole Genome Sequencing of 1,325 Individuals with Psychophysiological Endophenotypes Vrieze SI, Malone SM, Vaidyanathan U, Kwong A, Kang HM, Zhan X, Flickinger M, Irons D, Jun G, Locke AE, Pistis G, Porcu E, Levy S, Myers RM, Oetting W, McGue M, Abecasis G, Iacono WG. Psychophysiology. 2014 Dec; 51(12):1309-1320.
Whole genome sequencing was completed on 1,325 individuals from 602 families, identifying 27 million autosomal variants. Genetic association tests were conducted for those individuals who had been assessed for one or more of 17 endophenotypes (N range=802-1,185). No significant associations were found. These 27 million variants were then imputed into the full sample of individuals with psychophysiological data (N range=3,088-4,469) and again tested for associations with the 17 endophenotypes. No association was significant. Using a gene-based variable threshold burden test of nonsynonymous variants, the authors obtained five significant associations. These findings are preliminary and call for additional analysis of this rich sample. The authors argue that larger samples, alternative study designs, and additional bioinformatics approaches will be necessary to discover associations between these endophenotypes and genomic variation.

Genetic Variation in GABRA2 Moderates Peer Influence on Externalizing Behavior in Adolescents Villafuerte S, Trucco EM, Heitzeg MM, Burmeister M, Zucker RA. Drug Alcohol Depend. 2014 Aug 1;141:51-57.
Genetic predisposition and environmental influences are both important factors in the development of problematic behavior leading to substance use in adolescence. Involvement with delinquent peers also strongly predicts adolescent externalizing behavior. Several lines of evidence support a role of GABRA2 on externalizing behavior related to disinhibition. However, whether this genetic association is influenced by the environment such as peer behavior remains unknown. The authors examined the moderating role of GABRA2 genetic variation on the socialization model of delinquent peer affiliation (at ages 12-14 years) on externalizing behavior (at ages 15-17 years) in the Michigan Longitudinal Study (MLS) adolescent sample. The sample consisted of 244 adolescents (75 females and 152 with at least one parent with a DSM-IV lifetime alcohol dependence/abuse diagnosis). Peer delinquent activity reported by the participant and teacher-reported adolescent externalizing behavior (Teacher Report Form (TRF) were assessed. No main effect of the GABRA2 SNP rs279826, which tags a large haplotype, on externalizing behavior was observed. However, there was a statistically reliable GABRA2 × peer delinquency interaction. The effect of peer delinquent involvement on externalizing scores and the rule breaking subscale is significantly stronger for those with the GG genotype compared to A-carriers, whereas there was no effect of genotype on externalizing in the absence of peer delinquent involvement. No interaction was observed for the aggression subscale. These results suggest that the genetic effect of GABRA2 on externalizing behavior, more specifically on rule breaking is, at least in part, due to its effect on susceptibility to environmental exposure (i.e., peer delinquency).

Experimentation versus Progression in Adolescent Drug Use: A Test of an Emerging Neurobehavioral Imbalance Model Khurana A, Romer D, Betancourt LM, Brodsky NL, Giannetta JM, Hurt H. Dev Psychopathol. 2014 Aug 26:1-13. [Epub ahead of print].
Based on an emerging neuroscience model of addiction, this study examines how an imbalance between two neurobehavioral systems (reward motivation and executive control) can distinguish between early adolescent progressive drug use and mere experimentation with drugs. Data from four annual assessments of a community cohort (N = 382) of 11- to 13-year-olds were analyzed to

model heterogeneity in patterns of early drug use. Baseline assessments of working memory (an indicator of the functional integrity of the executive control system) and three dimensions of impulsivity (characterizing the balance between reward seeking and executive control systems) were used to predict heterogeneous latent classes of drug use trajectories from early to midadolescence. Findings revealed that an imbalance resulting from weak executive control and heightened reward seeking was predictive of early progression in drug use, while heightened reward seeking balanced by a strong control system was predictive of occasional experimentation only. Implications of these results are discussed in terms of preventive interventions that can target underlying weaknesses in executive control during younger years, and potentially enable at-risk adolescents to exercise greater self-restraint in the context of rewarding drug-related cues.

Physiological Correlates of Neurobehavioral Disinhibition that Relate to Drug Use and Risky Sexual Behavior in Adolescents with Prenatal Substance Exposure Conradt E, Lagasse LL, Shankaran S, Bada H, Bauer CR, Whitaker TM, Hammond JA, Lester BM. Dev Neurosci. 2014;36(3-4):306-315.

Physiological correlates of behavioral and emotional problems, substance use onset and initiation of risky sexual behavior have not been studied in adolescents with prenatal drug exposure. The authors studied the concordance between baseline respiratory sinus arrhythmia (RSA) at age 3 and baseline cortisol levels at age 11. They hypothesized that children who showed concordance between RSA and cortisol would have lower neurobehavioral disinhibition scores which would in turn predict age of substance use onset and first sexual intercourse. The sample included 860 children aged 16 years participating in the Maternal Lifestyle Study, a multisite longitudinal study of children with prenatal exposure to cocaine and other substances. Structural equation modeling was used to test pathways between prenatal substance exposure, early adversity, baseline RSA, baseline cortisol, neurobehavioral disinhibition, drug use, and sexual behavior outcomes. Concordance was studied by examining separate male and female models in which there were statistically significant interactions between baseline RSA and cortisol. Prenatal substance exposure was operationalized as the number of substances to which the child was exposed. An adversity score was computed based on caregiver postnatal substance use, depression and psychological distress, number of caregiver changes, socioeconomic and poverty status, quality of the home environment, and child history of protective service involvement, abuse and neglect. RSA and cortisol were measured during a baseline period prior to the beginning of a task. Neurobehavioral disinhibition, based on composite scores of behavioral dysregulation and executive dysfunction, substance use and sexual behavior were derived from questionnaires and cognitive tests administered to the child. Findings were sex specific. In females, those with discordance between RSA and cortisol (high RSA and low cortisol or low RSA and high cortisol) had the most executive dysfunction which, in turn, predicted earlier initiation of alcohol by age 16. Among boys, there also existed a significant baseline RSA by baseline cortisol interaction. Boys with low baseline RSA and high baseline cortisol had the highest levels of behavioral dysregulation. This increase in behavioral dysregulation was in turn related to initiation of alcohol use by age 16 and lower age of first sexual intercourse. The authors found sex-specific pathways to the initiation of alcohol use and risky sexual behavior through the combined activity of parasympathetic and neuroendocrine functioning. The study of multiple physiological systems may suggest new pathways to the study of age of onset of substance use and engagement in risky sexual behavior in adolescents.

Translational Analysis of Effects of Prenatal Cocaine Exposure on Human Infant Cries and Rat pup Ultrasonic Vocalizations Zeskind PS, McMurray MS, Cox Lippard ET, Grewen KM, Garber KA, Johns JM. PLoS One. 2014 Oct 22; 9(10):e110349.

Spectral and temporal features of human infant crying may detect neurobehavioral effects of prenatal cocaine exposure (PCE). Finding comparable measures of rodent ultrasonic vocalizations (USVs) would promote translational analyses by controlling the effects of correlated variables that confound human studies. To this end, two studies examined the sensitivity of similar acoustic structures in human infant and rat pup vocalizations to effects of PCE. In Study 1, cry sounds of 107 one month-old infants were spectrum analyzed to create a novel set of measures and to detect the presence of hyperphonation - a qualitative shift to an atypically high fundamental frequency (basic pitch) associated with neurobehavioral insult. Infants with PCE were compared to infants with prenatal polydrug-exposure (PPE) without cocaine and with infants in a standard comparison (SC) group with no prenatal drug exposure. In Study 2, USVs of 118 five day-old rat pups with either PCE, prenatal saline exposure or no prenatal exposures were spectrum analyzed to detect the presence of frequency shifts - acoustic features that have a frequency waveform similar to that of hyperphonation. Results of study 1 showed PCE had two sets of sex-dependent effects on human infants: PCE males had higher pitched cries with more dysphonation (turbulence); PCE females had longer pauses between fewer cry sounds that were of lower amplitude than comparison groups. PCE and PPE infants had more cries with hyperphonation than SC infants. In study 2, PCE pups had a greater percentage of USVs with shift in the acoustic structure than pups in the two control groups. As such, the novel measures of human infant crying and rat pup USVs were sensitive to effects of PCE. These studies provide the first known translational analysis of similar acoustic structures of vocalizations in two species to detect adverse effects of prenatal drug exposure.

Prenatal Cocaine Effects on Brain Structure in Early Infancy Grewen K, Burchinal M, Vachet C, Gouttard S, Gilmore JH, Lin W, Johns J, Elam M, Gerig G. Neuroimage. 2014 Nov 1;101:114-123.

Prenatal cocaine exposure (PCE) is related to subtle deficits in cognitive and behavioral function in infancy, childhood and adolescence. Very little is known about the effects of in utero PCE on early brain development that may contribute to these impairments. The purpose of this study was to examine brain structural differences in infants with and without PCE. The authors conducted MRI scans of newborns (mean age = 5 weeks) to determine cocaine's impact on early brain structural development. Subjects were three groups of infants: 33 with PCE co-morbid with other drugs, 46 drug-free controls and 40 with prenatal exposure to other drugs (nicotine, alcohol, marijuana, opiates, SSRIs) but without cocaine. Infants with PCE exhibited lesser total gray matter (GM) volume and greater total cerebral spinal fluid (CSF) volume compared with controls and infants with non-cocaine drug exposure. Analysis of regional volumes revealed that whole brain GM differences were driven primarily by lesser GM in prefrontal and frontal brain regions in infants with PCE, while more posterior regions (parietal, occipital) did not differ across groups. Greater CSF volumes in PCE infants were present in prefrontal, frontal and parietal but not occipital regions. Greatest differences (GM reduction, CSF enlargement) in PCE infants were observed in dorsal prefrontal cortex. Results suggest that PCE is associated with structural deficits in neonatal cortical gray matter, specifically in prefrontal and frontal regions involved in executive function and inhibitory control. Longitudinal study is required to determine whether these early differences persist and contribute to deficits in cognitive functions and enhanced risk for drug abuse seen at school age and in later life.

The Contributions of Early Adverse Experiences and Trajectories of Respiratory Sinus Arrhythmia on the Development of Neurobehavioral Disinhibition among Children with Prenatal Substance Exposure Conradt E, Degarmo D, Fisher P, Abar B, Lester BM, Lagasse LL, Shankaran S, Bada H, Bauer CR, Whitaker TM, Hammond JA. Dev Psychopathol. 2014 Nov; 26(4 Pt 1):901-916.

Neurobehavioral disinhibition (ND) is a complex condition reflecting a wide range of problems involving difficulties with emotion regulation and behavior control. Respiratory sinus arrhythmia (RSA) is a physiological correlate of emotion regulation that has been studied in a variety of at-risk populations; however, there are no studies of RSA in children with ND. Data were drawn from a prospective longitudinal study of prenatal substance exposure that included 1,073 participants. Baseline RSA and RSA reactivity to an attention-demanding task were assessed at 3, 4, 5, and 6 years. ND was assessed at ages 8/9, 11, and 13/14 years via behavioral dysregulation and executive dysfunction composite measures. Greater exposure to early adversity was related to less RSA reactivity at 3 years, increases in RSA reactivity from ages 3 to 6 years, and increased behavioral dysregulation from ages 8/9 to 13/14. RSA reactivity was examined as a moderator of the association between early adversity and changes in ND. A significant Early Adversity × RSA Reactivity quadratic interaction revealed that children with decelerations in RSA reactivity exhibited increases in behavioral dysregulation, regardless of their exposure to early adversity. However, greater exposure to early adversity was related to greater increases in behavioral dysregulation, but only if children exhibited accelerations in RSA reactivity from ages 3 to 6 years. The results contribute to our understanding of how interactions across multiple levels of analysis contribute to the development of ND.

Child Behavior Problems: Role of Cocaine Use, Parenting and Child Exposure to Violence Veira Y, Finger B, Eiden RD, Colder CR. Psychol Violence. 2014 Jul 1; 4(3):266-280.

Studies examining the association between prenatal cocaine exposure (PCE) and child behavior problems have yielded mixed results, suggesting a need to identify additional mediating and moderating influences. The authors hypothesized that the relation between PCE and behavior problems at kindergarten would be mediated/moderated by child exposure to violence; and that maternal warmth/sensitivity and harshness would moderate the association between violence exposure and behavior problems. Participants consisted of 216 (116 cocaine-exposed, 100 non-cocaine exposed (NCE) mother-child dyads participating in an ongoing longitudinal study of PCE. Results yielded no direct or mediated/moderated association between PCE and child behavior problems, and no significant interaction effects between PCE and parenting quality. However, higher exposure to violence in kindergarten was significantly associated with higher child behavior problems. This association was moderated by maternal warmth/sensitivity and harshness. High maternal warmth/sensitivity buffered the association between violence exposure and behavior problems while high maternal harshness exacerbated this association. This study highlights the role of violence exposure in the development of behavior problems among high-risk children, and emphasizes the significance of parenting quality in buffering or exacerbating this risk among these children. Implications for prevention include targeting the potential role of maternal warmth/sensitivity as a protective influence among children exposed to violence.

Problematic Substance Use in Urban Adolescents: Role of Intrauterine Exposures to Cocaine and Marijuana and Post-natal Environment Frank DA, Kuranz S, Appugliese D, Cabral H, Chen C, Crooks D, Heeren T, Liebschutz J, Richardson M, Rose-Jacobs R. Drug Alcohol Depend. 2014 Sep 1; 142:181-190.

Linkages between intrauterine exposures to cocaine and marijuana and adolescents' problematic substance use have not been fully delineated. Prospective longitudinal study with assessors unaware of intrauterine exposure history followed 157 urban participants from birth until late adolescence. Level of intrauterine exposures was identified by mother's report and infant's meconium. Problematic substance use, identified by the Voice Diagnostic Interview Schedule for Children (V-DISC) or the Audio Computer Assisted Self-Interview (ACASI) and urine assay, was a composite encompassing DSM-IV indication of tolerance, abuse, and dependence on alcohol, marijuana, and tobacco and any use of cocaine, glue, or opiates. Twenty percent (32/157) of the sample experienced problematic substance use by age 18 years, of whom the majority (22/157) acknowledged abuse, tolerance or dependence on marijuana with or without other substances. Structural equation models examining direct and indirect pathways linking a Cox survival model for early substance initiation to a logistic regression models found effects of post-natal factors including childhood exposure to violence and household substance use, early youth substance initiation, and ongoing youth violence exposure contributing to adolescent problematic substance use. The authors did not identify direct relationships between intrauterine cocaine or marijuana exposure and problematic substance use, but did find potentially modifiable post-natal risk factors also noted to be associated with problematic substance use in the general population including earlier substance initiation, exposure to violence and to household substance use.

Level of Intrauterine Cocaine Exposure and Neuropsychological Test Scores in Preadolescence: Subtle Effects on Auditory Attention and Narrative Memory Beeghly M, Rose-Jacobs R, Martin BM, Cabral HJ, Heeren TC, Frank DA. Neurotoxicol Teratol. 2014 Sep-Oct; 45:1-17.

Neuropsychological processes such as attention and memory contribute to children's higher-level cognitive and language functioning and predict academic achievement. The goal of this analysis was to evaluate whether level of intrauterine cocaine exposure (IUCE) alters multiple aspects of preadolescents' neuropsychological functioning assessed using a single age-referenced instrument, the NEPSY: A Developmental Neuropsychological Assessment (NEPSY) (Korkman et al., 1998), after controlling for relevant covariates. Participants included 137 term 9.5-year-old children from low-income urban backgrounds (51% male, 90% African American/Caribbean) from an ongoing prospective longitudinal study. Level of IUCE was assessed in the newborn period using infant meconium and maternal report. 52% of the children had IUCE (65% with lighter IUCE, and 35% with heavier IUCE), and 48% were unexposed. Infants with Fetal Alcohol Syndrome, HIV seropositivity, or intrauterine exposure to illicit substances other than cocaine and marijuana were excluded. At the 9.5-year follow-up visit, trained examiners masked to IUCE and background variables evaluated children's neuropsychological functioning using the NEPSY. The association between level of IUCE and NEPSY outcomes was evaluated in a series of linear regressions controlling for intrauterine exposure to other substances and relevant child, caregiver, and demographic variables. Results indicated that level of IUCE was associated with lower scores on the Auditory Attention and Narrative Memory tasks, both of which require auditory information processing and sustained attention for successful performance. However, results did not follow the expected ordinal, dose-dependent pattern. Children's neuropsycho-logical test scores were also altered by a variety of other biological and psychosocial factors.

Self-reported Adolescent Behavioral Adjustment: Effects of Prenatal Cocaine Exposure
Min MO, Minnes S, Yoon S, Short EJ, Singer LT. J Adolesc Health. 2014 Aug; 55(2):167-174. To assess the direct effects of prenatal cocaine exposure (PCE) on adolescent internalizing, externalizing, and attention problems, controlling for confounding drug and environmental factors. At 12 and 15 years of age, 371 adolescents (189 PCE and 182 noncocaine exposed), primarily African-American and of low socioeconomic status, participating in a longitudinal, prospective study from birth were assessed for behavioral adjustment using the Youth Self-Report. Longitudinal mixed model analyses indicated that PCE was associated with greater externalizing behavioral problems at ages 12 and 15 years and more attention problems at age 15, after controlling for confounders. PCE effects were not found for internalizing behaviors. PCE adolescents in adoptive/foster care reported more externalizing and attention problems than PCE adolescents in biological mother/relative care at age 12 or noncocaine-exposed adolescents at both ages. No PCE by gender interaction was found. Prenatal marijuana exposure, home environment, parental attachment and monitoring, family conflict, and violence exposure were also significant predictors of adolescent behavioral adjustment. PCE is a risk factor for poor behavioral adjustment in adolescence.

The Role of Parental Distress in Moderating the Influence of Child Neglect on Maladjustment
Berzenski SR, Bennett DS, Marini VA, Sullivan MW, Lewis M. J Child Fam Stud. 2014 Nov 1; 23(8):1325-1336.
Despite pervasive evidence of the harmful impact of neglect on children's adjustment, individual differences in adaptation persist. This study examines parental distress as a contextual factor that may moderate the relation between neglect and child adjustment, while considering the specificity of the relation between neglect and internalizing versus externalizing problems. In a sample of 66 children (33 with a documented child protective services history of neglect prior to age six), neglect predicted internalizing, and to a lesser extent externalizing, problems as rated by teachers at age seven. Parental distress moderated the relation between neglect and internalizing, but not externalizing, problems. Specifically, higher levels of neglect predicted more internalizing problems only among children of distressed parents. These findings indicate that parent-level variables are important to consider in evaluating the consequences of neglect, and point to the importance of considering contextual factors when identifying those children most at risk following neglect.

Reciprocal Influences between Maternal Parenting and Child Adjustment in a High-risk Population: A 5-year Cross-lagged Analysis of Bidirectional Effects Barbot B, Crossman E, Hunter SR, Grigorenko EL, Luthar SS. Am J Orthopsychiatry. 2014 Sep; 84(5):567-580.
This study examines longitudinally the bidirectional influences between maternal parenting (behaviors and parenting stress) and mothers' perceptions of their children's adjustment, in a multivariate approach. Data was gathered from 361 low-income mothers (many with psychiatric diagnoses) reporting on their parenting behavior, parenting stress, and their child's adjustment, in a 2-wave longitudinal study over 5 years. Measurement models were developed to derive 4 broad parenting constructs (involvement, control, rejection, and stress) and 3 child adjustment constructs (internalizing problems, externalizing problems, and social competence). After measurement invariance of these constructs was confirmed across relevant groups and over time, both measurement models were integrated in a single crossed-lagged regression analysis of latent constructs. Multiple reciprocal influences were observed between parenting and perceived child adjustment over time: Externalizing and internalizing problems in children were predicted by baseline maternal parenting behaviors, and child social competence was found to reduce parental stress and increase parental involvement and appropriate monitoring. These findings on the

motherhood experience are discussed in light of recent research efforts to understand mother-child bidirectional influences and their potential for practical applications.

Cortisol Reactivity to Social Stress as a Mediator of Early Adversity on Risk and Adaptive Outcomes Conradt E, Abar B, Lester BM, LaGasse LL, Shankaran S, Bada H, Bauer CR, Whitaker TM, Hammond JA. Child Dev. 2014 Nov; 85(6):2279-2298.
Children chronically exposed to stress early in life are at increased risk for maladaptive outcomes, though the physiological mechanisms driving these effects are unknown. Cortisol reactivity was tested as a mediator of the relation between prenatal substance exposure and/or early adversity on adaptive and maladaptive outcomes. Data were drawn from a prospective longitudinal study of prenatal substance exposure (N = 860). Cortisol reactivity was assessed at age 11. Among African Americans, prenatal substance exposure exerted an indirect effect through early adversity and cortisol reactivity to predict externalizing behavior, delinquency, and a positive student-teacher relationship at age 11. Decreased cortisol reactivity was related to maladaptive outcomes, and increased cortisol reactivity predicted better executive functioning and a more positive student-teacher relationship.

Maternal Smoking during Pregnancy and Infant Stress Response: Test of a Prenatal Programming Hypothesis Stroud LR, Papandonatos GD, Rodriguez D, McCallum M, Salisbury AL, Phipps MG, Lester B, Huestis MA, Niaura R, Padbury JF, Marsit CJ. Psychoneuro-endocrinology. 2014 Oct; 48:29-40.
Maternal smoking during pregnancy (MSDP) is associated with early and long-term neurobehavioral deficits; however mechanisms remain unknown. The authors tested the hypothesis that MSDP programs the hypothalamic pituitary adrenocortical (HPA) axis of the offspring leading to adverse outcomes. In an intensive, prospective study, they investigated associations between MSDP and infant cortisol stress response and explored whether alterations in cortisol response were mediated by epigenetic modulation of the placental glucocorticoid receptor gene (NR3C1). Participants were 100 healthy mother-infant pairs (53% MSDP-exposed; 42% female) from a low income, racially/ethnically diverse sample (55% minorities). MSDP was assessed by timeline followback interview verified by saliva and meconium cotinine. Infant cortisol responses to a neurobehavioral exam were assessed seven times over the first postnatal month. Methylation of placental NR3C1 promoter exon 1F was assessed using bisulfite pyrosequencing in a subsample (n=45). MSDP-exposed infants showed significantly and persistently attenuated basal and reactive cortisol levels over the first postnatal month vs. unexposed infants. Exploratory analyses revealed that MSDP was associated with altered methylation of the placental NR3C1 promoter; degree of methylation of the placental NR3C1 was associated with infant basal and reactive cortisol over the first postnatal month and mediated effects of MSDP on infant basal cortisol. Results provide initial support for our hypothesis that MSDP programs offspring HPA (dys)regulation. Epigenetic regulation of placental GR may serve as a novel underlying mechanism. Results may have implications for delineating pathways to adverse outcomes from MSDP.

The Relationship between Puberty and Risk Taking in the Real World and in the Laboratory. Collado-Rodriguez A, MacPherson L, Kurdziel G, Rosenberg LA, Lejuez CW. Pers Individ Dif. 2014 Oct 1;68:143-148.
Adolescence is marked by the emergence and escalation of risk taking. Puberty has been long-implicated as constituting vulnerability for risk behavior during this developmental period. Sole reliance on self-reports of risk taking however poses limitations to understanding this complex relationship. There exist potential advantages of complementing self-reports by using the BART-Y

laboratory task, a well-validated measure of adolescent risk taking. Toward this end, the authors examined the association between self-reported puberty and both self-reported and BART-Y risk taking in 231 adolescents. Results showed that pubertal status predicted risk taking using both methodologies above and beyond relevant demographic characteristics. Advantages of a multimodal assessment toward understanding the effects of puberty in adolescent risk taking are discussed and future research directions offered.

Rule Breaking Mediates the Developmental Association between GABRA2 and Adolescent Substance Abuse Trucco EM, Villafuerte S, Heitzeg MM, Burmeister M, Zucker RA. J Child Psychol Psychiatry. 2014 Dec; 55(12):1372-1379.
This study's primary aim was to examine age-specific associations between GABRA2, rule breaking, problematic alcohol use, and substance abuse symptomatology. The secondary aim was to examine the extent to which rule breaking mediates the GABRA2-substance abuse relationship. A sample (n = 518) of primarily male (70.9%) and White (88.8%) adolescents from the Michigan Longitudinal Study was assessed from ages 11-18. Age-specific effects of GABRA2 on rule breaking, problematic alcohol use, and substance abuse symptomatology were examined using nested path models. The role of rule breaking as a mediator in the association between GABRA2 and substance abuse outcomes was tested using prospective cross-lagged path models. GABRA2 is significantly ($p < 0.05$) associated with rule breaking in mid- to late-adolescence, but not substance abuse symptomatology across adolescence. GABRA2 effects on problematic alcohol use and substance abuse symptomatology operate largely (45.3% and 71.1%, respectively, $p < 0.05$) via rule breaking in midadolescence. GABRA2 represents an early risk factor for an externalizing pathway to the development of problematic alcohol and drug use.

Prenatal Cocaine Exposure Differentially Affects Stress Responses in Girls and Boys: Associations with Future Substance Use Chaplin TM, Visconti KJ, Molfese PJ, Susman EJ, Klein LC, Sinha R, Mayes LC. Dev Psychopathol. 2014 Jul 18:1-18.
Prenatal cocaine exposure may affect developing stress response systems in youth, potentially creating risk for substance use in adolescence. Further, pathways from prenatal risk to future substance use may differ for girls versus boys. The present longitudinal study examined multiple biobehavioral measures, including heart rate, blood pressure, emotion, and salivary cortisol and salivary alpha amylase (sAA), in response to a stressor in 193 low-income 14- to 17-year-olds, half of whom were prenatally cocaine exposed (PCE). Youth's lifetime substance use was assessed with self-report, interview, and urine toxicology/breathalyzer at Time 1 and at Time 2 (6-12 months later). PCE × Gender interactions were found predicting anxiety, anger, and sadness responses to the stressor, with PCE girls showing heightened responses as compared to PCE boys on these indicators. Stress Response × Gender interactions were found predicting Time 2 substance use in youth (controlling for Time 1 use) for sAA and sadness; for girls, heightened sadness responses predicted substance use, but for boys, dampened sAA responses predicted substance use. Findings suggest distinct biobehavioral stress response risk profiles for boys and girls, with heightened arousal for girls and blunted arousal for boys associated with prenatal risk and future substance use outcomes.

Child-evoked Maternal Negativity from 9 to 27 months: Evidence of Gene-environment Correlation and its Moderation by Marital Distress Fearon RM, Reiss D, Leve LD, Shaw DS, Scaramella LV, Ganiban JM, Neiderhiser JM. Dev Psychopathol. 2014 Sep 12:1-15.
Past research has documented pervasive genetic influences on emotional and behavioral disturbance across the life span and on liability to adult psychiatric disorder. Increasingly, interest is turning to

mechanisms of gene-environment interplay in attempting to understand the earliest manifestations of genetic risk. The authors report findings from a prospective adoption study, which aimed to test the role of evocative gene-environment correlation in early development. Included in the study were 561 infants adopted at birth and studied between 9 and 27 months, along with their adoptive parents and birth mothers. Birth mother psychiatric diagnoses and symptoms scales were used as indicators of genetic influence, and multiple self-report measures were used to index adoptive mother parental negativity. The authors hypothesized that birth mother psychopathology would be associated with greater adoptive parent negativity and that such evocative effects would be amplified under conditions of high adoptive family adversity. The findings suggested that genetic factors associated with birth mother externalizing psychopathology may evoke negative reactions in adoptive mothers in the first year of life, but only when the adoptive family environment is characterized by marital problems. Maternal negativity mediated the effects of genetic risk on child adjustment at 27 months. The results underscore the importance of genetically influenced evocative processes in early development.

Momentary Positive and Negative Affect Preceding Marijuana Use Events in Youth. Shrier LA, Ross CS, Blood EA. J Stud Alcohol Drugs. 2014 Sep; 75(5):781-789.
This study examined how positive and negative affect differ before marijuana use compared with other times. Forty medical outpatients ages 15-24 years who used marijuana recreationally at least twice a week (M = 18.7 years; 58% female) reported momentary positive affect, negative affect, and companionship, perceived ease of obtaining marijuana, and marijuana use several times a day for 2 weeks on a handheld computer. Mean momentary positive affect and negative affect scores in the 24 hours leading up to a marijuana use event (n = 294) were compared with affect scores in times further from subsequent use. Generalized estimating equation models considered as potential moderators perceived ease of obtaining marijuana and being with friends. Positive affect did not differ in the 24 hours before marijuana use compared with times further before use. Negative affect was significantly higher before marijuana use compared with other times. Being with friends and perceived easy marijuana availability did not moderate the associations. The association between negative affect and subsequent marijuana use was attenuated when negative affect was examined only for the moment just before use, suggesting that use may follow a period of increased negative affect. The findings support an affect regulation model for marijuana use among frequently using youth. Specifically, these youth may use marijuana to manage increased negative affect.

It Depends on When You Ask: Motives for Using Marijuana Assessed before Versus after a Marijuana Use Event. Shrier LA, Scherer EB. Addict Behav. 2014 Dec; 39(12):1759-1765.
Marijuana use motives are typically evaluated retrospectively using measures that summarize or generalize across episodes of use, which may compromise validity. Using Ecological Momentary Assessment data, the authors examined the main reason for a specific marijuana use event measured both prospectively and retrospectively. They then determined reason types, event characteristics, and user characteristics that predicted change in reason. Thirty-six medical outpatients age 15 to 24 years who used marijuana two times a week or more used a handheld computer to select their main reason for use from the five categories of the Marijuana Motives Measure (Simons, Correia, & Carey, 1998) just before and after each time they used marijuana over two weeks (n=263 events with before/after reason). The reasons were examined individually and according to dimensions identified in motivational models of substance use (positive/negative, internal/external). The reason assessed before use changed to a different reason after use for 20% of events: 10% of events for pleasure; 21%, to cope; 35%, to be more social; 55%, to expand my mind; and 100%, to conform. In the multivariable model, external and expansion reasons each predicted change in reason for use

($p<0.0001$ and $p=0.001$, respectively). Youth were also more likely to change their reason if older ($p=0.04$), if male ($p=0.02$), and with weekend use ($p=0.002$). Retrospective assessments of event-specific motives for marijuana use may be unreliable and therefore invalid for a substantial minority of events, particularly if use is for external or expansion reasons.

Cortical Thickness and Neurocognition in Adolescent Marijuana and Alcohol Users following 28 days of Monitored Abstinence. Jacobus J, Squeglia LM, Sorg SF, Nguyen-Louie TT, Tapert SF. J Stud Alcohol Drugs. 2014 Sep; 75(5):729-743.
Adolescent marijuana use continues to increase in prevalence as harm perception declines. Better understanding of marijuana's impact on neurodevelopment is crucial. This prospective study aimed to investigate cortical thickness and neurocognitive performance before and after 28 days of monitored abstinence in adolescent marijuana and alcohol users. Subjects (N = 54; >70% male) were adolescent marijuana users (ages 15-18 years) with regular alcohol use (MJ + ALC; (n = 24) and non-using controls (CON; n = 30) who were compared before and after 4 weeks of sequential urine toxicology to confirm abstinence. Participants underwent magnetic resonance imaging, neuropsychological assessment, and substance use assessment at both time points. Repeated-measures analysis of covariance was used to look at the main effects of group, time, and Group × Time interactions on cortical thickness and neurocognitive functioning. Bivariate correlations estimated associations between cortical thickness, substance use severity, and cognitive performance. Marijuana users showed thicker cortices than controls in the left entorhinal cortex (ps < .03) before and after monitored abstinence, after adjusting for lifetime alcohol use. More lifetime marijuana use was linked to thinner cortices in temporal and frontal regions, whereas more lifetime alcohol use and heavy episodic drinking episodes was linked to thicker cortices in all four lobes (ps < .05). Age of onset of regular marijuana use was positively related to cortical thickness (ps < .03). Adolescent alcohol and marijuana use may be linked to altered longer-term neurodevelopmental trajectories and compromised neural health. Cortical thickness alterations and dose-dependent associations with thickness estimates were observed both before and after monitored abstinence and suggest neural differences continue to persist 28 days after cessation of marijuana use. Neural recovery may be identified with longer follow-up periods; however, observed changes related to use severity could have implications for future psychosocial outcomes.

Effects of Incentives, Age, and Behavior on Brain Activation during Inhibitory Control: A Longitudinal fMRI Study Paulsen DJ, Hallquist MN, Geier CF, Luna B. Dev Cogn Neurosci. 2014 Sep 19. pii: S1878-9293(14)00066-8.
The authors investigated changes in brain function supporting inhibitory control under age-controlled incentivized conditions, separating age- and performance-related activation in an accelerated longitudinal design including 10- to 22-year-olds. Better inhibitory control correlated with striatal activation during neutral trials, while Age X Behavior interactions in the striatum indicated that in the absence of extrinsic incentives, younger subjects with greater reward circuitry activation successfully engage in greater inhibitory control. Age was negatively correlated with ventral amygdala activation during Loss trials, suggesting that amygdala function more strongly mediates bottom-up processing earlier in development when controlling the negative aspects of incentives to support inhibitory control. Together, these results indicate that with development, reward-modulated cognitive control may be supported by incentive processing transitions in the amygdala, and from facilitative to obstructive striatal function during inhibitory control.

Age Differences in the Impact of Peers on Adolescents' and Adults' Neural Response to Reward Smith AR, Steinberg L, Strang N, Chein J. Dev Cogn Neurosci. 2014 Sep 2. [Epub ahead of print]**.**

Prior research suggests that increased adolescent risk-taking in the presence of peers may be linked to the influence of peers on the valuation and processing of rewards during decision-making. The current study explores this idea by examining how peer observation impacts the processing of rewards when such processing is isolated from other facets of risky decision-making (e.g. risk-perception and preference, inhibitory processing, etc.). In an fMRI paradigm, a sample of adolescents (ages 14-19) and adults (ages 25-35) completed a modified High/Low Card Guessing Task that included rewarded and un-rewarded trials. Social context was manipulated by having participants complete the task both alone and while being observed by two, same-age, same-sex peers. Results indicated an interaction of age and social context on the activation of reward circuitry during the receipt of reward; when observed by peers, adolescents exhibited greater ventral striatal activation than adults, but no age-related differences were evinced when the task was completed alone. These findings suggest that, during adolescence, peers influence recruitment of reward-related regions even when they are engaged outside of the context of risk-taking. Implications for engagement in prosocial, as well as risky, behaviors during adolescence are discussed.

The Relationship between Child Abuse and Negative Outcomes among Substance Users: Psychopathology, Health, and Comorbidities Banducci AN, Hoffman E, Lejuez CW, Koenen KC. Addict Behav. 2014 Oct; 39(10):1522-1527.

Adults with substance use disorders (SUDs) report higher rates of child abuse than adults without SUDs. Prior work suggests that this abuse is associated with higher rates of psychosis, posttraumatic stress disorder, physical health problems, alcohol dependence, and cannabis dependence among substance users. Little is known about other problems associated with child abuse experienced by substance users. The authors hypothesized that among adults with SUDs, child abuse would be associated with elevated rates of all Diagnostic and Statistical Manual (DSM-IV-TR) psychiatric disorders, substance dependencies, and comorbidities assessed. The authors assessed 280 inpatients in substance use treatment with the Structured Clinical Interview for the DSM-IV-TR, the Diagnostic Instrument for Personality Disorders, and Childhood Trauma Questionnaire (CTQ). They used chi-square and regression analyses to establish whether rates of psychiatric disorders, substance dependencies, and comorbidities differed as a function of child abuse. Consistent with the authors' hypotheses, higher scores on the CTQ were associated with elevated rates of psychiatric disorders (mood disorders, anxiety disorders, psychotic symptoms, and personality disorders) and substance dependencies (alcohol dependence and cocaine dependence). Moreover, higher rates of all comorbidity patterns (e.g. comorbid alcohol dependence and anxiety) were observed among individuals who reported experiencing child abuse. Across all substance dependencies examined, individuals who had been abused had significantly higher rates of all psychiatric disorders assessed. Individuals with substance use disorders who have been abused have particularly elevated rates of psychiatric and substance use disorders as a function of their abuse experiences. These findings have important treatment implications for individuals in residential substance use treatment settings.

Chronic Δ9-Tetrahydrocannabinol Administration May Not Attenuate Simian Immunodeficiency Virus Disease Progression in Female Rhesus Macaques Amedee AM, Nichols WA, LeCapitaine NJ, Vande Stouwe C, Birke LL, Lacour N, Winsauer PJ, Molina PE. AIDS Res Hum Retroviruses. 2014 Sep 5. [Epub ahead of print]**.**

Persons living with HIV/AIDS (PLWHA) frequently use cannabinoids, either recreationally by smoking marijuana or therapeutically (delta-9-tetrahydrocannabinol; Δ^9-THC dronabinol). Previously, the authors demonstrated that chronic Δ^9-THC administration decreases early mortality in male simian immunodeficiency virus (SIV)-infected macaques. In this study, the authors sought to examine whether similar protective effects resulted from chronic cannabinoid administration in SIV-infected female rhesus macaques. Clinical and viral parameters were evaluated in eight female rhesus macaques that received either Δ^9-THC (0.18-0.3mg/kg, intramuscularly, twice daily) or vehicle (VEH) starting 28 days prior to intravenous inoculation with SIVmac251. SIV disease progression was assessed by changes in body weight, mortality, viral levels in plasma and mucosal sites, and lymphocyte subsets. In contrast to these results in male animals, chronic Δ^9-THC did not protect SIV-infected female rhesus macaques from early mortality. Markers of SIV disease, including viral load and $CD4^+/CD8^+$ ratio, were not altered by Δ^9-THC compared to control females; however, females that received chronic Δ^9-THC did not gain as much weight as control animals. In addition, Δ^9-THC administration increased total CXCR4 expression in both peripheral and duodenal $CD4^+$ and $CD8^+$ T lymphocytes prior to SIV inoculation. Although protection from early mortality was not evident, chronic Δ^9-THC did not affect clinical markers of SIV disease progression. The contrasting effects of chronic Δ^9-THC in males versus females remain to be explained, but highlight the need for further studies to explore the sex-dependent effects of Δ^9-THC and other cannabinoids on the HIV disease course and their implications for virus transmission.

Prenatal Drug Exposure Moderates the Association between Stress Reactivity and Cognitive Function in Adolescence Buckingham-Howes S, Bento SP, Scaletti LA, Koenig JI, Granger DA, Black MM. Dev Neurosci. 2014;36(3-4):329-337.

Prenatal drug exposure (PDE) can undermine subsequent health and development. In a prospective longitudinal study he authors examine whether PDE moderates the link between stress reactivity and cognitive functioning in adolescence. Participants were 76 prenatally drug-exposed and 61 nonexposed (NE) community comparison African American youth (50% male, mean age 14.17 years) living in an urban setting. All participants completed neuropsychological and academic achievement tests (Children's Memory Scales, the California Verbal Learning
Test - Children's version and the Wide Range Achievement Test 4) over the course of 1 day in a laboratory setting. Two mild stressors (Balloon Analog Risk Task - Youth and Behavioral Indicator of Resilience to Distress) were administered, with saliva samples (assayed for cortisol) collected pre- and poststress task. A higher percentage in the NE group, compared to the PDE group (26% vs. 12%, $\chi(2) = 4.70$, d.f. = 1, n = 137, p = 0.03), exhibited task-related increases in salivary cortisol. PDE moderated the association between stress reactivity and 11 of 15 cognitive performance scales. In each case, the NE stress reactive group had better cognitive performance than either the NE lower cortisol reactive group or the PDE group regardless of stress reactivity status. Stress-related reactivity and regulation of the hypothalamic-pituitary-adrenal axis in adolescence may be disrupted by PDE, and the disruption may be linked to lower cognitive performance.

Prenatal Drug Exposure, Behavioral Problems, and Drug Experimentation among African-American Urban Adolescents Wang Y, Buckingham-Howes S, Nair P, Zhu S, Magder LS, Black MM. J Adolesc Health. 2014 Sep; 55(3):423-431.
The aim of this study was to examine how prenatal drug exposure (PDE) to heroin/cocaine and behavioral problems relate to adolescent drug experimentation. The sample included African-American adolescents (mean age = 14.2 years, SD = 1.2) with PDE (n = 73) and a nonexposed community comparison (n = 61). PDE status was determined at delivery through toxicology analysis and maternal report. Internalizing/externalizing problems were assessed during adolescence with the Behavior Assessment System for Children, Second Edition. Drug experimentation was assessed by adolescent report and urine analysis. Logistic regression evaluated the likelihood of drug experimentation related to PDE and behavioral problems, adjusting for age, gender, PDE, perceived peer drug use, and caregiver drug use. Interaction terms examined gender modification. Sixty-seven subjects (50%) used drugs: 25 (19%) used tobacco/alcohol only and 42 (31%) used marijuana/illegal drugs. Ninety-four subjects (70%) perceived peer drug use. PDE significantly increased the risk of tobacco/alcohol experimentation (odds ratio = 3.07, 95% confidence interval [CI] 1.09-8.66, p = .034) but not after covariate adjustment (adjusted odds ratio [aOR] = 1.16, 95% CI .31-4.33, p > .05). PDE was not related to the overall or marijuana/illegal drug experimentation. The likelihood of overall drug experimentation was doubled per SD increase in externalizing problems (aOR = 2.28, 95% CI 1.33-3.91, p = .003) and, among girls, 2.82 times greater (aOR = 2.82, 95% CI 1.34-5.94, p = .006) per SD increase in internalizing problems. Age and perceived peer drug use were significant covariates. Drug experimentation was relatively common (50%), especially in the context of externalizing problems, internalizing problems (girls only), older age, and perceived peer drug use. Findings support the Problem Behavior Theory and suggest that adolescent drug prevention addresses behavioral problems and promotes prosocial peer groups.

Preliminary Evidence for the Interaction of the Oxytocin Receptor Gene (oxtr) and Face Processing in Differentiating Prenatal Smoking Patterns Massey SH, Estabrook R, O'Brien TC, Pine DS, Burns JL, Jacob S, Cook EH, Wakschlag LS. Neurosci Lett. 2014 Nov 1;584C:259-264.
Prenatal smoking cessation has been described as an empathic action "for the baby," but this has not been empirically demonstrated. The authors capitalized on a genetically-characterized extant dataset with outstanding measurement of prenatal smoking patterns and maternal face processing data (as an indicator of empathy) to test this hypothesis, and explore how empathy and smoking patterns may be moderated by a genetic substrate of empathy, the oxytocin receptor gene (OXTR). Participants were 143 Caucasian women from the East Boston family study with repeated prospective reports of smoking level, adjusted based on repeated cotinine bioassays. Salivary DNA and face processing (Diagnostic Analysis of Nonverbal Accuracy-2) were assessed 14 years later at an adolescent follow-up of offspring. Two-thirds of participants reported smoking prior to pregnancy recognition. Of these, 21% quit during pregnancy; 56% reduced smoking, and 22% smoked persistently at the same level. A significant interaction between face processing and OXTR variants previously associated with increased sensitivity to social context, rs53576GG and rs2254298A, was found (β=-.181; p=.015); greater ability to identify distress in others was associated with lower levels of smoking during pregnancy for rs53576(GG)/rs2254298(A) individuals (p=.013), but not for other genotypes (p=.892). Testing this "empathy hypothesis of prenatal smoking cessation" in larger studies designed to examine this question can elucidate whether interventions to enhance empathy can improve prenatal smoking cessation rates.

Heavy Alcohol Use, Marijuana Use, and Concomitant Use by Adolescents are Associated with Unique and Shared Cognitive Decrements Winward JL, Hanson KL, Tapert SF, Brown SA. J Int Neuropsychol Soc. 2014 Sep; 20(8):784-795.
To assess recovery of cognitive effects, the authors investigated neuropsychological performance after 1 month of monitored abstinence in teens with histories of heavy episodic drinking, protracted marijuana use, or concomitant use of alcohol and marijuana. Adolescents (ages 16-18 years) with histories of heavy episodic drinking (HED; n=24), marijuana use (MJ; n=20), both heavy alcohol and marijuana use (HED+MJ; n=29), and socio-demographically similar control teens (CON; n=55) completed a neuropsychological battery following 4 weeks of monitored abstinence. Groups were similar on 5th grade standardized test scores, suggesting comparable academic functioning before onset of substance use. Relative to CON, HED showed poorer cognitive flexibility (p=.006), verbal recall (p=.024), semantic clustering (p=.011), and reading skills (p=.018). MJ performed worse than CON on inhibition task accuracy (p=.015), cued verbal memory (p=.031), and psychomotor speed (p=.027). Similar to HED youth, HED+MJ showed differences relative to CON on cognitive flexibility (p=.024) and verbal recall (p=.049). As with MJ teens, HED+MJ showed poorer task accuracy (p=.020). Unique to the HED+MJ group was poorer working memory (p=.012) relative to CON. For all substance using participants, worse performance across domains correlated with more lifetime use of alcohol and of marijuana, more withdrawal symptoms from alcohol, and earlier age of onset of marijuana use (ps<.05). Heavy alcohol use, marijuana use, and concomitant use of both substances during adolescence appear to be associated with decrements in cognitive functioning, and each substance (or combination of substances) may be linked to poorer performance in specific cognitive domains.

Adolescent Marijuana Users Have Elevated Risk-taking on the Balloon Analog Risk Task Hanson KL, Thayer RE, Tapert SF. J Psychopharmacol. 2014 Nov; 28(11):1080-1087. Adolescents who engage in regular marijuana use may have a higher propensity to take unsafe risks despite the possible negative consequences. The authors compared adolescents with a history of regular marijuana use to non-using teens on a behavioral measure of risk-taking. Given the involvement of the pre-frontal cortex in both risk-taking and executive functioning, they also examined whether risk-taking was associated with measures of executive functioning. Fifty-eight demographically similar community youth (ages 17-20; 29% female), including 24 marijuana users and 34 non-using controls, completed the computerized Balloon Analog Risk Task (BART; Lejuez et al., 2002) and measures of substance use and executive function. Primary BART outcome measures included total number of popped balloons and average adjusted pumps (mean pumps excluding popped balloons). Marijuana users had more popped balloons than controls ($p<0.05$) but did not differ on average adjusted pumps. Using hierarchical multiple regression controlling for age, riskier BART performance (popped balloons) was predictive of past 18-month hard drug use ($\beta=0.30$; $p<0.05$). Having a higher number of popped balloons was also predictive of past 18-month marijuana use ($p<0.05$), but age was a stronger predictor than marijuana use. Marijuana users performed worse on one test of executive functioning (psychomotor set-shifting, $p<0.05$), but this did not correlate with risk-taking. He authors' finding of elevated risk-taking among marijuana users is consistent with previous research that substance users may have impaired risk processing. Further, their results suggest that risk-taking is not always associated with executive dysfunction, implying the involvement of distinct neural subsystems.

Effects of Prenatal Cocaine Exposure on Early Postnatal Rodent Brain Structure and Diffusion Properties McMurray MS, Oguz I, Rumple AM, Paniagua B, Styner MA, Johns JM. Neurotoxicol Teratol. 2014 Nov 22. pii: S0892-0362(14)00194-9.

Prenatal cocaine exposure has been associated with numerous behavioral phenotypes in clinical populations, including impulsivity, reduced attention, alterations in social behaviors, and delayed language and sensory-motor development. Detecting associated changes in brain structure in these populations has proven difficult, and results have been inconclusive and inconsistent. Due to their more controlled designs, animal models may shed light on the neuroanatomical changes caused by prenatal cocaine; however, to maximize clinical relevance data must be carefully collected using translational methods. The goal of this study was two-fold: 1) determine if prenatal cocaine alters developmental neuroanatomy using methods that are available to human researchers, specifically structural MRI and diffusion tensor imaging; and 2) to determine the feasibility of rodent in vivo neuroimaging for usage in longitudinal studies of developmental disorders. Cocaine-exposed (prenatal days 1-20, 30mg/kg/day) rat pups were sedated and imaged live using diffusion tensor imaging and postmortem (fixed) using magnetic resonance histology on postnatal day 14. Volume and diffusion properties in whole brain as well as specific regions of interest were then assessed from the resulting images. Whole brain analyses revealed that cocaine-exposed animals showed no change in whole brain volume. Additionally, the authors found alterations in fractional anisotropy across regions associated with reward processing and emotional regulation, especially in the thalamus and globus palladus, as well as sex-dependent effects of cocaine in the right cortex. Reductions in fractional anisotropy were paired with reductions only in axial diffusivity, which preliminarily suggests that the changes observed here may be due to axonal damage, as opposed to reductions in myelination of the affected regions/pathways. These data indicate that prenatal cocaine may target a number of developing brain structures, but does not result in overt changes to brain volumes. These results highlight not only the brain alterations that result from prenatal cocaine, but also the advancements in live imaging that allow longitudinal study designs in other models.

Early Postpartum Pup Preference is Altered by Gestational Cocaine Treatment: Associations with Infant Cues and Oxytocin Expression in the MPOA Lippard ET, Jarrett TM, McMurray MS, Zeskind PS, Garber KA, Zoghby CR, Glaze K, Tate W, Johns JM. Behav Brain Res. 2014 Oct 6; 278C:176-185.

Cross-fostering studies suggest cocaine-induced deficits in maternal behavior could be associated with altered behavior of offspring following prenatal cocaine-exposure. Neonatal vocalizations are an important offspring cue facilitating early interactions between dam and rodent pup offspring and have been shown to be altered following prenatal cocaine-exposure. It is unclear how variations in acoustic parameters of USVs impact maternal behavior and the mechanism(s) underlying these processes. The present study examined differences in cocaine-exposed and control rodent dam maternal preference of cocaine-exposed or untreated pups in a dual choice apparatus. Relationship of preference-like behavior with pup USVs and dam oxytocin expression was explored. Gestational cocaine-exposure interfered with preference-like behavior of dams on postpartum day 1 with cocaine-exposure associated with decreased time spent on the cocaine-exposed pup side compared to the control pup side, and decreases in preference-like behavior associated in part with decreased number of USVs being emitted by cocaine-exposed pups. On postpartum day 5, decreased oxytocin expression in the medial preoptic area was associated with altered preference-like behavior in cocaine-exposed dams, including frequency and latency to touch/sniff pups. Results indicate cocaine's effects on the mother-infant relationship is likely synergistic, in that cocaine influences

mother and offspring both independently and concertedly and that variations within pup vocalizations.

Increased Pain Sensitivity in Chronic Pain Subjects on Opioid Therapy: A Cross-Sectional Study Using Quantitative Sensory Testing Zhang Y, Ahmed S, Vo T, St Hilaire K, Houghton M, Cohen AS, Mao J, Chen L. Pain Med. 2014 Nov 6. doi: 10.1111/pme.12606. [Epub ahead of print]**.** The aim of this study was to compare the sensitivity to experimental pain of chronic pain patients on opioid therapy vs chronic pain patients on non-opioid therapy and healthy subjects by quantitative sensory testing (QST). There is a growing body of evidence demonstrating that chronic use of opioid drugs may alter pain sensitivity. Identifying the characteristic changes in thermal pain sensitivity in chronic opioid users will be helpful in diagnosing pain sensitivity alterations associated with chronic opioid use. Utilizing an office-based QST technique, the authors examined thermal pain threshold, tolerance, and temporal summation in 172 chronic pain subjects receiving opioid therapy, 121 chronic pain subjects receiving non-opioid therapy, and 129 healthy subjects. In chronic pain subjects receiving opioid therapy, there were detectable differences in QST characteristics compared with both chronic pain subjects receiving non-opioid therapy and healthy subjects. Specifically, in chronic pain subjects receiving opioid therapy, 1) sensitivity to heat pain was increased; threshold to heat pain was significantly lower; 2) tolerance to supra-threshold heat pain was significantly decreased; and 3) temporal pain summation was exacerbated, as compared with chronic pain subjects receiving non-opioid therapy. In a subgroup of chronic pain subjects receiving opioid therapy with increased heat pain sensitivity, their average opioid medication dosage was significantly higher than those who had an above-average heat pain threshold. Moreover, a subset of chronic pain subjects on opioid therapy exhibited a significant decrease in diffuse noxious inhibitory control (DNIC) compared with chronic pain subjects on non-opioid therapy. These findings suggest that a subset of QST parameters can reflect opioid-associated thermal pain sensitivity alteration, including decreased heat pain threshold, decreased cold and heat pain tolerance, diminished DNIC, and/or exacerbated temporal summation.

Does Depression and Substance Abuse Co-morbidity Affect Socioeconomic Status? Evidence from a Prospective Study of Urban African Americans Dagher RK, Green KM. Psychiatry Res. 2014 Nov 11. [Epub ahead of print].
Studies have established a graded association between mental health and socioeconomic status (SES). However, scarce research has examined the impact of substance use disorders (SUD) and depression comorbidity on SES. The authors use data from the Woodlawn Study, a longitudinal cohort study, which recruited a cohort of first graders from Chicago starting 1966-1967 (N=1242). Analyses focus on those interviewed in young adulthood and followed up through midlife. Regression analyses adjusting for childhood confounders showed that young adults with depression and SUD comorbidity had higher likelihood of having any periods of unemployment, higher likelihood of being unemployed for 3 or more months, and lower household income in midlife than those with neither disorder. Moreover, young adults with SUD without depression had higher odds of having any periods of unemployment and higher odds of being unemployed for 3 or more months than those with neither disorder. Findings point to the possibility of social selection where depression and SUD comorbidity contributes to a downward drift in SES. Clinical interventions that integrate the treatment of SUD and depression may be more effective at reducing socioeconomic disparities among minority populations.

Increased Forebrain Activations in Youths with Family Histories of Alcohol and Other Substance Use Disorders Performing a Go/NoGo Task. Acheson A, Tagamets MA, Rowland LM, Mathias CW, Wright SN, Hong LE, Kochunov P, Dougherty DM. Alcohol Clin Exp Res. 2014 Nov 18. doi: 10.1111/acer.12571. [Epub ahead of print].

Youths with a family history of alcohol and other drug use disorders (FH+) are at a greater risk of developing substance use disorders than their peers with no such family histories (FH-), and this increased risk may be related to impaired maturation of forebrain circuitry. FH+ individuals have shown altered forebrain activity at rest and while performing cognitive tasks. However, it is not fully understood how forebrain activity is altered in FH+ individuals, and ultimately how these alterations may contribute to substance use disorder risk. In this study, the authors tested 72 FH+ and 32 FH- youths performing a go/no-go task and examined activations in blocks with only go trials (Go Only), blocks with 50% go and 50% no-go trials (Go/NoGo), and a contrast of those 2 blocks. FH+ youths had significantly greater cerebral activations in both the Go and Go/NoGo blocks than FH- youths in regions including the posterior cingulate/precuneus, bilateral middle/superior temporal gyrus, and medial superior frontal gyrus with no significant group differences in the subtraction between Go Only and Go/NoGo blocks. Additionally, FH+ youths had moderately slower reaction times on go trials in the Go Only blocks. These findings suggest that global activation increase in FH+ youths are modulated by FH density and are not specific to the inhibitory components of the task. This pattern of increased activations in FH+ youths may be at least partially due to impaired forebrain white matter development leading to greater activations/less efficient neural communication during task performance.

Parental-adolescent Drug Use Discussions: Physiological Responses and Associated Outcomes Chaplin TM, Hansen A, Simmons J, Mayes LC, Hommer RE, Crowley MJ. J Adolesc Health. 2014 Dec; 55(6):730-735.

Although talking to youth about drugs is often recommended to parents, little is known about how parents actually discuss drugs with their children in the moment and how parental advice is linked to youth arousal and substance use. This study examined observed parental drug use advice and parenting behaviors during parent-adolescent drug use discussions and associations with adolescent physiological responses and substance use. Fifty-eight 12-17 year olds and their primary caregivers participated in a laboratory session in which parents and youth discussed the topic of alcohol and/or drug use for 10 minutes. This discussion was videotaped and coded for drug use advice (rules against drug use, information on drug use consequences, scenarios or learning advice [discussing drug use scenarios and what the child has learned about drugs]) and general parenting behaviors (parental warmth and/or support, negative and/or critical parenting). Before, during, and after the discussions, adolescents' heart rate, blood pressure (BP), and salivary cortisol levels were assessed. Parental discussion of scenarios and/or learning was associated with lower adolescent BP responses to the discussions and lower likelihood of substance use. Parental discussion of rules against drug use was associated with higher heart rate and BP responses and greater likelihood of substance use. Criticism and/or negative parenting was associated with higher cortisol responses and greater likelihood of substance use at a trend level. Parenting characterized by greater discussion of drug use scenarios and less stating of rules against drug use and criticism may make youth feel more comfortable and be linked to lower substance use.

Attention Regulates Anger and Fear to Predict Changes in Adolescent Risk-taking Behaviors
Kim-Spoon J, Holmes C, Deater-Deckard K. J Child Psychol Psychiatry. 2014 Oct 3. doi: 10.1111/jcpp.12338. [Epub ahead of print].
Regulation of negative affect is critical to healthy development in childhood and adolescence. The authors conducted a longitudinal study examining the moderating role of attention control in the effects of anger and fear on changes in risk-taking behaviors from early to middle adolescence. The sample involved participants from the Study of Early Child Care and Youth Development (SECCYD), assessed at 9, 11, and 15 years of age. Composite scores for anger, fear, and attention control were computed using indicators from multiple informants, and risk-taking behaviors were assessed based on adolescents' self-reports. Latent difference score analysis indicated significant moderating effects of attention control showing that increased anger between 9 and 11 years was related to increases in risk-taking behaviors between 11 and 15 years only for adolescents with low attention control but not for adolescents with high attention control. In contrast, significant moderating effects of attention control for the link between fear and risk-taking behaviors suggested increased fear between 9 and 11 years tended to be associated with decreases in risk-taking behaviors between 11 and 15 years only for adolescents with high attention control, but not for adolescents with low attention control. Attention control regulates the connections between negative affect such as anger and fear with changes in adolescent risk-taking behaviors. These data suggest the protective role of strong attention control against the development of risk-taking behaviors in adolescence as it demotes the effects of anger and promotes the effects of fear.

Maternal Smoking during Pregnancy and Bipolar Disorder in Offspring Talati A, Bao Y, Kaufman J, Shen L, Schaefer CA, Brown AS. Am J Psychiatry. 2013 Oct; 170(10):1178-1185.
Maternal smoking during pregnancy is associated with a number of adverse externalizing outcomes for offspring from childhood to adulthood. The relationship between maternal smoking and bipolar disorder in offspring, which includes externalizing symptoms among its many manifestations, has not been investigated in depth. The authors examined whether offspring exposed to maternal smoking in utero would be at increased lifetime risk for bipolar disorder after accounting for other factors related to maternal smoking. Individuals with bipolar disorder (N=79) were ascertained from the birth cohort of the Child Health and Development Study. Case subjects were identified by a combination of clinical, database, and direct mailing sources; all case subjects were directly interviewed and diagnosed using DSM-IV criteria. Comparison subjects (N=654) were matched to case subjects on date of birth (±30 days), sex, membership in the cohort at the time of illness onset, and availability of maternal archived sera. After adjusting for potential confounders, offspring exposed to in utero maternal smoking exhibited a twofold greater risk for bipolar disorder (odds ratio=2.014, 95% confidence interval=1.48-2.53, p=0.01). The associations were noted primarily among bipolar offspring without psychotic features. Prenatal tobacco exposure may be one suspected cause of bipolar disorder. However, it will be necessary to account for other unmeasured familial factors before causal teratogenic effects can be suggested.

Heritability and Molecular-genetic Basis of the P3 Event-related Brain Potential: A Genome-wide Association Study Malone SM, Vaidyanathan U, Basu S, Miller MB, McGue M, Iacono WG. Psychophysiology. 2014 Dec; 51(12):1246-1258.
P3 amplitude is a candidate endophenotype for disinhibitory psychopathology, psychosis, and other disorders. The present study is a comprehensive analysis of the behavioral- and molecular-genetic basis of P3 amplitude and a P3 genetic factor score in a large community sample (N=4,211) of adolescent twins and their parents, genotyped for 527,829 single nucleotide polymorphisms (SNPs). Biometric models indicated that as much as 65% of the variance in each measure was due to

additive genes. All SNPs in aggregate accounted for approximately 40% to 50% of the heritable variance. However, analyses of individual SNPs did not yield any significant associations. Analyses of individual genes did not confirm previous associations between P3 amplitude and candidate genes but did yield a novel association with myelin expression factor 2 (MYEF2). Main effects of individual variants may be too small to be detected by GWAS without larger samples.

Genetic Associations of Nonsynonymous Exonic Variants with Psychophysiological Endophenotypes Vrieze SI, Malone SM, Pankratz N, Vaidyanathan U, Miller MB, Kang HM, McGue M, Abecasis G, Iacono WG. Psychophysiology. 2014 Dec; 51(12):1300-1308.
The authors mapped ~85,000 rare nonsynonymous exonic single nucleotide polymorphisms (SNPs) to 17 psychophysiological endophenotypes in 4,905 individuals, including antisaccade eye movements, resting EEG, P300 amplitude, electrodermal activity, affect-modulated startle eye blink. Nonsynonymous SNPs are predicted to directly change or disrupt proteins encoded by genes and are expected to have significant biological consequences. Most such variants are rare, and new technologies can efficiently assay them on a large scale. The authors assayed 247,870 mostly rare SNPs on an Illumina exome array. Approximately 85,000 of the SNPs were polymorphic, rare (MAF<.05), and nonsynonymous. Single variant association tests identified a SNP in the PARD3 gene associated with theta resting EEG power. The sequence kernel association test, a gene-based test, identified a gene PNPLA7 associated with pleasant difference startle, the difference in startle magnitude between pleasant and neutral images. No other single nonsynonymous variant, or gene-based group of variants, was strongly associated with any endophenotype.

CLINICAL NEUROSCIENCE RESEARCH

Value-Driven Attentional Priority Signals in Human Basal Ganglia and Visual Cortex. Anderson BA, Laurent PA, Yantis S. Brain Res. 2014; 1587: 88–96. Goal-directed and stimulus-driven factors determine attentional priority through a well-defined dorsal frontal-parietal and ventral temporal-parietal network of brain regions, respectively. Recent evidence demonstrates that reward-related stimuli also have high attentional priority, independent of their physical salience and goal-relevance. The neural mechanisms underlying such value-driven attentional control are unknown. Using human functional magnetic resonance imaging, we demonstrate that the tail of the caudate nucleus and extrastriate visual cortex respond preferentially to task-irrelevant but previously reward-associated objects, providing an attentional priority signal that is sensitive to reward history. The caudate tail has not been implicated in the control of goal-directed or stimulus-driven attention, but is well suited to mediate the value-driven control of attention. Our findings reveal the neural basis of value-based attentional priority.

Long-term Effects of Marijuana Use on the Brain Filbey FM, Aslan S, Calhoun VD, Spence JS, Damaraju E, Caprihan A, Segall J. Proc Natl Acad Sci U S A. 2014 Nov 10 [Epub ahead of print]. 111(47):16913-16918.
Questions surrounding the effects of chronic marijuana use on brain structure continue to increase. To date, however, findings remain inconclusive. In this comprehensive study that aimed to characterize brain alterations associated with chronic marijuana use, the authors measured gray matter (GM) volume via structural MRI across the whole brain by using voxel-based morphology, synchrony among abnormal GM regions during resting state via functional connectivity MRI, and white matter integrity (i.e., structural connectivity) between the abnormal GM regions via diffusion tensor imaging in 48 marijuana users and 62 age- and sex-matched nonusing controls. The results showed that compared with controls, marijuana users had significantly less bilateral orbitofrontal gyri volume, higher functional connectivity in the orbitofrontal cortex (OFC) network, and higher structural connectivity in tracts that innervate the OFC (forceps minor) as measured by fractional anisotropy (FA). Increased OFC functional connectivity in marijuana users was associated with earlier age of onset. Lastly, a quadratic trend was observed suggesting that the FA of the forceps minor tract initially increased following regular marijuana use but decreased with protracted regular use. This pattern may indicate differential effects of initial and chronic marijuana use that may reflect complex neuroadaptive processes in response to marijuana use. Despite the observed age of onset effects, longitudinal studies are needed to determine causality of these effects.

Perceived Control Influences Neural Responses to Setbacks and Promotes Persistence Bhanji JP, Delgado MR. Neuron. 2014 Sep 17; 83(6): 1369-1375.
How do people cope with setbacks and persist with their goals? The authors examine how perceiving control over setbacks alters neural processing in ways that increase persistence through adversity. For example, a student might retake a class if initial failure was due to controllable factors (e.g., studying) but give up if failure was uncontrollable (e.g., unfair exam questions). Participants persisted more when they perceived control over setbacks, and when they experienced increased negative affect to setbacks. Consistent with previous observations involving negative outcomes, ventral striatum and ventromedial prefrontal (VMPFC) activity was decreased in response to setbacks. Critically, these structures represented distinct neural mechanisms for persistence through adversity. Ventral striatum signal change to controllable setbacks correlated with greater persistence, whereas VMPFC signal change to uncontrollable setbacks mediated the

relationship between increased negative affect and persistence. Taken together, the findings highlight how people process setbacks and adapt their behavior for future goal pursuit.

Large-Scale Brain Network Coupling Predicts Acute Nicotine Abstinence Effects on Craving and Cognitive Function Lerman C, Gu H, Loughead J, Ruparel K, Yihong Yang Y, Stein EA. JAMA Psychiatry. 2014; 71(5): 523-530.
Interactions of large-scale brain networks may underlie cognitive dysfunctions in psychiatric and addictive disorders. The aim of this study was to test the hypothesis that the strength of coupling among 3 large-scale brain networks—salience, executive control, and default mode—will reflect the state of nicotine withdrawal (vs smoking satiety) and will predict abstinence-induced craving and cognitive deficits and to develop a resource allocation index (RAI) that reflects the combined strength of interactions among the 3 large-scale networks. A within-subject functional magnetic resonance imaging study in an academic medical center compared resting-state functional connectivity coherence strength after 24 hours of abstinence and after smoking satiety. The authors examined the relationship of abstinence-induced changes in the RAI with alterations in subjective, behavioral, and neural functions. They included 37 healthy smoking volunteers, aged 19 to 61 years, for analyses. Twenty-four hours of abstinence vs smoking satiety. Inter-network connectivity strength (primary) and the relationship with subjective, behavioral, and neural measures of nicotine withdrawal during abstinence vs smoking satiety states (secondary). The RAI was significantly lower in the abstinent compared with the smoking satiety states (left RAI, P = .002; right RAI, P = .04), suggesting weaker inhibition between the default mode and salience networks. Weaker inter-network connectivity (reduced RAI) predicted abstinence-induced cravings to smoke ($r = -0.59$; P = .007) and less suppression of default mode activity during performance of a subsequent working memory task (ventromedial prefrontal cortex, $r = -0.66$, P = .003; posterior cingulate cortex, $r = -0.65$, P = .001). Alterations in coupling of the salience and default mode networks and the inability to disengage from the default mode network may be critical in cognitive/affective alterations that underlie nicotine dependence.

Sex Differences in Guanfacine Effects on Drug Craving and Stress Arousal in Cocaine-Dependent Individuals Fox HC, Morgan PT, Sinha R. Neuropsychopharm. 2014; 39(6): 1527-1537.
Currently, no FDA-approved medication exists for the treatment of cocaine use disorder. Furthermore, as women become increasingly more at risk for the consequences of cocaine addiction, the need to establish better-tailored treatment medications is paramount. The authors examine the effects of the alpha2 adrenergic agonist, guanfacine HCl, on responses to stress and drug cue in a group of cocaine dependent men and women who also abuse alcohol and nicotine. Forty early abstinent treatment-seeking cocaine-dependent males and females were randomly assigned to receive either daily placebo (12 M/7 F) or guanfacine (2 or 3 mg) (15 M/6 F) for 3 weeks. In week 4, they participated in a laboratory experiment and were exposed to three 10-min guided imagery conditions (stress/stress, cue/cue, and stress/cue), one per day, consecutively in a random, counterbalanced order. Craving, negative emotion, anxiety, and cardiovascular function were assessed at baseline, immediately following imagery exposure, and at various recovery time points. Guanfacine significantly attenuated cocaine craving, alcohol craving, anxiety, and negative emotion following exposure to all three imagery conditions in females, but not males. Guanfacine did, however, reduce sympathetic tone as well as stress and cue-induced nicotine craving and systolic blood pressure (SBP) in both males and females. These findings highlight sex-specific effects of guanfacine on drug craving, anxiety, and negative mood with significant effects in women and not men. The findings suggest further evaluation of guanfacine in the treatment of cocaine use

disorder with a specific focus on sex differences in treatment response.

Impaired Functional Connectivity of Brain Reward Circuitry in Patients with Schizophrenia and Cannabis Use Disorder: Effects of Cannabis and THC Fischer AS, Whitfield-Gabrieli S, Roth RM, Brunette MF, Green AI. Schizophr Res. 2014 Sep; 158(1-3): 176-182.
Cannabis use disorder (CUD) occurs in up to 42% of patients with schizophrenia and substantially worsens disease progression. The basis of CUD in schizophrenia is unclear and available treatments are rarely successful at limiting cannabis use. The authors have proposed that a dysregulated brain reward circuit (BRC) may underpin cannabis use in these patients. In the present pilot study, they used whole-brain seed-to-voxel resting state functional connectivity (rs-fc) to examine the BRC of patients with schizophrenia and CUD, and to explore the effects of smoked cannabis and orally administered delta-9-tetrahydrocannabinol (THC) on the BRC. 12 patients with schizophrenia and CUD and 12 control subjects each completed two fMRI resting scans, with patients administered either a 3.6% THC cannabis cigarette (n=6) or a 15 mg THC capsule (n=6) prior to their second scan. Results revealed significantly reduced connectivity at baseline in patients relative to controls, with most pronounced hypoconnectivity found between the nucleus accumbens and prefrontal cortical BRC regions (i.e., anterior prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex). Both cannabis and THC administration increased connectivity between these regions, in direct correlation with increases in plasma THC levels. This study is the first to investigate interregional connectivity of the BRC and the effects of cannabis and THC on this circuit in patients with schizophrenia and CUD. The findings from this pilot study support the use of rs-fc as a means of measuring the integrity of the BRC and the effects of pharmacologic agents acting on this circuit in patients with schizophrenia and CUD.

Mind Matters: Placebo Enhances Reward Learning in Parkinson's Disease Schmidt L, Braun EK, Wager TD, Shohamy D. Nat Neurosci. 2014 Dec; 17(12): 1793-1797.
Expectations have a powerful influence on how we experience the world. Neurobiological and computational models of learning suggest that dopamine is crucial for shaping expectations of reward and that expectations alone may influence dopamine levels. However, because expectations and reinforcers are typically manipulated together, the role of expectations per se has remained unclear. The authors separated these two factors using a placebo dopaminergic manipulation in individuals with Parkinson's disease. They combined a reward learning task with functional magnetic resonance imaging to test how expectations of dopamine release modulate learning-related activity in the brain. They found that the mere expectation of dopamine release enhanced reward learning and modulated learning-related signals in the striatum and the ventromedial prefrontal cortex. These effects were selective to learning from reward: neither medication nor placebo had an effect on learning to avoid monetary loss. These findings suggest a neurobiological mechanism by which expectations shape learning and affect.

Young Men's Shame about Their Desire for Other Men Predicts Risky Sex and Moderates the Knowledge - Self-Efficacy Link Park M, Anderson JN, Christensen JL, Miller LC, Appleby PR, Read SJ. Front Public Health. 2014 Oct 20; 2:183.
Nationally, HIV incidence is rising rapidly among young (18-24years old) men who have sex with men (YMSM). Knowledge of safer sex generally enhances self-efficacy for safer sex, an important predictor of safer-sex behaviors. Recent findings suggest that a strong negative social emotion (i.e., shame) increases YMSM's sexual risk-taking. Unchangeable shame (e.g., desire for other men) might undermine (moderate) the link between knowledge and self-efficacy or between self-efficacy and unprotected anal intercourse (UAI): this may be less likely for changeable shame (e.g., shame

about risky sexual behavior). AIM: To test the hypotheses that shame (i.e., sexual desire shame), but not shame about behavior (i.e., sexual behavior shame), will be positively related to UAI and will moderate the relationship between knowledge and self-efficacy and/or self-efficacy and UAI among YMSM. In an online national study, 1177 young adult (18-24 years old) MSM reported one or more acts of UAI in the past 90days with a casual partner. Eligible MSM filled out a survey in which they provided information about their knowledge of safer sex, self-efficacy for safer sex, reported levels of shame, and reported past 90-day UAI. Sexual desire shame was negatively correlated with knowledge and self-efficacy and positively correlated with UAI, the pattern reversed for sexual behavior shame. Sexual desire shame significantly lowered the knowledge to self-efficacy and the self-efficacy to UAI links. Sexual behavior shame also reduced the link from knowledge to self-efficacy, but not the self-efficacy to UAI link. The present study shows that there are different types of shame that may produce different effects with different implications for health behavior. Sexual desire shame may better reflect an emotion that is activated prior to risky behavior (e.g., when men reflect upon or feel desire for another man). Sexual behavior shame, on the other hand, better reflects what has already happened, thus, those higher in knowledge, efficacy, and therefore, safer sex are least likely to experience shame behavior.

A Dual-Systems Perspective on Addiction: Contributions from Neuroimaging and Cognitive Training McClure SM, Bickel WK. Ann N Y Acad Sci. 2014 Oct; 1327(1): 62-78. Dual-systems theories explain lapses in self-control in terms of a conflict between automatic and deliberative modes of behavioral control. Numerous studies have now tested whether the brain areas that control behavior are organized in a manner consistent with dual-systems models. Brain regions directly associated with the mesolimbic dopamine system, the nucleus accumbens and ventromedial prefrontal cortex in particular, capture some of the features assumed by automatic processing. Regions in the lateral prefrontal cortex are more closely linked to deliberative processing and the exertion of self-control in the suppression of impulses. While identifying these regions crudely supports dual-systems theories, important modifications to what constitutes automatic and deliberative behavioral control are also suggested. Experiments have identified various means by which automatic processes may be sculpted. Additional work decomposes deliberative processes into component functions such as generalized working memory, reappraisal of emotional stimuli, and prospection. The importance of deconstructing dual-systems models into specific cognitive processes is clear for understanding and treating addiction. The authors discuss intervention possibilities suggested by recent research, and focus in particular on cognitive training approaches to bolster deliberative control processes that may aid quit attempts.

Placebo and Nocebo Effects: an Introduction to Psychological and Biological Mechanisms
Kong J, Benedetti F. Handb Exp Pharmacol. 2014; 225: 3-15.
Placebo and nocebo effects are essential components of medical practice and efficacy research, and can be regarded as a special case of context learning. A fundamental function of the central nervous system is to configure the way in which previous learned context becomes linked to corresponding responses. These responses could be either automatic procedures with little flexibility or highly adaptive procedures modified by associated contexts and consequences. Placebo and nocebo effects may represent a typical example of the combination of the two: conditioning effect, which is an inflexible, instinctual, and automatic response, and cognitive expectancy effect, which is a flexible adaptive response modified by prevailing conscious context. Given the fact that contextual learning originates in the brain, neuroimaging tools have been widely used to study placebo and nocebo effects. In addition, pretest resting state fMRI may be a valuable biomarker to predict placebo responses.

Chronic Methamphetamine Abuse and Corticostriatal Deficits Revealed by Neuroimaging London ED, Kohno M, Morales AM, Ballard ME. Brain Res. 2014 Nov 4. [Epub ahead of print].
Despite aggressive efforts to contain it, methamphetamine use disorder continues to be a major public health problem; and with generic behavioral therapies still the mainstay of treatment for methamphetamine abuse, rates of attrition and relapse remain high. This review summarizes the findings of structural, molecular, and functional neuroimaging studies of methamphetamine abusers, focusing on cortical and striatal abnormalities and their potential contributions to cognitive and behavioral phenotypes that can serve to promote compulsive drug use. These studies indicate that individuals with a history of chronic methamphetamine abuse often display several signs of corticostriatal dysfunction, including abnormal gray- and white-matter integrity, monoamine neurotransmitter system deficiencies, neuroinflammation, poor neuronal integrity, and aberrant patterns of brain connectivity and function, both when engaged in cognitive tasks and at rest. More importantly, many of these neural abnormalities were found to be linked with certain addiction-related phenotypes that may influence treatment response (e.g., poor self-control, cognitive inflexibility, maladaptive decision-making), raising the possibility that they may represent novel therapeutic targets.

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

Butyrylcholinesterase Levels and Subjective Effects of Smoked Cocaine in Healthy Cocaine Users Askalsky P, Kalapatapu RK, Foltin RW, Comer SD. Am J Drug Alcohol Abuse. 2014; Oct 16: 1-5. [Epub ahead of print].
Butyrylcholinesterase (BChE) is beginning to attract attention as a possible target for cocaine abuse treatment because of its role in metabolizing cocaine. The purpose of this analysis was to assess whether endogenous BChE levels are associated with the subjective effects of cocaine. Data from 28 participants in five inpatient cocaine self-administration studies were included in the present analysis. Four minutes after each smoked cocaine dose, participants rated their drug-related effects

from 0-100 using a computerized self-report Visual Analogue Scale (VAS). The main outcome measures were nine change-in-VAS ratings between a baseline placebo dose and a 25-mg smoked cocaine dose. After controlling for age, sex, total years of cocaine use, total milligrams of cocaine administered before the 25-mg dose being analyzed, and baseline diastolic blood pressure, endogenous BChE was not significantly associated with any of the nine change-in-VAS ratings. Though BChE appears to be a possible target for cocaine abuse treatment, these data suggest that endogenous levels of BChE may not play a role in modifying the subjective effects of cocaine. Future larger studies of BChE in respect to the subjective effects produced by cocaine are needed to confirm or refute these findings.

Pilot Study of the 5-HT2AR Agonist Psilocybin in the Treatment of Tobacco Addiction Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. J Psychopharmacol. 2014 Nov; 28(11): 983-992.

Despite suggestive early findings on the therapeutic use of hallucinogens in the treatment of substance use disorders, rigorous follow-up has not been conducted. To determine the safety and feasibility of psilocybin as an adjunct to tobacco smoking cessation treatment the authors conducted an open-label pilot study administering moderate (20 mg/70 kg) and high (30 mg/70 kg) doses of psilocybin within a structured 15-week smoking cessation treatment protocol. Participants were 15 psychiatrically healthy nicotine-dependent smokers (10 males; mean age of 51 years), with a mean of six previous lifetime quit attempts, and smoking a mean of 19 cigarettes per day for a mean of 31 years at intake. Biomarkers assessing smoking status, and self-report measures of smoking behavior demonstrated that 12 of 15 participants (80%) showed seven-day point prevalence abstinence at 6-month follow-up. The observed smoking cessation rate substantially exceeds rates commonly reported for other behavioral and/or pharmacological therapies (typically <35%). Although the open-label design does not allow for definitive conclusions regarding the efficacy of psilocybin, these findings suggest psilocybin may be a potentially efficacious adjunct to current smoking cessation treatment models. The present study illustrates a framework for future research on the efficacy and mechanisms of hallucinogen-facilitated treatment of addiction.

Neural Correlates of Substance Abuse: Reduced Functional Connectivity between Areas Underlying Reward and Cognitive Control Motzkin JC, Baskin-Sommers A, Newman JP, Kiehl KA, Koenigs M. Human Brain Mapping. 2014; 35(9): 4282–4292.

Substance use disorders (SUD) have been associated with dysfunction in reward processing, habit formation, and cognitive-behavioral control. Accordingly, neurocircuitry models of addiction highlight roles for nucleus accumbens, dorsal striatum, and prefrontal/anterior cingulate cortex. However, the precise nature of the disrupted interactions between these brain regions in SUD, and the psychological correlates thereof, remain unclear. Here the authors used magnetic resonance imaging to measure rest-state functional connectivity of three key striatal nuclei (nucleus accumbens, dorsal caudate, and dorsal putamen) in a sample of 40 adult male prison inmates (n = 22 diagnosed with SUD; n = 18 without SUD). Relative to the non-SUD group, the SUD group exhibited significantly lower functional connectivity between the nucleus accumbens and a network of frontal cortical regions involved in cognitive control (dorsal anterior cingulate cortex, dorsolateral prefrontal cortex, and frontal operculum). There were no group differences in functional connectivity for the dorsal caudate or dorsal putamen. Moreover, the SUD group exhibited impairments in laboratory measures of cognitive-behavioral control, and individual differences in functional connectivity between nucleus accumbens and the frontal cortical regions were related to individual differences in measures of cognitive-behavioral control across groups. The strength of the relationship between functional connectivity and cognitive control did not differ

between groups. These results indicate that SUD is associated with abnormal interactions between subcortical areas that process reward (nucleus accumbens) and cortical areas that govern cognitive-behavioral control.

Distinct Regions of Anterior Cingulate Cortex Signal Prediction and Outcome Evaluation Jahn A, Nee DE, Alexander WH, Brown JW. NeuroImage. 2014; 95: 80–89.
A number of theories have been proposed to account for the role of anterior cingulate cortex (ACC) and the broader medial prefrontal cortex (mPFC) in cognition. The recent Prediction of Response Outcome (PRO) computational model casts the mPFC in part as performing two theoretically distinct functions: learning to predict the various possible outcomes of actions, and then evaluating those predictions against the actual outcomes. Simulations have shown that this new model can account for an unprecedented range of known mPFC effects, but the central theory of distinct prediction and evaluation mechanisms within ACC remains untested. Using combined computational neural modeling and fMRI, the authors show here that prediction and evaluation signals are indeed each represented in the ACC, and furthermore, they are represented in distinct regions within ACC. The authors' task independently manipulated both the number of predicted outcomes and the degree to which outcomes violated expectancies, the former providing assessment of regions sensitive to prediction and the latter providing assessment of regions sensitive to evaluation. Using quantitative regressors derived from the PRO computational model, we show that prediction-based model signals load on a network including the posterior and perigenual ACC, but outcome evaluation model signals load on the mid-dorsal ACC. These findings are consistent with distinct prediction and evaluation signals as posited by the PRO model and provide new perspective on a large set of known effects within ACC.

Inhibitory Motor Control Based on Complex Stopping Goals Relies on the Same Brain Network as Simple Stopping Wessel JR, Aron AR. NeuroImage. 2014; 103C: 225–234.
Much research has modeled action-stopping using the stop-signal task (SST), in which an impending response has to be stopped when an explicit stop-signal occurs. A limitation of the SST is that real-world action-stopping rarely involves explicit stop-signals. Instead, the stopping-system engages when environmental features match more complex stopping goals. For example, when stepping into the street, one monitors path, velocity, size, and types of objects and only stops if there is a vehicle approaching. Here, the authors developed a task in which participants compared the visual features of a multidimensional go-stimulus to a complex stopping-template, and stopped their go-response if all features matched the template. They used independent component analysis of EEG data to show that the same motor inhibition brain network that explains action-stopping in the SST also implements motor inhibition in the complex-stopping task. Furthermore, the authors found that partial feature overlap between go-stimulus and stopping-template led to motor slowing, which also corresponded with greater stopping-network activity. This shows that the same brain system for action-stopping to explicit stop-signals is recruited to slow or stop behavior when stimuli match a complex stopping goal. The results imply a generalizability of the brain's network for simple action-stopping to more ecologically valid scenarios.

You Are the Danger: Attenuated Insula Response in Methamphetamine Users during Aversive Interoceptive Decision-Making Stewart JL, May AC, Poppa T, Davenport PW, Tapert SF, Paulus MP. Drug Alcohol Depend. 2014; 142: 110–119.
Drug dependent individuals often make drug-taking decisions when they do not feel well. Yet, few studies have examined the influence of an aversive state on decision-making related neural processing. The authors investigate brain activation to decision-making during an aversive

interoceptive challenge in methamphetamine users using functional magnetic resonance imaging (fMRI). Recently abstinent inpatients with methamphetamine use disorder (METH; n=20) and healthy comparison subjects (CTL; n=22) performed a two-choice prediction task at three fixed error rates (ER; 20%=reward, 50%=uncertainty, 80%=punishment) while anticipating and experiencing episodes of inspiratory breathing load during fMRI. METH exhibited higher trait anxiety in conjunction with lower anterior insula (AI) and inferior frontal gyrus (IFG) activation than CTL across trials. METH also showed lower posterior insula (PI) and anterior cingulate cortex (ACC) activation than CTL during breathing load independent of ER. For the crucial ER by interoception interaction, METH displayed lower ACC activation to punishment/loss than CTL during breathing load. Within METH, lower trait anxiety was linked to AI/IFG attenuation across trials. AI/IFG attenuations in METH are suggestive of an executive functioning deficit, particularly in users with low anxiety, reflecting reduced resources allocated to choice selection. In contrast, PI/ACC reductions in METH appear specific to impairments in registering and evaluating interoceptive experiences. Taken together, inadequate activation of brain areas that are important for regulating when one does not feel well may be the neural basis for poor decision-making by METH.

EPIDEMIOLOGY RESEARCH

The Association Between Cannabis Abuse and Subsequent Schizophrenia: A Swedish National Co-relative Control Study Giordano GN, Ohlsson H, Sundquis K, Sundquist J, Kendler KS. Psychol Med. 2014; 1-8.

Although cannabis abuse (CA) is known to be associated with schizophrenia, the causal nature of this association is unclear, with prodromal effects complicating its interpretation. From Swedish national registry databases, the authors used a co-relative case-control design with full-sibling, half-sibling and first-cousin comparisons, alongside a general Swedish population sample. Using ICD codes, 5456 individuals with an initial diagnosis of schizophrenia (2000-2010) were matched with five schizophrenia-free controls. They further identified first-cousin, half-sibling and full-sibling pairs discordant for CA and statistically extrapolated results for discordant monozygotic (MZ) twins. Within the general Swedish population, CA was strongly associated with later schizophrenia [odds ratio (OR) 10.44, 95% confidence interval (CI) 8.99-12.11]. This association was substantially attenuated both by increasing temporal delays between CA exposure and schizophrenia diagnosis and by controlling for increasing degrees of familial confounding. Extrapolated discordant MZ pairs suggested that fully controlling for confounding familial factors reduced the association between CA and later schizophrenia to more modest levels (ORs of approximately 3.3 and 1.6 with 3- and 7-year temporal delays respectively). Opiate, sedative, cocaine/stimulant and hallucinogen abuse were also strongly associated with subsequent schizophrenia in the general population. After controlling for familial confounding, only cocaine/stimulant exposure remained associated.CA has an appreciable causal impact on future risk for schizophrenia. However, population-based estimates of cannabis-schizophrenia co-morbidity substantially overestimate their causal association. Predictions of the cases of schizophrenia that might be prevented by reduced cannabis consumption based on population associations are therefore likely to be considerably overestimated.

The Causal Nature Of the Association Between Neighborhood Deprivation and Drug Abuse: A Prospective National Swedish Co-relative Control Study Kendler KS, Ohlsson H, Sundquist K, Sundquist J. Psychol Med. 2014; 44(12): 2537-2546.

Risk for drug abuse (DA) is strongly associated with neighborhood social deprivation (SD). However, the causal nature of this relationship is unclear. Three Swedish population-based cohorts were followed up over 5 years for incident registration of DA in medical, legal or pharmacy records. In each cohort, the authors examined the SD-DA association, controlling carefully for individual socio-economic status (SES) with multiple measures, in the entire sample and among pairs of first cousins, paternal and maternal half-siblings, full siblings and monozygotic (MZ) twins discordant for SD exposure. The number of informative relative pairs ranged from 6366 to 166,208.In all cohorts, SD was prospectively related to risk for incident DA. In relative pairs discordant for SD exposure, the SD-DA association was similar to that seen in the entire population in cousins, half-siblings, full siblings and MZ twins. Eliminating subjects who were residentially unstable or had DA in the first two follow-up years did not alter this pattern. When divided by age, in the youngest groups, the SD-DA association was weaker in siblings than in the entire population. Across three cohorts, controlling for individual SES and confounding familial factors, SD prospectively predicted risk for incident DA registration. These results support the hypothesis that the SD-DA association is in part causal and unlikely to result entirely from personal attributes, which both increase risk for DA and cause selection into high SD environments. At least part of the SD-DA association arises because exposure to SD causes an increased risk of DA.

Gender and Risk Behaviors For HIV And Sexually Transmitted Infections Among Recently Released Inmates: A Prospective Cohort Study Binswanger IA, Mueller SR, Beaty BL, Min S-J, Corsi KF. AIDS Care. 2014; 26(7): 872-881.
Women in prison have a higher prevalence of HIV than men. After release from prison, former inmates have the opportunity to engage in risk behaviors for HIV and other sexually transmitted infections (STIs). The authors sought to assess change in risk behaviors over time and the association of gender with risk behavior in the post release period. In this prospective cohort study, they interviewed 200 former inmates (51 women) approximately two weeks (baseline) and three months (follow-up) after release and tested them for HIV infection at follow-up. They examined the association of gender with unprotected vaginal or anal sex in the last seven days using chi-square and Fisher exact tests and multivariable logistic regression. At baseline, 22% of men and 41% of women reported unprotected vaginal sex ($p < 0.01$) and 5% of men and 8% of women reported unprotected anal sex ($p = 0.51$). Being younger (OR for each decade increase 0.48, 95% CI = 0.29-0.80), being gay/lesbian or being bisexual (compared with being heterosexual, OR = 4.74, 95% CI = 1.01-22.17 and OR = 3.98, 95% CI = 1.41-11.26, respectively), or reporting a drug of choice of heroin/speedballs or cocaine/crack (compared with marijuana/no drug of choice, OR = 24.00, 95% CI = 5.15-111.81 and OR = 3.49, 95% CI = 1.20-10.18, respectively) was associated with unprotected vaginal or anal sex after adjusting for race, homelessness, and hazardous drinking. At follow-up, 21% of men and 44% of women reported unprotected sex ($p = 0.005$), and female gender (OR = 4.42, 95% CI = 1.79-10.94) and hazardous drinking (compared with not meeting criteria for hazardous drinking, OR = 3.64, 95% CI = 1.34-9.86) were associated with unprotected sex, adjusting for race and homelessness. In this population with a high prevalence of HIV, we demonstrated persistent engagement in sexual risk behavior during the post release period. Enhanced efforts to promote sexual health and reduced risk behavior among both male and female current and former prison inmates are needed, including improved access to preventive care and HIV and STI screening, testing, and treatment.

Probability and Predictors Of the Cannabis Gateway Effect: A National Study Secades-Villa R, Garcia-Rodriguez O, Jin CJ, Wang S, Blanco C. Int J Drug Policy. 2014.
While several studies have shown a high association between cannabis use and use of other illicit drugs, the predictors of progression from cannabis to other illicit drugs remain largely unknown. This study aims to estimate the cumulative probability of progression to illicit drug use among individuals with lifetime history of cannabis use, and to identify predictors of progression from cannabis use to other illicit drugs use. Analyses were conducted on the sub-sample of participants in Wave 1of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) who started cannabis use before using any other drug (n=6624). Estimated projections of the cumulative probability of progression from cannabis use to use of any other illegal drug use in the general population were obtained by the standard actuarial method. Univariate and multivariable survival analyses with time-varying covariates were implemented to identify predictors of progression to any drug use. Lifetime cumulative probability estimates indicated that 44.7% of individuals with lifetime cannabis use progressed to other illicit drug use at some time in their lives. Several sociodemographic characteristics, internalizing and externalizing psychiatric disorders and indicators of substance use severity predicted progression from cannabis use to other illicit drugs use. A large proportion of individuals who use cannabis go on to use other illegal drugs. The increased risk of progression from cannabis use to other illicit drugs use among individuals with mental disorders underscores the importance of considering the benefits and adverse effects of changes in cannabis regulations and of developing prevention and treatment strategies directed at curtailing cannabis use in these populations.

Alcohol Consumption Mediates the Relationship Between ADH1B and DSM-IV Alcohol Use Disorder and Criteria Kilcoyne B, Shmulewitz D, Meyers JL, Aharonovich E, Greenstein E, Frisch A, Weizman A, Spivak B, Edenberg HJ, Gelernter J, Hasin DS. J Stud Alcohol Drugs. 2014; 75(4): 635-642.

A single nucleotide variation in the alcohol dehydrogenase 1B (ADH1B) gene, rs1229984, produces an ADH1B enzyme with faster acetaldehyde production. This protective variant is associated with lower alcohol consumption and lower risk for alcohol use disorders (AUDs). Based on the premise that faster ADH1B kinetics decreases alcohol consumption, the authors formally tested if the association between ADH1B variant rs1229984 and AUDs occurs through consumption. They also tested whether the association between rs1229984 and each of the 11 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), AUD criteria occurs through consumption. A total of 1,130 lifetime drinkers from an Israeli household sample were assessed with a structured interview and genotyped for rs1229984 (protective allele frequency = 0.28). Logistic regression evaluated the association between rs1229984 and each phenotype (AUDs, 11 individual DSM-IV criteria). For phenotypes significantly related to rs1229984, the effect through consumption was tested with logistic regression and bootstrapping.ADH1B rs1229984 was significantly associated with AUDs and six criteria, with odds ratios ranging from 1.32 to 1.96. The effect through consumption was significant for these relationships, explaining 23%-74% of the total ADH1B effect. This is the first study to show that ADH1B rs1229984 is related to 6 of the 11 DSM-IV AUD criteria and that alcohol consumption explained a significant proportion of these associations and the association of ADH1B with AUDs. Better understanding of the relationship between ADH1B and the DSM-IV AUD criteria, including effects through consumption, will enhance our understanding of the etiologic model through which AUDs can occur.

Community HIV-1 Drug Resistance Is Associated With Transmitted Drug Resistance Tilghman MW; Perez-Santiag J, Osorio G, Little SJ, Richman DD, Mathews WC, Haubrich RH, Smith DM. HIV Med. 2014; 15(6): 339-346.

As community viral load (CVL) measurements are associated with the incidence of new HIV-1 infections in a population, the authors hypothesized that similarly measured community drug resistance (CDR) could predict the prevalence of transmitted drug resistance (TDR).Between 2001 and 2011, the prevalence's of HIV-1 drug resistance for patients with established infection receiving HIV care (i.e. CDR) and TDR in recently infected patients were determined in San Diego. At each position in HIV-1 reverse transcriptase (RT) and protease (pro), drug resistance was evaluated both as the overall prevalence of resistance-associated mutations and by weighting each resistance position to the concurrent viral load of the patient and its proportion to the total viral load of the clinic (CVL). The weighting was the proportion of the CVL associated with patients identified with resistance at each residue. Spearman ranked correlation coefficients were used to determine associations between CDR and TDR. The authors analyzed 1088 resistance tests for 971 clinic patients and baseline resistance tests for 542 recently infected patients. CDR at positions 30, 46, and 88 in pro was associated with TDR between 2001 and 2011. When CDR was weighted by the viral load of patients, CDR was associated with TDR at position 103 in RT. Each of these associations was corroborated at least once using shorter measurement intervals. Despite evaluation of a limited percentage of chronically infected patients in San Diego, CDR correlated with TDR at key resistance positions and therefore may be a useful tool with which to predict the prevalence of TDR.

The Heritability Of Alcohol Use Disorders: A Meta-analysis Of Twin and Adoption Studies Verhulst B, Neale MC, Kendler KS. Psychol Med. 2014; 1-12.
To clarify the role of genetic and environmental risk factors in alcohol use disorders (AUDs), the authors performed a meta-analysis of twin and adoption studies and explored the impact of sex, assessment method (interview v. hospital/population records), and study design (twin v. adoption study) on heritability estimates. The literature was searched for all unique twin and adoption studies of AUD and identified 12 twin and five adoption studies. The data were then reconstructed and analyzed using ordinal data full information maximum likelihood in the OpenMx program. Heterogeneity was tested with likelihood ratio tests by equating the parameters across studies. There was no evidence for heterogeneity by study design, sex or assessment method. The best-fit estimate of the heritability of AUD was 0.49 [95% confidence interval (CI) 0.43-0.53], and the proportion of shared environmental variance was 0.10 (95% CI 0.03-0.16). Estimates of unique environmental proportions of variance differed significantly across studies. AUD is approximately 50% heritable. The multiple genetically informative studies of this syndrome have produced consistent results that support the validity of this heritability estimate, especially given the different potential methodological weaknesses of twin and adoption designs, and of assessments of AUD based on personal interviews v. official records. The authors also found evidence for modest shared environmental effects suggesting that environmental factors also contribute to the familial aggregation of AUDs.

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

Sexual Risk Behavior In Young Adulthood: Broadening The Scope Beyond Early Sexual Initiation Epstein M, Bailey JA, Manhart LE, Hill KG, Hawkins JD. J Sex Res. 2014; 51(7): 721-730.
A robust link between early sexual initiation and sexual risk-taking behavior is reported in previous studies. The relationship may not be causal, however, as the effect of common risk factors are often not considered. The current study examined whether early initiation was a key predictor of risky sexual behavior in the 20s and 30s, over and above co-occurring individual and environmental

factors. Data were drawn from the Seattle Social Development Project, a longitudinal panel of 808 youth. Early predictors (ages 10 to 15) and sexual risk taking (ages 21 to 24 and 30 to 33) were assessed prospectively. Early sexual initiation (before age 15) was entered into a series of profit regressions that also included family, neighborhood, peer, and individual risk factors. Although a positive bivariate relation between early sexual initiation and sexual risk taking was observed at both ages, the link did not persist when co-occurring risk factors were included. Behavioral disinhibition and antisocial peer influences emerged as the strongest predictors of sexual risk over and above early sexual initiation. These results suggest that early sexual initiation must be considered in the context of common antecedents; public health policy aimed at delaying sexual intercourse alone is unlikely to substantially reduce sexual risk behavior in young adulthood.

Childhood And Adolescent Predictors Of Heavy Episodic Drinking And Alcohol Use Disorder At Ages 21 And 33: A Domain-specific Cumulative Risk Model Lee JO, Hill KG, Guttmannova K, Hartigan LA, Catalano RF, Hawkins JD. J Stud Alcohol Drugs. 2014; 75(4): 684-694.
Guided by a domain-specific cumulative risk model and an emerging notion of general and alcohol-specific influences, this study examined whether general and alcohol-specific influences from family, peer, and school contexts in childhood and adolescence differentially predict heavy episodic drinking and alcohol use disorder at two developmental periods: the transition to adulthood (age 21) and later in adulthood (age 33). Data are from a longitudinal panel study (n = 808) examining the etiology of substance use problems and associated behavior problems from age 10 to age 33 in a Northwest United States urban community sample. The sample is ethnically diverse and evenly distributed by gender (51% male).At age 21, alcohol problems were most consistently predicted by adolescent family alcohol and peer alcohol environments and by peer general environment, but not by general family functioning. Conversely, by age 33, alcohol problems were more consistently predicted by general poor family functioning in adolescence and not by family alcohol or any of the peer environment measures. Adolescent family and peer alcohol environment influenced alcohol problems at the transition to adulthood. However, alcohol problems later in adulthood were more strongly associated with general poor family functioning in adolescence. These results suggest that alcohol prevention efforts should involve both components designed to reduce alcohol-specific risk and components to improve general family and peer environments during childhood and adolescence.

General and Specific Predictors Of Nicotine and Alcohol Dependence In Early Adulthood: Genetic and Environmental Influences Samek DR, Keyes MA, Hicks BM, Bailey J, McGue M, Iacono WG. J Stud Alcohol Drugs. 2014; 75(4): 623-634.
This study builds on previous work delineating a hierarchical model of family environmental risk in relation to a hierarchical model of externalizing disorders (EXTs) by evaluating for gene-environment interplay in these relationships. The associations between parent-child relationship quality (conflict, bonding, and management) and substance-specific adolescent family environments (parental/sibling tobacco/alcohol use) in relation to young adult EXTs (age 22, years nicotine, alcohol, and other drug dependence; antisocial and risky sexual behavior) were evaluated. The sample included 533 adopted offspring and 323 biological offspring. Because adopted youth do not share genes with their parents, a significant association between parent-child relationship quality and EXTs would provide evidence against passive gene-environment correlation (rGE). Significant associations between parental tobacco/alcohol use in relation to offspring nicotine/alcohol dependence in the adopted offspring support common environmental influence. Significant associations detected for the biological offspring only suggest common genetic influence. For both adoptive and biological offspring, there was a significant association between parent-child

relationship quality and EXTs. Parental tobacco/alcohol use was unrelated to EXTs. Sibling tobacco/alcohol use was related to EXTs, but only for the biological siblings. Parental tobacco use was associated with the residual variance in nicotine dependence in adopted offspring. Findings replicate a long-term influence of adolescent parent-child relationship quality on adult EXTs. Findings extend previous research by providing evidence against passive rGE in this association. The association between parental tobacco use and adult nicotine dependence appears to be environmentally mediated, but caution is warranted as we found this relationship only for adopted youth.

The Role Of Alcohol Perceptions As Mediators Between Personality and Alcohol-related Outcomes Among Incoming College-student Drinkers Hustad JTP, Pearson MR, Neighbors C, Borsari B. Psychol Addict Behav. 2014; 28(2): 336-347.
After high school, college students escalate their drinking at a faster rate than their noncollege-attending peers, and alcohol use in high school is one of the strongest predictors of alcohol use in college. Therefore, an improved understanding of the role of predictors of alcohol use during the critical developmental period when individuals transition to college has direct clinical implications to reduce alcohol-related harms. The authors used path analysis in the present study to examine the predictive effects of personality (e.g., impulsivity, sensation seeking, hopelessness, and anxiety sensitivity) and three measures of alcohol perception: descriptive norms, injunctive norms, and perceptions regarding the perceived role of drinking in college on alcohol-related outcomes. Participants were 490 incoming freshmen college students. Results indicated that descriptive norms, injunctive norms, and the role of drinking largely mediated the effects of personality on alcohol outcomes. In contrast, both impulsivity and hopelessness exhibited direct effects on alcohol-related problems. The perceived role of drinking was a particularly robust predictor of outcomes and mediator of the effects of personality traits, including sensation seeking and impulsivity on alcohol outcomes. The intertwined relationships observed in this study between personality factors, descriptive norms, injunctive norms, and the role of drinking highlight the importance of investigating these predictors simultaneously. Findings support the implementation of interventions that target these specific perceptions about the role of drinking in college. (PsycINFO Database Record (c) 2014 APA, all rights reserved).

Venue-based Network Analysis To Inform HIV Prevention Efforts Among Young Gay, Bisexual, And Other Men Who Have Sex With Men Holloway IW, Rice E, Kipke MD. Prev Sci. 2014; 15(3): 419-427.
In the USA, human immunodeficiency virus (HIV) incidence rates continue to increase among young gay, bisexual, and other men have sexual intercourse with men. Young men who have sex with men (YMSM) indicate interest in HIV prevention programming that is implemented in the social venues that they frequent when they want to socialize with other men. The authors sought to understand YMSM venues as a networked space to provide insights into venue-based HIV prevention intervention delivery. The present study used survey data reported by 526 YMSM (ages 18-24) in 2005 to conduct a venue-based social network analysis. The latter sought to determine if the structure and composition of the networks in Los Angeles could be used to facilitate the delivery of HIV prevention messages to YMSM. Degree of person sharing between venues was used to demonstrate interconnectivity between venues classified as low risk (e.g., coffee shops) and high risk (e.g., bars and clubs) by a Community Advisory Board. Sixty-five percent of the 110 venues nominated were bars and clubs. Nearly all YMSM were connected by a single venue and over 87ýý% were connected by the six most central venues. A handful of highly connected low-risk venues was central to the venue network and connected to popular high-risk venues. Venue-based

network analysis can inform tailored HIV prevention messaging for YMSM. Targeted delivery of prevention messaging at low-risk centralized venues may lead to widespread diffusion among venue-attending YMSM.

Attention-Deficit/Hyperactivity Disorder Subtypes and Substance Use and Use Disorders In NESARC De Alwis D, Lynskey MT, Reiersen AM, Agrawal A. Addict Behav. 2014; 39(8): 1278-1285.
Attention-deficit/hyperactivity disorder (ADHD) is associated with substance use and substance use disorders (SUD). However, relatively little is known about the relationship between DSM-IV ADHD subtypes and substance use or DSM-IV abuse/dependence in epidemiological samples. Data were obtained from the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC, N = 33,588). Respondents reported on ADHD symptoms (DSM-IV) for the period of time when they were 17 years or younger. Lifetime use and DSM-IV abuse/dependence of alcohol, nicotine, cannabis, cocaine, sedatives, stimulants and heroin/opiates were compared across those with ADHD symptoms but no diagnosis (ADHDsx; N = 17,009), the Combined (ADHD-C; N = 361), Predominantly Inattentive (ADHD-I; N = 325), and the Predominantly Hyperactive-Impulsive (ADHD-HI; N = 279) ADHD subtypes. Taking a more dimensional approach, inattentive and hyperactive-impulsive symptom counts and their associations with substance use and misuse were also examined. After adjustments for conduct disorder, major depressive disorder, any anxiety disorder and other socio-demographic covariates, substance use and SUD were associated with ADHDsx, ADHD-C, ADHD-I and ADHD-HI. Overall, substance use and SUD were more weakly associated with the ADHDsx group compared to the three ADHD diagnostic groups. Statistically significant differences were not evident across the three diagnostic groups. Hyperactive-impulsive symptoms were more consistently associated with substance use and SUD compared to inattentive symptoms. ADHD subtypes are consistently associated with substance use and SUD. The relatively stronger association of hyperactive/impulsive symptoms with substance use and abuse/dependence is consistent with the extant literature noting impulsivity as a precursor of substance use and SUD.

Taking A Life Course Approach To Studying Substance Use Treatment Among A Community Cohort Of African American Substance Users Evans-Polce, RJ; Doherty EE, Ensminger ME. Drug Alcohol Depend. 2014; 142: 216-223.
Life course theory emphasizes the need to examine a wide variety of distal factors along with proximal factors, longitudinally. Yet research on who obtains substance use treatment is generally cross-sectional and limited to examining developmentally proximal factors (e.g., substance use severity) and demographic factors. To investigate treatment within a life-course framework, the authors studied 522 drug and/or alcohol users from a community cohort of African Americans followed prospectively from age 6. Developmentally distal factors of childhood and adolescent social behavior, family environment, academic achievement, mental health, and substance use along with the key proximal factors of substance use severity and socioeconomic status were examined using regression analyses to assess their impact on obtaining adult substance use treatment. One-fifth of the study population obtained treatment for substance use by age 32 (20.5%). Although adult socioeconomic status was not associated with substance use treatment in adulthood in the multivariable model, the proximal factor of substance use severity was a strong predictor of obtaining substance use treatment, as expected. After including several developmentally distal factors in the model, childhood aggression also had an independent effect on adult substance use treatment, above and beyond substance use severity. These findings emphasize the importance of using a life course framework when exploring predictors of treatment; early life characteristics are

important influences beyond the more proximal factors in adulthood. Research should continue to take a life course approach to better understand pathways to substance use treatment.

Genetic Variation In Personality Traits Explains Genetic Overlap Between Borderline Personality Features And Substance Use Disorders Few LR, Grant JD, Trull TJ, Statham DJ, Martin NG, Lynskey MT, Agrawal A. Addiction. 2014.
The aims of this study were to examine the genetic overlap between borderline personality features (BPF) and substance use disorders (SUDs) and the extent to which variation in personality traits contributes to this covariance. Genetic structural equation modelling was used to partition the variance in and covariance between personality traits, BPF and SUDs into additive genetic, shared and individual-specific environmental factors. All participants were registered with the Australian Twin Registry. A total of 3127 Australian adult twins participated in the study. Diagnoses of DSM-IV alcohol and cannabis abuse/dependence (AAD; CAD) and nicotine dependence (ND) were derived via computer-assisted telephone interview. BPF and five-factor model personality traits were derived via self-report questionnaires. Personality traits, BPF and substance use disorders were partially influenced by genetic factors with heritability estimates ranging from 0.38 (neuroticism; 95% confidence interval: 0.30-0.45) to 0.78 (CAD; 95% confidence interval: 0.67-0.86). Genetic and individual-specific environmental correlations between BPF and SUDs ranged from 0.33 to 0.56 (95% CI=0.19-0.74) and 0.19-0.32 (95% CI=0.06-0.43), respectively. Overall, there was substantial support for genetic influences that were specific to AAD, ND and CAD (30.76-68.60%). Finally, genetic variation in personality traits was responsible for 11.46% (extraversion for CAD) to 59.30% (neuroticism for AAD) of the correlation between BPF and SUDs. Both genetic and individual-specific environmental factors contribute to comorbidity between borderline personality features and substance use disorders. A substantial proportion of this comorbidity can be attributed to variation in normal personality traits, particularly neuroticism.

Exposure To Violence Predicting Cortisol Response During Adolescence and Early Adulthood: Understanding Moderating Factors Aiyer SM, Heinze JE, Miller AL, Stoddard SA, Zimmerman MA. J Youth Adolesc. 2014; 43(7): 1066-1079.
Previous research on the association between violence and biological stress regulation has been largely cross-sectional, and has also focused on childhood. Using longitudinal data from a low-income, high-risk, predominantly African-American sample (n=266; 57% female), the authors tested hypotheses about the influence of cumulative exposure to violence during adolescence and early adulthood on cortisol responses in early adulthood. They found that cumulative exposure to violence predicted an attenuated cortisol response. Further, they tested whether sex, mothers; support, or fathers; support moderated the effect of exposure to violence on cortisol responses. They found that the effect of cumulative exposure to violence on cortisol was modified by sex; specifically, males exposed to violence exhibited a more attenuated response pattern. In addition, the effect of cumulative exposure to violence on cortisol was moderated by the presence of fathers; support during adolescence. The findings contribute to a better understanding of how cumulative exposure to violence influences biological outcomes, emphasizing the need to understand sex and parental support as moderators of risk.

Polygenic Risk Scores For Smoking: Predictors For Alcohol and Cannabis Use?
Vink JM, Hottenga JJ, de Geus EJC, Willemsen G, Neale MC, Furberg H, Boomsma DI. Addiction. 2014; 109(7): 1141-1151.
A strong correlation exists between smoking and the use of alcohol and cannabis. This paper uses polygenic risk scores to explore the possibility of overlapping genetic factors. Those scores reflect a

combined effect of selected risk alleles for smoking. Summary-level P-values were available for smoking initiation, age at onset of smoking, cigarettes per day and smoking cessation from the Tobacco and Genetics Consortium (n between 22,000 and 70,000 subjects). Using different P-value thresholds (0.1, 0.2 and 0.5) from the meta-analysis, sets of risk alleles; were defined and used to generate a polygenic risk score (weighted sum of the alleles) for each subject in an independent target sample from the Netherlands Twin Register (n=1583). The association between polygenic smoking scores and alcohol/cannabis use was investigated with regression analysis. The polygenic scores for; cigarettes per day; were associated significantly with the number of glasses alcohol per week (P=0.005, R2 =0.4-0.5%) and cannabis initiation (P=0.004, R2 =0.6-0.9%). The polygenic scores for age at onset of smoking; were associated significantly with age at regular drinking; (P=0.001, R2 =1.1-1.5%), while the scores for smoking initiation; and smoking cessation; did not significantly predict alcohol or cannabis use. Smoking, alcohol and cannabis use are influenced by aggregated genetic risk factors shared between these substances. The many common genetic variants each have a very small individual effect size.

Suicidal Ideation and Substance Use Among Adolescents and Young Adults: A Bidirectional Relation? Zhang X, Wu L-T. Drug Alcohol Depend. 2014; 142: 63-73.
The objective of this study was to examine reciprocal associations between substance use (cigarette smoking, use of alcohol, marijuana, and other illegal drugs) and suicidal ideation among adolescents and young adults (aged 11-21 at wave 1; aged 24-32 at wave 4). Four waves public-use Add Health data were used in the analysis (N=3342). Respondents were surveyed in 1995, 1996, 2001-2002, and 2008-2009. Current regular smoking, past-year alcohol use, past-year marijuana use, and ever use of other illegal drugs as well as past-year suicidal ideation were measured at the four waves (1995, 1996, 2001-2002, and 2008-2009). Fixed effects models with lagged dependent variables were modeled to test unidirectional associations between substance use and suicidal ideation, and nonrecursive models with feedback loops combining correlated fixed factors were conducted to examine reciprocal relations between each substance use and suicidal ideation, respectively. After adjusting for the latent time-invariant effects and lagged effects of dependent variables, the unidirectional associations from substance use to suicidal ideation were consistently significant, and vice versa. Nonrecursive model results showed that use of cigarette or alcohol increased risk of suicidal ideation, while suicidal ideation was not associated with cigarette or alcohol use. Reversely, drug use (marijuana and other drugs) did not increase risk of suicidal ideation, but suicidal ideation increased risk of illicit drug use. The results suggest that relations between substance use and suicidal ideation are unidirectional, with cigarette or alcohol use increasing risk of suicidal ideation and suicidal ideation increasing risk of illicit drug use.

Month-Wise Estimates Of Tobacco Smoking During Pregnancy For The United States, 2002-2009 Alshaarawy O, Anthony JC. Matern Child Health J. 2014.
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 12-44year 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 our advance hypotheses. Nonetheless, our 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 TDs 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.

Obesity and Depression In Adolescence and Beyond: Reciprocal Risks Marmorstein NR, Iacono WG, Legrand L. Int J Obes (Lond). 2014; 38(7): 906-911.
Obesity and major depressive disorder (MDD) are associated, but evidence about how they relate over time is conflicting. The goal of this study was to examine prospective associations between depression and obesity from early adolescence through early adulthood. Participants were drawn from a statewide, community-based, Minnesota sample. MDD and obesity with onsets by early adolescence (by age 14), late adolescence (between 14 and 20) and early adulthood (ages 20-24) were assessed via structured interview (depression) and study-measured height and weight. Cross-sectional results indicated that depression and obesity with onsets by early adolescence were concurrently associated, but the same was not true later in development. Prospective results indicated that depression by early adolescence predicted the onset of obesity (odds ratio (OR) =3.76, confidence interval =1.33-10.59) during late adolescence among female individuals. Obesity that developed during late adolescence predicted the onset of depression (OR=5.89, confidence interval=2.31-15.01) during early adulthood among female individuals.:For girls, adolescence is a high-risk period for the development of this comorbidity, with the nature of the risk varying over the course of adolescence. Early adolescent-onset depression is associated with elevated risk of later onset obesity, and obesity, particularly in late adolescence, is associated with increased odds of later depression. Further investigation into the mechanisms of these effects and the reasons for the observed gender and developmental differences is needed. Prevention programs focused on early-onset cases of depression and adolescent-onset cases of obesity, particularly among female individuals, may help in reducing risk for this form of comorbidity.

Health and Social Harms Associated With Crystal Methamphetamine Use Among Street-involved Youth In A Canadian Setting Uhlmann S, DeBeck K, Simo A, Kerr T, Montaner JSG, Wood E. Am J Addict. 2014; 23(4): 393-398.
Despite recent increases in crystal methamphetamine use among high-risk populations such as street-involved youth, few prospective studies have examined the health and social outcomes associated with active crystal methamphetamine use. The authors enrolled 1,019 street-involved youth in Vancouver, Canada, in a prospective cohort known as the at-risk youth study (ARYS). Participants were assessed semi-annually and a generalized estimating equation (GEE) logistic regression was used to identify factors independently associated with active crystal methamphetamine use. Among 1,019 participants recruited into ARYS between 2005 and 2012 the median follow up duration was 17 months, 320 (31.4%) participants were female and 454 (44.6%) had previously used crystal methamphetamine at baseline. In adjusted GEE analyses, active crystal methamphetamine use was independently associated with Caucasian ethnicity (adjusted odds ratio

[AOR] = 1.37; 95% confidence interval [CI]: 1.04-1.81), homelessness (AOR = 1.34; 95% CI: 1.15-1.56), injection drug use (AOR = 3.40; 95% CI: 2.76-4.19), non-fatal overdose (AOR = 1.46; 95%CI: 1.07-2.00), being a victim of violence (AOR = 1.19; 95% CI: 1.02-1.38), involvement in sex work (AOR = 1.39; 95% CI: 1.03-1.86), and drug dealing (AOR = 1.60; 95% CI: 1.35-1.90).Prevalence of crystal methamphetamine use was high in this setting and active use was independently associated with a range of serious health and social harms. Evidence-based strategies to prevent and treat crystal methamphetamine use are urgently needed.

Parental History Of Substance Use Disorders (SUD) and SUD In Offspring: A Controlled Family Study Of Bipolar Disorder Wilens TE, Yule A, Martelon MK, Zulauf C, Faraone SV. Am J Addict. 2014; 23(5): 440-446.
Adolescents with bipolar disorder (BPD) have been previously shown to be at very high risk for substance use disorders (SUD). The authors now examine the influence of a parental history of substance use disorders on SUD risk in offspring with and without BPD. They studied 190 parents ascertained through 104 adolescent BPD probands and 189 parents ascertained through 98 control probands using structured interviews. The authors compared the prevalence of SUD using logistic regression. While adjusting for BPD in our combined sample, probands with a parental history of SUD were more likely to have an alcohol use disorder compared to probands without a parental history. Probands with a parental history of SUD were not more likely to have a drug use disorder or overall SUD compared to probands without a parental history. BPD in the offspring did not pose any additional risk between parental history of SUD and offspring SUD. Alcohol use disorders were more common in the offspring of parents with a SUD history compared to parents without SUD and the risk was not influenced by offspring BPD. Clarifying the mechanisms linking parental SUD to offspring SUD, particularly in children and adolescents with BPD, would help clinicians to educate and monitor high-risk families, which would facilitate strategies to mitigate risks associated with parental substance abuse.

The Role Of Common Mental and Physical Disorders In Days Out Of Role In the Iraqi General Population: Results From the WHO World Mental Health Surveys Al-Hamzawi AO, Rosellini AJ, Lindberg M, Petukhova M, Kessler RC, Bruffaerts R. J Psychiatr Res. 2014; 53: 23-29.
In an effort to support mental health policy planning efforts in conjunction with the reconstruction of Iraq, a nationally representative face-to-face household survey was carried out that assessed the prevalence and correlates of common mental disorders in the Iraqi population. A total of 4332 adult (ages 18+) respondents were interviewed (95.2% response rate). The current report presents data on the role impairments (number of days out-of-role in the past 30 days) associated with the nine mental disorders assessed in the survey in comparison to the impairments associated with ten chronic physical disorders also assessed in the survey. These disorders were all assessed with the WHO Composite International Diagnostic Interview. Days out-of-role were assessed with the WHO Disability Assessment Schedule. Both individual-level and societal-level effects of the disorders were estimated. Strongest individual-level predictors were bipolar and drug abuse disorders (176-195 days per year), with mental disorders making up five of the seven strongest predictors. The strongest population-level predictors were headache/migraine and arthritis (22-12% population proportions). Overall population proportions were 57% of days out-of-role due to the chronic physical disorders considered here and 18% for the mental disorders. Despite commonly-occurring mental disorders accounting for more individual-level days out-of-role than the physical disorders, mental disorders are much less likely to receive treatment in Iraq (e.g., due to stigma). These results highlight the need for culturally tailored mental health prevention and treatment programs in Iraq.

CHRNA5 Variant Predicts Smoking Cessation In Patients With Acute Myocardial Infarction Chen L-S, Bach RG, Lenzini PA, Spertus JA, Bierut LJ, Cresci S. Nicotine Tob Res. 2014; 16(9): 1224-1231.
While smoking is a major modifiable risk factor for secondary prevention of myocardial infarction (MI), active smoking is common among patients hospitalized with acute MI. Recent studies suggest that nicotinic receptor variants, and specifically the high-risk CHRNA5 rs16969968 A allele, are associated with cessation failure among noncardiac patients. This study investigates the association between CHRNA5 rs16969968 and smoking cessation in patients hospitalized with acute MI. Using data from the TRIUMPH study, the authors ascertained smoking status at the time of index hospitalization for acute MI and 1 year after hospitalization. After adjusting for age and sex, the authors used logistic regression to model the association between smoking cessation and CHRNA5 rs16969968.At index admission, 752 Caucasian subjects were active smokers and 699 were former smokers. Among these ever-smokers, the A allele was associated with significantly decreased abstinence (45.0% abstinence for A allele carriers vs. 51.7% for GG homozygotes; odds ratio [OR] = 0.70, 95% confidence interval [CI] = 0.56-0.88, p = .0027). The A allele was also significantly associated with decreased abstinence at 1 year (69.1% abstinence for A allele carriers vs. 76.0% for GG homozygotes; OR = 0.70, 95% CI = 0.53-0.94, p = .0185). Among patients who have smoked and who are hospitalized with acute MI, the high-risk CHRNA5 allele was associated with lower likelihood of quitting before hospitalization and significantly less abstinence 1 year after hospitalization with MI. The CHRNA5 rs16969968 genotype may therefore identify patients who would benefit from aggressive, personalized smoking cessation intervention.

Employment Status Of People With Mental Illness: National Survey Data From 2009 and 2010 Luciano A, Meara E. Psychiatr Serv. 2014; 65(10): 1201-1209.
The aim of this study was to describe employment according to mental illness severity in the United States during 2009 and 2010.The sample included all working-age participants (ages 18-64) from the 2009 and 2010 National Survey on Drug Use and Health (N=77,326). Two well-established scales of mental health distinguished participants with none, mild, moderate, and serious mental illness. Analyses compared employment rate and income by mental illness severity. Employment status was estimated with logistic regression models that controlled for demographic characteristics and substance use disorders. In secondary analyses the relationship between mental illness and employment was assessed for variation by age and education status. Employment rates decreased with increasing mental illness severity (no mental illness, 75.9% employment; mild, 68.8%; moderate, 62.7%; and serious, 54.5%, p<.001). Over a third of people with serious mental illness, 38.5%, had incomes <$10,000 (compared with 23.1% of people with no mental illness, p<.001). The gap in adjusted employment rates comparing persons with serious versus no mental illness was 1% among people 18-25 years old versus 21% among people 50-64 (p<.001).More severe mental illness was associated with lower employment rates in 2009 and 2010. People with serious mental illness are less likely than people with no, mild, or moderate mental illness to be employed after age 49.

The Multiple Truths About Crystal Meth Among Young People Entrenched In An Urban Drug Scene: A Longitudinal Ethnographic Investigation Fast D, Kerr T, Wood E, Small W. Soc Sci Med. 2014; 110: 41-48.
Transitions into more harmful forms of illicit drug use among youth have been identified as important foci for research and intervention. In settings around the world, the transition to crystal methamphetamine (meth) use among youth is considered a particularly dangerous and growing problem. Epidemiological evidence suggests that, particularly among young, street-involved

populations, meth use is associated with numerous sex- and drug-related "risks behaviors" and negative health outcomes. Relatively few studies, however, have documented how youth themselves understand, experience and script meth use over time. From 2008 to 2012, the authors conducted over 100 in-depth interviews with 75 street-entrenched youth in Vancouver, Canada, as well as ongoing ethnographic fieldwork, in order to examine youths understandings and experiences of meth use in the context of an urban drug scene. Findings revealed positive understandings and experiences of meth in relation to other forms of drug addiction and unaddressed mental health issues. Youth were simultaneously aware of the numerous health-related harms and social costs associated with heavy meth use. Over time, positive understandings of meth may become entirely contradictory to a lived reality in which escalating meth use is a factor in further marginalizing youth, although this may not lead to cessation of use. Recognition of these multiple truths about meth, and the social structural contexts that shape the scripting of meth use among youth in particular settings, may help us to move beyond moralizing debates about how to best educate youth on the "risks" associated with meth, and towards interventions that are congruent with youths lived experiences and needs across the life course.

Moderating the Covariance Between Family Member's Substance Use Behaviors Verhulst B, Eaves LJ, Neale MC. Behav Genet. 2014; 44(4): 337-346.
Twin and family studies implicitly assume that the covariation between family members remains constant across differences in age between the members of the family. However, age-specificity in gene expression for shared environmental factors could generate higher correlations between family members who are more similar in age. Cohort effects (cohort genotype or cohort common environment) could have the same effects, and both potentially reduce effect sizes estimated in genome-wide association studies where the subjects are heterogeneous in age. In this paper the authors describe a model in which the covariance between twins and non-twin siblings is moderated as a function of age difference. They describe the details of the model and simulate data using a variety of different parameter values to demonstrate that model fitting returns unbiased parameter estimates. Power analyses are then conducted to estimate the sample sizes required to detect the effects of moderation in a design of twins and siblings. Finally, the model is applied to data on cigarette smoking. The authors find that (1) the model effectively recovers the simulated parameters; (2) the power is relatively low and therefore requires large sample sizes before small to moderate effect sizes can be found reliably, and (3) the genetic covariance between siblings for smoking behavior decays very rapidly. Result 3 implies that, e.g., genome-wide studies of smoking behavior that use individuals assessed at different ages, or belonging to different birth-year cohorts may have had substantially reduced power to detect effects of genotype on cigarette use. It also implies that significant special twin environmental effects can be explained by age-moderation in some cases. This effect likely contributes to the missing heritability paradox.

Time To First Cigarette Predicts 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) In Adolescent Regular and Intermittent Smokers, National Health and Nutrition and Examination Survey (NHANES) 2007-10 Branstetter SA, Mercincavage M, Muscat JE. Addiction. 2014; 109(6): 1005-1012.
The time to first cigarette (TTFC) of the day is an indicator of nicotine intake in adults and adolescents. However, the relation between TTFC and biological markers of nicotine addiction and health risk in youths has not been well described. The current study examined whether an earlier TTFC predicts higher levels of a tobacco-specific carcinogen, 4-(methylnitrosamino)-1-(3-pyridal)-1 (NNAL), in regular and intermittent adolescent smokers and if this relation is mediated by nicotine intake (measured by cotinine) or cigarettes per day (CPD).A cross-sectional analysis of a

nationally representative subsample of adolescents. A general community sample from the 2007-08 and 2009-10 National Health and Nutrition and Examination Survey. A total of 215 adolescents in the United States between the ages of 12 and 19 years who reported smoking at least once in the 5 days prior to data collection. The primary outcome measure was urinary levels of NNAL. In both regular and intermittent smokers, earlier TTFC was associated dose-dependently with higher levels of NNAL (P<0.03 in both cases). TTFC had an indirect effect on NNAL, mediated by nicotine intake (cotinine) in both regular [*-0.08, standard error (SE) =0.03, 95% confidence interval (CI) =-0.15, -0.03] and intermittent (*-0.02, SE=0.01, 95% CI=-0.05, -0.002) smokers. CPD was not found to be an important mediator of the relation between TTFC and NNAL. Time between waking and the first cigarette of the day is correlated in daily and non-daily adolescent smokers with overall nicotine and therefore carcinogen intake.

Trauma and Posttraumatic Stress Disorder In Japan: Results From The World Mental Health Japan Survey Kawakami N, Tsuchiya M, Umeda M, Koenen KC, Kessler RC. World Mental Health Survey Japan. J Psychiatr Res. 2014; 53: 157-165.
The purpose of the study was to report the prevalence of trauma exposure and PTSD, conditional risk of PTSD associated with each trauma exposure in the community population in Japan. An interview survey was conducted of a random sample of adult residents in 11 communities of Japan. Among 4134 respondents (response rate, 55%), data from those who completed the part 2 interview (n=1682) were analyzed with a weight for this subsample. Lifetime experiences of 27 trauma events and PTSD were assessed using the WHO-Composite International Diagnostic Interview version 3.0. Sixty percent of the part 2 sample reported exposure to at least one lifetime traumatic event. Lifetime and 12-month PTSD prevalence's were 1.3% and 0.7%, respectively. Percentage of all months lived with PTSD in the population was predominantly accounted for by physical/sexual assaults and having a child with serious illness, and unexpected death of loved one. Ten percent of respondents reported "private events", for which respondents did not have to describe the content, which accounted for 19% of months with PTSD. The lower prevalence of PTSD in Japan seems attributable to lower conditional risks of PTSD following these events, as well as different distributions of the events. The greater impact of events that occurred to loved ones rather than to oneself and "private events" on PTSD in Japan warrants further research of cross-cultural assessment of trauma exposure and cultural heterogeneity in the trauma-PTSD relationship.

Evidence For Risk Reduction Among Amphetamine-Injecting Men Who Have Sex With Men; Results From National HIV Behavioral Surveillance Surveys In The Seattle Area 2008-2012 Burt RD, Thiede H. AIDS Behav. 2014; 18(10): 1998-2008.
In the Seattle area men who have sex with men and also inject amphetamines (amphetamine-injecting MSM/IDU) are disproportionately likely to be infected with HIV. To characterize their distinctive characteristics, the authors combined data from two Seattle-area surveys of men who have sex with men (MSM) and two surveys of injection drug users (IDU). Amphetamine-injecting MSM/IDU were compared with: male IDU, MSM and other MSM/IDU. Amphetamine-injecting MSM/IDU were older than MSM but younger than IDU, more likely to be white than either group, or had an educational level higher than IDU but below MSM. They had the highest HIV prevalence (56 vs. 4-19%). However, reported HIV cases among them fell from 92 in 1990 to 25 in 2012. They were most likely to report ten or more sex partners (49 vs. 4-26%), an STD diagnosis (22 vs. 1-7%) and be tested for HIV (odds ratio 1.00 vs. 0.34-0.52), and least likely to share needles (odds ratio 1.00 vs. 6.80-10.50). While sexual risk remains high, these data suggest measurable and effective risk reduction with respect to sharing injection equipment and HIV testing among Seattle-area amphetamine-injecting MSM/IDU.

Dopamine Receptor Gene D4 Polymorphisms and Early Sexual Onset: Gender and Environmental Moderation In A Sample Of African-American Youth Kogan SM, Lei M-K, Beach SRH, Brody GH, Windle M, Lee S, MacKillop J, Chen Y-F. J Adolesc Health. 2014; 55(2): 235-240.
Early sexual onset and its consequences disproportionately affect African-American youth, particularly male youth. The dopamine receptor D4 gene (DRD4) has been linked to sexual activity and other forms of appetitive behavior, particularly for male youth and in combination with environmental factors (gene environment [GE] effects). The differential susceptibility perspective suggests that DRD4 may exert this effect by amplifying the effects of both positive and negative environments. The authors hypothesized that DRD4 status would amplify the influence of both positive and negative neighborhood environments on early sexual onset among male, but not female, African-Americans. Hypotheses were tested with self-report, bio specimen, and census data from five prospective studies of male and female African-American youth in rural Georgia communities, N=1,677. Early sexual onset was defined as intercourse before age 14.No significant GE findings emerged for female youth. Male youth with a DRD4 long allele were more likely than those with two DRD4 short alleles to report early sexual onset in negative community environments and not to report early onset in positive community environments. Dopaminergic regulation of adolescent sexual behaviors may operate differently by gender. DRD4 operated as an environmental amplification rather than a vulnerability factor.

The Mediating Role Of Depression In the Relationship Between Anxiety Sensitivity and Alcohol Dependence Lechner WV, Shadur JM, Banducci AN, Grant, DM, Morse M, Lejuez CW. Addict Behav. 2014; 39(8): 1243-1248.
Many studies have reported that Anxiety Sensitivity (AS) is positively associated with alcohol use or other alcohol-related variables. More recent mediator and moderator models have shown promise in elucidating mechanisms within this relationship; the literature to date suggests that the relationship between AS and alcohol is likely mediated by problematic coping motives. However, few studies have considered the effects of depression within the AS-alcohol use relationship, despite a strong body of evidence linking AS to subsequent depression and depression to subsequent alcohol use problems, independently. Therefore, the current study assessed depression as a potential mediator of this relationship. Participants were 418 sequential admissions to a substance abuse treatment facility. A mediation analysis using bootstrapping was utilized in order to estimate indirect effects of AS on alcohol dependence through depression. Results reveal an indirect effect suggesting that the effects of anxiety sensitivity on alcohol dependence are mediated by symptoms of depression. More specifically, the effects of AS total score and AS somatic sensations on alcohol dependence were mediated by symptoms of depression. Lastly, a dual mediator model demonstrated that both depression and problematic coping uniquely mediate the relationship between AS and alcohol dependence. While preliminary in nature, the current study provides evidence supporting the hypothesis that depression is an important factor to consider when examining the relationship between AS and alcohol dependence.

Growth Trajectories Of Alcohol Information Processing and Associations With Escalation Of Drinking In Early Adolescence Colder CR, O'Connor RM, Read JP, Eiden RD, Lengua LJ, Hawk LW, Wieczorek WF. Psychol Addict Behav. 2014; 28(3): 659-670.
This longitudinal study provided a comprehensive examination of age-related changes in alcohol outcome expectancies, subjective evaluation of alcohol outcomes, and automatic alcohol associations in early adolescence. A community sample (52% female, 75% White/non-Hispanic) was assessed annually for 3 years (mean age at the first assessment = 11.6 years). Results from

growth modeling suggested that perceived likelihood of positive outcomes increased and that subjective evaluations of these outcomes were more positive with age. Perceived likelihood of negative outcomes declined with age. Automatic alcohol associations were assessed with an Implicit Association Task (IAT), and were predominantly negative, but these negative associations weakened with age. High initial levels of perceived likelihood of positive outcomes at age 11 were associated with escalation of drinking. Perceived likelihood of negative outcomes was associated with low risk for drinking at age 11, but not with changes in drinking. Increases in positive evaluations of positive outcomes were associated with increases in alcohol use. Overall, findings suggest that at age 11, youth maintain largely negative attitudes and perceptions about alcohol, but with the transition into adolescence, there is a shift toward a more neutral or ambivalent view of alcohol. Some features of this shift are associated with escalation of drinking. Our findings point to the importance of delineating multiple aspects of alcohol information processing for extending cognitive models of alcohol use to the early stages of drinking.

Response Inhibition Moderates The Association Between Drug Use And Risky Sexual Behavior Nydegger LA, Ames SL, Stacy AW, Grenard JL. Subst Use Misuse. 2014; 49(11): 1457-1464.
HIV infection is problematic among all drug users, not only injection drug users. Drug users are at risk for contracting HIV by engaging in risky sexual behaviors. The present study sought to determine whether inhibitory processes moderate the relationship between problematic drug use and HIV-risk behaviors (unprotected sex and multiple sex partners). One hundred ninety-six drug offenders enrolled in drug education programs were administered a battery of computer-based assessments. Measures included a cued go/no-go assessment of inhibitory processes, the Drug Abuse Screening Test (DAST) assessment of problematic drug use, and self-report assessment of condom use and multiple sex partners. Findings revealed that response inhibition assessed by the proportion of false alarms on the cued go/no-go moderated the relationship between problematic drug use and an important measure of HIV risk (condom nonuse) among drug offenders. However, response inhibition did not moderate the relationship between problematic drug use and another measure of HIV risk: multiple sex partners. Among this sample of drug offenders, the authors have found a relationship between problematic drug use and condom nonuse, which is exacerbated by poor control of inhibition. These findings have implications for the development of HIV intervention components among high-risk populations.

HIV-associated Obstructive Lung Diseases: Insights and Implications For the Clinician
Drummond MB, Kirk GD. Lancet Respir Med. 2014; 2(7): 583-592.
The effectiveness of antiretroviral therapy to control HIV infection has led to the emergence of an older HIV population who are at risk of chronic diseases. Through a comprehensive search of major databases, this Review summarizes information about the associations between chronic obstructive pulmonary disease (COPD), asthma, and HIV infection. Asthma and COPD are more prevalent in HIV-infected populations; 16-20% of individuals with HIV infection have asthma or COPD, and poorly controlled HIV infection worsens spirometric and diffusing capacity measurements, and accelerates lung function decline by about 55-75 mL/year. Up to 21% of HIV-infected individuals have obstructive ventilatory defects and reduced diffusing capacity is seen in more than 50% of HIV-infected populations. Specific pharmacotherapy considerations are needed to care for HIV-infected populations with asthma or COPD-protease inhibitor regimens to treat HIV (such as ritonavir) can result in systemic accumulation of inhaled corticosteroids and might increase pneumonia risk, exacerbating the toxicity of this therapy. Therefore, it is essential for clinicians to have a heightened awareness of the increased risk and manifestations of obstructive lung diseases in

HIV-infected patients and specific therapeutic considerations to care for this population. Screening spirometry and tests of diffusing capacity might be beneficial in HIV-infected people with a history of smoking or respiratory symptoms.

Five-factor Model Personality Traits As Predictors Of Incident Coronary Heart Disease In The Community: A 10.5-year Cohort Study Based On The Baltimore Epidemiologic Catchment Area Follow-up Study Lee HB, Offidani E, Ziegelstein RC, Bienvenu O , Samuels J, Eaton WW, Nestadt G. Psychosomatics. 2014; 55(4): 352-361.
Certain personality and behavioral traits (e.g., type A and type D) have been reported to be associated with development and progression of coronary heart disease (CHD), but few have examined the relationship using a comprehensive assessment of personality along with a structured assessment of psychiatric disorders. Based on participants (age: 47.3 12.8; female: 62.6%) of the Baltimore Epidemiologic Catchment Area follow-up study, the authors examined the relationship between the 5 major domains of personality traits (neuroticism, extraversion, openness, agreeableness, and conscientiousness) and incident CHD between Wave III (1993-1996) and Wave IV (2004-2005).Incident CHD developed in 65 participants during the follow-up. Those with incident CHD had lower on openness (44.06 9.29 vs. 47.18 8.80; p = 0.007) and extraversion (45.98 9.25 vs. 49.12 8.92; p = 0.007) scores than those without. Logistic regression models revealed an inverse association (OR = 0.73; 95% CI = 0.54-0.98) between openness factor z-scores and incident CHD after adjusting for putative confounding factors, including DSM III-R Major Depressive Disorder. High openness appears to be an independent protective factor for incident CHD in the community. Future studies should examine behavioral and pathophysiologic mechanisms underlying this association.

The Social Contexts Of Drug Offers and Their Relationship To Drug Use Of Rural Hawaiian Youth Okamoto SK, Kulis S, Helm S, Edwards C, Giroux D. J Child Adolesc Subst Abuse. 2014; 23(4): 242-252.
This paper examines the differences in drug offers and recent drug use between Hawaiian and non-Hawaiian youth residing in rural communities, and the relationship between drug offers and drug use of Hawaiian youth in these communities. Two hundred forty nine youth (194 Hawaiian youth) from 7 different middle or intermediate schools completed a survey focused on the social context of drug offers. Hawaiian youth in the study received significantly more offers from peers and family, and had significantly higher rates of recent alcohol and marijuana use, compared with non-Hawaiian youth. Logistic regression analysis indicated that the social context differentially influenced drug use of Hawaiian youth, with family drug offers and context influencing overall drug use and the use of the widest variety of substances. Implications for prevention practices are discussed.

Anxiety Disorders And Risk For Alcohol Use Disorders: The Moderating Effect Of Parental Support Gorka SM, Shankman SA, Olino TM, Seeley JR, Kosty DB, Lewinsohn PM. Drug Alcohol Depend. 2014; 140: 191-197.
There have been mixed findings on the temporal relation between anxiety disorders and alcohol use disorders (AUDs), suggesting that the pathway to AUDs may differ among individuals. The aim of the current study was to test whether parental support moderated the association between anxiety disorders and the development of AUDs. The authors also tested whether their effects differed as a function of age of AUD onset.817 individuals were assessed for lifetime diagnoses of psychopathology during 4-waves between adolescence (mean age=16) and adulthood (mean age=30). Proportional hazards model analyses indicated that baseline anxiety disorders interacted

with baseline perceived maternal support to prospectively predict onset of AUDs. At high levels of maternal support, anxiety disorders were associated with a reduced risk for AUD onset (HR=0.74, 95% CI=0.55-1.00). However, this effect was more robust for AUDs that developed prior to age 20. At low levels of maternal support, anxiety disorders were associated with an increased risk for AUD onset (HR=1.65, 95% CI=1.21-2.26). This effect was present for AUDs that developed across adolescence and adulthood. Paternal support was not associated with AUDs and did not interact with anxiety disorders. Prevention and intervention efforts targeted at maternal support in adolescents with anxiety disorders may be valuable, as this may represent a factor that has a significant impact on the developmental course of AUDs.

"A Cool Little Buzz": Alcohol Intoxication In The Dance Club Scene Hunt G, Moloney M, Fazio A. Subst Use Misuse. 2014; 49(8): 968-981.
In recent years, there has been increasing concern about youthful "binge" drinking and intoxication. Yet the meaning of intoxication remains under-theorized. This paper examines intoxication in a young adult nightlife scene, using data from a 2005-2008 National Institute on Drug Abuse-funded project on Asian American youth and nightlife. Analyzing in-depth qualitative interview data with 250 Asian American young adults in the San Francisco area, the authors examine their narratives about alcohol intoxication with respect to sociability, stress, and fun, and their navigation of the fine line between being "buzzed" and being "wasted." Finally, limitations of the study and directions for future research are noted.

Trends In Medical Use, Diversion, and Nonmedical Use Of Prescription Medications Among College Students From 2003 To 2013: Connecting the Dots McCabe SE, West BT,; Teter CJ, Boyd C. J. Addict Behav. 2014; 39(7): 1176-1182.
The objectives of this study were to examine trends in the lifetime and past-year prevalence of medical use, diversion, and nonmedical use of four prescription medication classes (i.e., sedative/anxiety, opioid, sleeping, and stimulant) among college students between 2003 and 2013; and to identify demographic and background characteristics associated with trends in past-year nonmedical use of prescription medications. A self-administered, cross-sectional Web survey was conducted in 2003, 2005, 2007, 2009, 2011, and 2013 at a large public four-year university in the Midwest United States. Approximately one in every five individuals reported nonmedical use of at least one prescription medication class in their lifetime. The past-year prevalence of medical use, diversion and nonmedical use of prescription stimulants increased significantly between 2003 and 2013 while the past-year prevalence of medical use, diversion and nonmedical use of prescription opioids decreased significantly over this same time period. The odds of past-year nonmedical use of each prescription medication class were generally greater among males, Whites, members of social fraternities and sororities, and those with a lifetime history of medical use of prescription medications or a past-year history of being approached to divert their prescription medications. The present study represents the first investigation to demonstrate that trends in medical use of controlled medications parallel changes in diversion and nonmedical use of the same medication class among college students. The findings reinforce the importance of continued monitoring of prescription medication use at colleges to help guide prevention and intervention efforts.

Alcohol and Marijuana Use In Early Adulthood For At-risk Men: Time-varying Associations With Peer And Partner Substance Use Washburn IJ, Capaldi DM, Kim HK, Feingold A. Drug Alcohol Depend. 2014; 140: 112-117.
Time-varying associations of 185 at-risk men's (from the Oregon Youth Study) substance use with that of their peers and partner over a 10-year period (ages 23 to 32 years) were examined.

Moderation of effects by time with peers and partner and their age were tested. Growth models were used to predict changes in heavy episodic drinking (HED) alcohol use and marijuana use as a function of substance use by their female partners and male peers. Time with peers and peer substance use significantly predicted HED (ORs=1.6, 2.3), alcohol use (ORs=1.6, 2.1), volume of alcohol use (IRRs=1.5, 1.3), and marijuana use (ORs=12.8, 1.7); peer marijuana use predicted volume of marijuana use (B=2.5). Partner substance use significantly predicated marijuana volume (B=2.7). Partner alcohol use predicted alcohol volume (IRR=1.1), but was moderated by time with partner and age (IRR=1.0). Time with partner and partner marijuana use predicted marijuana use (OR=0.5, 2.7), as did the interaction of the two (OR=3.8). Outcome-specific substance use of peers and partners was significantly associated with indicators of alcohol and marijuana use in men's early adulthood, with robust effects of peer substance use through age 30 years and with time spent with peers influencing alcohol use. Time with partner was protective against marijuana use unless the partner used marijuana. Peers and partners should be considered in intervention efforts to effectively reduce mens substance use in early adulthood.

The Developmental Dynamics Of Joining A Gang In Adolescence: Patterns and Predictors Of Gang Membership Gilman AB, Hill KG, Hawkins JD, Howell JC, Kosterman R. J Res Adolesc. 2014; 24(2): 204-219.
Researchers have examined the predictors of adolescent gang membership, finding significant factors in the neighborhood, family, school, peers, and individual domains. However, little is known about whether risk and protective factors differ in predictive salience at different developmental periods. The present study examines predictors of joining a gang, tests whether these factors have different effects at different ages, and whether they differ by gender using the Seattle Social Development Project (SSDP) sample (n=808). By age 19, 173 participants had joined a gang. Using survival analysis, results showed that unique predictors of gang membership onset included living with a gang member, antisocial neighborhood, and antisocial peer influences in the previous year. No time or gender interactions with predictors were statistically significant.

The Problematic and Risky Internet Use Screening Scale (PRIUSS) For Adolescents and Young Adults: Scale Development and Refinement Jelenchick LA, Eickhoff J, Christakis DA, Brown RL, Zhang C, Benson M, Moreno MA. Comput Human Behav. 2014; 35.
Problematic Internet use (PIU) is a growing health concern among adolescents and young adults. The purpose of this mixed-methods study was to develop and refine a theoretically-grounded and psychometrically-validated assessment instrument for PIU specifically tailored to adolescents and young adults. An item pool was developed using concept mapping and a review of the literature, and administered to 714 students from two universities between 18 and 25 years of age. Exploratory and confirmatory factor analyses were used in a development subsample (n=500) to construct the scale. A cross-validation sample (n=214) was used to confirm the scales reliability. The Problematic and Risky Internet Use Screening Scale (PRIUSS) is an 18-item scale with three subscales: Social Impairment, Emotional Impairment, and Risky/Impulsive Internet Use. Based on its strong theoretical foundation and promising psychometric performance, the PRIUSS may be a valuable tool for screening and prevention efforts in this population.

Associations Between Ethnic Labels and Substance Use Among Hispanic/Latino Adolescents In Los Angeles Unger JB, Thing J, Soto DW Baezconde-Garbanati L. Subst Use Misuse. 2014; 49(8): 1007-1016.
Self-identification with ethnic-specific labels may indicate successful ethnic identity formation, which could protect against substance use. Alternatively, it might indicate affiliation with

oppositional subcultures, a potential risk factor. This study examined longitudinal associations between ethnic labels and substance use among 1,575 Hispanic adolescents in Los Angeles. Adolescents who identified as Cholo or La Raza in 9th grade were at increased risk of past-month substance use in 11th grade. Associations were similar across gender and were not confounded by socioeconomic status, ethnic identity development, acculturation, or language use. Targeted prevention interventions for adolescents who identify with these subcultures may be warranted.

Recent Medical Service Utilization and Health Conditions Associated With A History Of Suicide Attempts Ballard ED, Cwik M, Storr CL, Goldstein M, Eaton WW, Wilcox HC. Gen Hosp Psychiatry. 2014; 36(4): 437-441.
Suicide is a leading cause of death; unfortunately most individuals at risk for suicide are not identified, assessed or treated by the mental health system. Investigating medical healthcare utilization among individuals with a history of suicide attempt may identify alternative settings for case finding and brief intervention. The study sample (n=1422, 58% female, 72% African-American) is from a prospective cohort of adults (27-31 years) who participated in a randomized trial of school-based interventions. Logistic regression evaluated the relationship between lifetime history of suicide attempt with past year medical service utilization and selected self- reported health conditions, controlling for lifetime Major Depressive Disorder (MDD), demographic factors, health insurance status and employment. A suicide attempt history was associated with past year emergency department medical visits [aOR 1.51, 95% CI 1.04-2.18, P=.03], but not primary care visits or inpatient hospitalization, when controlling for MDD and other covariates. Severe headaches and chronic gastrointestinal conditions were also associated with lifetime suicide attempt [aOR 1.50, 95% CI 1.03-2.17 and aOR 1.67, 95% CI 1.06-2.63, respectively]. Suicide prevention, including universal screening and brief intervention, is indicated in emergency department settings. Restricting screening to subgroups, such as those individuals presenting with depression, may miss at-risk individuals with somatic concerns.

Social Network Drinking and Family History Contribute Equally To First-onset Alcohol Dependence In High Risk Adults McCutcheon VV, Lessov-Schlaggar CN, Steinley D, Bucholz KK. Drug Alcohol Depend. 2014; 141: 145-148.
Adult alcohol consumption is influenced by peer consumption, but whether peer drinking is associated with first-onset alcohol dependence (AD) in adults after age 30 is unknown.703 adult participants in the St. Louis Epidemiologic Catchment Area Survey (ECA) with no prior history of AD, but with high risk based on previously reported drinking or family history, were re-interviewed 11 years after the last ECA assessment to detect new cases of AD (age at follow-up: M(S.D.)=42.9 (8.2)). Incident AD during the assessment interval was examined in relation to drinking patterns in the social network and history of alcohol problems in parents. Fifteen percent of the sample had a first-onset of AD; another 19.5% never developed AD but were high-risk drinkers at follow-up. Of those who developed AD, 32.1% were remitted and 67.9% were unremitted (current AD) or unstably remitted (asymptomatic high-risk drinkers). Compared to abstinent or low-risk drinkers who did not develop AD, high-risk drinkers with no AD and unremitted/unstably remitted individuals were 4 times as likely to report moderate drinkers in their networks and remitted individuals were nearly 3 times as likely to report network members in recovery from alcohol problems. Associations of social network drinking with remitted and current AD were similar in strength to those of parental alcohol problems. Social network drinking patterns are associated with high-risk drinking and with the development of incident AD in adults, with effects equal to that of alcohol problems in both parents.

Childhood Maltreatment and the Course Of Bipolar Disorders Among Adults: Epidemiologic Evidence Of Dose-response Effects Sala R, Goldstein BI, Wang S, Blanco C.. J Affect Disord. 2014; 165: 74-80.
Childhood maltreatment (CM) is highly prevalent among individuals with bipolar disorders (BP); however few studies have examined its potential role in the course and outcome of individuals with BP. The authors aim to examine the dose response relationship between the number of types of CM and the course of individuals with BP.As part of the National Epidemiologic Survey on Alcohol and Related Conditions, 1600 adults who met lifetime DSM-IV criteria for BP-I (n=1172) and BP-II (n=428) were included. Individuals were evaluated using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DMS-IV Version and data was analyzed lifetime and from Waves 1 and 2, approximately 3 years apart. Around half of individuals with BP had a history of at least one type of CM. Overall, there was a clear dose-response relationship between number of CM and severity of BP across several domains, including clinical characteristics, probability of treatment, lifetime prevalence of psychiatric comorbidity, incidence of anxiety disorders, substance use disorder, and nicotine dependence, and level of psychosocial functioning. The interviews were conducted by lay professional interviewers rather than clinicians, use of retrospective report to determine CM in individuals with BP, and not all respondents from Wave 1 were able to be interviewed in Wave 2.The number of types of CM confers developmental differences in the course of BP with a worse course and outcome of BP. Early identification and treatment of CM are warranted to improve the course and outcome of individuals with BP.

Psychiatric Comorbidity and Perceived Alcohol Stigma In A Nationally Representative Sample Of Individuals With DSM-5 Alcohol Use Disorder Glass JE, Williams EC, Bucholz KK. Alcohol Clin Exp Res. 2014; 38(6): 1697-1705.
Alcohol use disorder (AUD) is among the most stigmatized health conditions and is frequently comorbid with mood, anxiety, and drug use disorders. Theoretical frameworks have conceptualized stigma-related stress as a predictor of psychiatric disorders. The authors described profiles of psychiatric comorbidity among people with AUD and compared levels of perceived alcohol stigma across profiles. Cross-sectional data were analyzed from a general population sample of U.S. adults with past-year DSM-5 AUD (n=3,368) from the National Epidemiologic Survey on Alcohol and Related Conditions, which was collected from 2001 to 2005. Empirically derived psychiatric comorbidity profiles were established with latent class analysis, and mean levels of perceived alcohol stigma were compared across the latent classes while adjusting for sociodemographic characteristics and AUD severity. Four classes of psychiatric comorbidity emerged within this AUD sample, including those with: (i) high comorbidity, reflecting internalizing (i.e., mood and anxiety disorders) and externalizing (i.e., antisocial personality and drug use disorders) disorders; (ii) externalizing comorbidity; (iii) internalizing comorbidity; and (iv) no comorbidity. Perceived alcohol stigma was significantly higher in those with internalizing comorbidity (but not those with high comorbidity) as compared to those with no comorbidity or externalizing comorbidity. Perceived stigma, as manifested by anticipations of social rejection and discrimination, may increase risk of internalizing psychiatric comorbidity. Alternatively, internalizing psychiatric comorbidity could sensitize affected individuals to perceive more negative attitudes toward them. Future research is needed to understand causal and bidirectional associations between alcohol stigma and psychiatric comorbidity.

Host Society Acculturation And Health Practices and Outcomes In the United States: Public Health Policy and Research Implications Worldwide Andreeva VA, Unger JB. J Public Health Policy. 2014; 35(3): 278-291.
The unprecedented ethno cultural diversity in the United States and other Western countries likely changes the social norms for various health practices in the host populations, thus impacting prevalence of such practices and leading to the need for modification of public health policies. However, application of host acculturation (HA) principles in the public health domain remains underdeveloped. The authors conducted a narrative review of theoretical and empirical information about the association between HA and health practices or outcomes, drawing on evidence from health-care services, complementary and alternative medicine, diet, smoking, alcohol use, and psychological well-being. Given the experience of different countries with large immigrant populations, future multidisciplinary studies are needed both to supply additional empirical evidence and to identify ubiquitous HA processes, and thus inform public health promotion initiatives in the United States and worldwide.

Providing Alcohol To Underage Youth: the View From Young Adulthood Arria AM, Caldeira KM, Moshkovich O, Bugbee BA, Vincent KB, O'Grady KE. Alcohol Clin Exp Res. 2014; 38(6): 1790-1798.
Many underage drinkers obtain alcohol from legal-age family, friends, and acquaintances. This study aimed to understand the attitudes and behaviors of young adults related to providing alcohol to underage drinkers. Participants were 755 current or recent college students of legal drinking age (ages 22 to 26) who were approached by a minor to provide alcohol at least once since turning 21. Interviewers assessed frequency of providing alcohol, relationship to the recipients, and general attitudes about providing alcohol to minors. Separate questions asked about younger (under 18) and older (18 to 20) minors. Correlates and predictors of provision and frequency of provision were examined via logistic regression and Poisson regression, focusing on demographics, sensation-seeking, behavioral dysregulation, age at first drink, parental history of alcohol problems, fraternity/sorority involvement, attitudes about provision, violations, peer drinking norms, and alcohol use disorder (AUD) risk during and post-college. Most participants (84.6%) provided alcohol to minors at least once. Provision to older minors was more prevalent (82.8%) than to younger minors (20.7%); it was also more frequent. Few (2.4%) were ever caught providing alcohol. Recipients were more commonly friends or family members rather than acquaintances or strangers. Legal concerns about providing alcohol (82.5 and 53.7% for younger and older minors, respectively) were more prevalent than health concerns (55.7 and 9.5%). Legal concerns consistently predicted lower likelihood of provision, independent of demographics. Health concerns and lower post-college AUD risk scores also independently predicted lower likelihood of provision, but only to older minors. Fraternity/sorority involvement and higher peer drinking norms were associated with higher provision frequency, whereas legal concerns and college violations were associated with lower provision frequency. Young adults who have recently turned 21 could represent an important target for prevention strategies to reduce underage drinking on college campuses. More research is needed to understand the motivations of young adults who provide alcohol to underage drinkers.

Acculturation and Perceived Discrimination: Predictors Of Substance Use Trajectories From Adolescence To Emerging Adulthood Among Hispanics Unger JB, Schwartz SJ, Huh J, Soto DW; Baezconde-Garbanati L. Addict Behav. 2014; 39(9): 1293-1296.
Previous studies have documented associations between cultural factors and substance use among Hispanic adolescents. Negative cultural experiences such as discrimination have been associated

with an increased risk of substance use among Hispanic adolescents, whereas positive cultural resources, such as maintenance of Hispanic cultural orientations, have shown protective effects. However, few studies have examined the continuing influence of cultural factors on substance use from adolescence to emerging adulthood. The authors surveyed a cohort of Hispanic adolescents in Southern California in 9th, 10th, and 11th grades, and 3-4 years after high school. Growth curve analyses were conducted to examine the effects of U.S. acculturation, Hispanic acculturation, ethnic identity, and perceived discrimination on change in tobacco, alcohol, and marijuana use over time. Higher perceived discrimination at baseline was significantly associated with a higher intercept (initial level) of tobacco, alcohol, and marijuana use. Higher initial level of Hispanic acculturation was significantly associated with a lower slope of tobacco, alcohol, and marijuana use. Cultural phenomena such as acculturation and perceived discrimination can continue to affect substance use through the transition to emerging adulthood. Health education interventions are needed to help Hispanics navigate this developmental transition without engaging in substance use.

Problematic Substance Use Among Hispanic Adolescents and Young Adults: Implications For Prevention Efforts Halley Grigsby TJ, Forster M, Soto DW, Baezconde-Garbanati L, Unger JB. Subst Use Misuse. 2014; 49(8): 1025-1038.
Using data collected between 2005 and 2012 from a longitudinal study of acculturation patterns and substance use among Hispanic youth in Southern California (N = 2722), the authors fit multivariate logistic regression models to estimate the association of type and frequency of drug use, friend and parent drug use, cultural orientation (measured by the ARSMA-II), and psychological distress (CES-D score) in 10th grade with problematic substance use (measured with the RAPI) in (i) 11th grade and (ii) young adulthood. The authors conclude that future intervention efforts with Hispanic adolescents and young adults should target polysubstance and problem users and emphasize inter-individual, structural, and cultural processes as they relate to problematic substance use.

Stability Of Smoking Status In The US Population: A Longitudinal Investigation Weinberger AH, Pilver CE, Mazure CM, McKee SA. Addiction. 2014; 109(9): 1541-1553.
The objective of this study was to determine smoking transitions in a representative sample of US adults. This was a longitudinal study using data from the National Epidemiologic Survey on Alcohol and Related Conditions (wave 1, 2001-02; wave 2, 2004-05).The general US adult population. A total of 33ýýý309 adults (53.6% female) classified as wave 1 current daily, current non-daily, former daily, former non-daily or never smokers. Smoking transitions were determined from waves 1 and 2 data. Smoking status remained stable for the majority of current daily (79.8%), former daily (95.8%), and former non-daily (96.3%) and never (97.1%) smokers. Among current non-daily smokers, 54.5% quit smoking while 22.5% increased to daily smoking. Current daily smokers who were older [30-44, odds ratio (OR)=0.62; 95% confidence interval (CI)=0.49-0.78; 45+, OR=0.75; 95% CI=0.61-0.93] and unmarried (OR=0.80, 95% CI=0.66-0.96) were less likely to report smoking cessation. Current daily smokers who were Hispanic (OR=2.15, 95% CI=1.65-2.81) and college educated (OR=1.27, 95% CI=1.05-1.53) were more likely to report smoking cessation. Relapse in former daily smokers was greater in women (OR=1.44, 95% CI=1.01-2.06) and lower in older adults (OR=0.44; 95% CI=0.27-0.74). Smoking initiation occurred less in women (OR=0.65; 95% CI=0.49-0.87) and Hispanic adults (OR=0.57; 95% CI=0.36-0.91) and more in unmarried adults (OR=1.84; 95% CI=1.37-2.47) and adults with less education (OR=1.63; 95% CI=1.09-2.44).From 2001 to 2005, smoking status was extremely stable in the US population. Specific gender, race and educational groups need increased prevention and intervention efforts.

Triple Comorbid Trajectories Of Tobacco, Alcohol, and Marijuana Use As Predictors Of Antisocial Personality Disorder and Generalized Anxiety Disorder Among Urban Adults
Brook JS, Lee JY, Rubenstone E, Brook DW, Finch S. J. Am J Public Health. 2014; 104(8): 1413-1420.
The authors modeled triple trajectories of tobacco, alcohol, and marijuana use from adolescence to adulthood as predictors of antisocial personality disorder (ASPD) and generalized anxiety disorder (GAD). They assessed urban African American and Puerto Rican participants (n=816) in the Harlem Longitudinal Development Study, a psychosocial investigation, at 4 time waves (mean ages=19, 24, 29, and 32 years). They used Mplus to obtain the 3 variable trajectories of tobacco, alcohol, and marijuana use from time 2 to time 5 and then conducted logistic regression analyses. A 5-trajectory group model, ranging from the use of all 3 substances (23%) to a nonuse group (9%), best fit the data. Membership in the trajectory group that used all 3 substances was associated with an increased likelihood of both ASPD (adjusted odds ratio [AOR]=6.83; 95% CI=1.14, 40.74; P<.05) and GAD (AOR=4.35; 95% CI=1.63, 11.63; P<.001) in adulthood, as compared with the nonuse group, with control for earlier proxies of these conditions. Adults with comorbid tobacco, alcohol, and marijuana use should be evaluated for use of other substances and for ASPD, GAD, and other psychiatric disorders. Treatment programs should address the use of all 3 substances to decrease the likelihood of comorbid psychopathology.

Latinos' Access To Online and Formal Mental Health Support Parra-Cardona JR, DeAndrea DC. J Behav Health Serv Res. 2014.
Research on mental health services disparities affecting minority populations of the USA tends to neglect online mental health support (OMHS). The main objective of this study was to investigate online mental health support and help-seeking of Latino citizens living in US communities by estimating associations linking OMHS with a selection of individual and community variables. In addition, the extent to which unmet mental health treatment needs among adults are associated with key variables was examined. Variables of interest included economic resources, health insurance and coverage, confidentiality, perceived stigma, and accessibility. Data are from 39,630 Latino adult participants in the National Surveys on Drug Use and Health (NSDUH), 2004-2010. Results indicate that for every 10,000 US Latino adults, fewer than 25 individuals received recent OMHS, as compared to a recently published estimate of 270-330 per 10,000 for the US population generally. Among Latinos with self-described unmet mental health needs, an estimated 40% identified cost of treatment as a prominent barrier that explained why they had not received formal mental health treatment services. Research and policy health disparities implications are discussed.

Serious Delinquency and Gang Participation: Combining and Specializing In Drug Selling, Theft and Violence Gordon RA, Rowe HL, Pardini D, Loeber R, White HR, Farrington DP. J Res Adolesc. 2014; 24(2): 235-251.
Using Pittsburgh Youth Study data, the authors examined the extent to which over 600 gang members and non-gang involved young men specialized in drug selling, serious theft, or serious violence or engaged simultaneously in these serious delinquent behaviors, throughout the 1990s. The authors found that the increase in delinquency associated with gang membership was concentrated in two combinations: serious violence and drug selling; serious violence, drug selling, and serious theft. Several covariates were similarly associated with multi-type serious delinquency and gang membership (age, historical time, Black race, and residential mobility), suggesting that these behaviors may share common developmental, familial, and contextual risks. The authors encourage future research to further examine the association of gang membership with engagement in particular configurations of serious delinquency.

Factors Associated With Suicidal Ideation and Attempts In Spain For Different Age Groups. Prevalence Before and After the Onset Of the Economic Crisis Miret M, Caballero FF, Huerta-Ramirez R, Moneta MV, Olaya B, Chatterji S, Haro JM, Ayuso-Mateos JL. J Affect Disord. 2014; 163: 1-9.
Little is known about whether the prevalence of suicidal ideation and attempts has changed in the wake of the economic crisis. The aim of this study was to estimate current prevalence of suicidal ideation and attempts in the general population in Spain, to compare it with the prevalence found before the economic crisis, and to analyze the factors associated with suicidality in different age groups. A total of 4583 non-institutionalized adults were interviewed in a cross-sectional household survey of a nationally representative sample in Spain. Several modules of an adapted version of the Composite International Diagnostic Interview were administered to the participants, and logistic regression models were employed in each age group. Lifetime prevalence of suicidal ideation and attempts in Spain were respectively, 3.67% and 1.46%. Mental disorders presented the highest significant effects on lifetime suicidal ideation. Marital status, heavy alcohol consumption, and occupational status were associated with lifetime suicidal ideation in people aged 18-49, whereas loneliness was associated with the 50-64 group, and financial problems with the 65+ group. A younger age, poor health status and the presence of depression were all associated with lifetime suicide attempts. The cross-sectional design of the study represents a methodological limitation. The current prevalence of suicidal ideation and attempts in Spain is similar to the one found ten years ago, before the recent economic crisis. The factors associated with suicidality vary among age groups. Suicide prevention programmers should focus on early detection and prevention for depression and anxiety disorders.

Alcohol Use Disorder In Women: Risks and Consequences Of An Adolescent Onset and Persistent Course Foster KT, Hicks BM, Iacono WG, McGue M. Psychol Addict Behav. 2014; 28(2): 322-335.
Women are more vulnerable to the deleterious effects of both acute and protracted alcohol use than men, but women's lower levels of alcohol consumption and alcohol use disorder (AUD) have resulted in a paucity of investigations on the development of alcohol problems in women. In particular, it is not clear to what extent the cascading effects of key etiological factors that contribute to an especially severe course of AUD in men also underlie the development of AUD in women. To fill this gap, the authors examined the adolescent risk factors and adult consequences associated with an adolescent onset and persistent course of AUD in a community sample of women (n = 636) from ages 17 to 29. Women with AUD exhibited greater psychopathology and psychosocial impairment than those without, with an adolescent onset and persistent course indicative of the greatest severity. Notably, high levels of impairment across all women with AUD reduced the utility of onset and course to differentiate profiles of risk and impairment. In contrast to previous work in men, even women whose AUD symptoms desisted continued to exhibit impairment, suggesting that an adolescent onset of AUD is associated with enduring consequences for women's health and functioning, even after ostensible "recovery."

Genetic and Environmental Risk For Major Depression In African-American And European-American Women Duncan AE, Munn-Chernoff MA, Hudson DL, Eschenbacher MA, Agrawal A, Grant JD, Nelson EC, Waldron M, Glowinski AL, Sartor CE, Bucholz KK, Madden PAF, Heath AC. Twin Res Hum Genet. 2014; 17(4): 244-253.
It is unknown whether there are racial differences in the heritability of major depressive disorder (MDD) because most psychiatric genetic studies have been conducted in samples comprised largely of white non-Hispanics. To examine potential differences between African-American (AA) and

European-American (EA) young adult women in (1) Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) MDD prevalence, symptomatology, and risk factors, and (2) genetic and/or environmental liability to MDD, we analyzed data from a large population-representative sample of twins ascertained from birth records (n = 550 AA and n = 3226 EA female twins) aged 18-28 years at the time of MDD assessment by semi-structured psychiatric interview. AA women were more likely to have MDD risk factors; however, there were no significant differences in lifetime MDD prevalence between AA and EA women after adjusting for covariates (odds ratio = 0.88, 95% confidence interval [CI]: 0.67-1.15). Most MDD risk factors identified among AA women were also associated with MDD at similar magnitudes among EA women. Although the MDD heritability point estimate was higher among AA women than EA women in a model with paths estimated separately by race (56%, 95% CI: 29-78% vs. 41%, 95% CI: 29-52%), the best fitting model was one in which additive genetic and non-shared environmental paths for AA and EA women were constrained to be equal (A = 43%, 33-53% and E = 57%, 47-67%). In spite of a marked elevation in the prevalence of environmental risk exposures related to MDD among AA women, there were no significant differences in lifetime prevalence or heritability of MDD between AA and EA young women.

Measurement and Structural Invariance Of the Antisocial Process Screening Device Dong L, Wu H, Waldman ID. Psychol Assess. 2014; 26(2): 598-608.
Despite increasing study of psychopathic traits in children and adolescents, evidence regarding the factor structure of these traits has been inconsistent across community, clinic-referred, and incarcerated samples. Empirical support exists for both 2-factor (Impulsivity-Conduct Problems and Callous-Unemotional) and 3-factor (Narcissism, Callous-Unemotional, and Impulsivity) models, and factorial invariance across various samples has not been either tested or supported in the extant literature. The authors conducted confirmatory factor analyses of the Antisocial Process Screening Device (APSD; Frick & Hare, 2001) in 838 nonreferred twin pairs (M = 10.57 years, SD = 3.19 years) and 251 clinic-referred children (M = 10.82 years, SD = 3.39 years). Factorial invariance was tested across zygosity (monozygotic vs. dizygotic twins), sex (males vs. females), and age (younger vs. older children, divided by median age of 10.37 years) in the community sample and across sample type in both the community and clinic-referred samples. Results suggested that the 3-factor model fit better than did the 2-factor model in both community and clinic-referred samples. Using the best fitting 3-factor model, full measurement and structural invariance were found across zygosity, sex, and age in the community sample. Full measurement and structural invariance were also found across sample type except for differences in factor means across samples, suggesting excellent psychometric properties of the APSD. These results strongly support the robustness of the 3-factor model of psychopathic traits in children as well as the generalizability of the APSD across samples.

Family Ties: Maternal-offspring Attachment and Young Adult Nonmedical Prescription Opioid Use Cerda M, Bordelois P, Keyes KM, Roberts AL, Martins SS, Reisner SL, Austin SB, Corliss HL, Koenen KC. Drug Alcohol Depend. 2014; 142: 231-238.
Nonmedical prescription drug use is prevalent among young adults, yet little is known about modifiable determinants of use. The authors examined whether maternal-offspring attachment reported at mean age 21 was associated with nonmedical prescription opioid use at mean age 26, and investigated whether a history of depressive symptoms and substance use played a role in associations between maternal-offspring attachment and nonmedical prescription opioid use. The authors used data from the Growing Up Today Study, a longitudinal cohort of United States adolescents followed into young adulthood. Maternal-offspring attachment was reported by young

adults and their mothers, and defined as mutual low, mutual medium or high, and dissonant. Analyses were carried out in the full sample using generalized estimating equation models, and in a sibling subsample, using conditional fixed effects models to control for stable aspects of the family environment. Analyses with the full sample and the sibling subsample both showed that mutual medium/high maternal-offspring attachment at age 21 was associated with lower odds of nonmedical prescription opioid use at age 26 (RR=0.74; 95% CI=0.57-0.97 in full sample). The association was partly mediated by mean age 23 offspring smoking, heavy episodic drinking, and illicit drug use. Promoting reciprocal attachment in the maternal-offspring dyad should be investigated as a strategy to prevent nonmedical prescription opioid use by young adulthood. Even in young adulthood, programs that target both parents and offspring may have greater impact on offspring substance use than programs that target offspring alone.

The Influence Of Religious Attendance On Smoking Brown QL, Linton SL; Harrell PT, Mancha BE, Alexandre PK, Chen K-F, Eaton WW. Subst Use Misuse. 2014; 49(11): 1392-1399.
Generalized linear models were used to assess the relationship between religious attendance and lifetime smoking status among middle-aged adults (n = 666) sampled from waves three (1993 to 1996) and four (2004 to 2005) of the Baltimore Epidemiologic Catchment Area (ECA) study. Religious attendance once per week or greater as compared to never was inversely associated with smoking status. Future research should explore potential mediating factors of the association between religious attendance and smoking among middle-aged adults in order to gain a greater understanding of the mechanisms underlying this relationship. NIMH grant DA026652; NIDA grant T32DA007292.

Gender Differences In the Long-Term Associations Between Posttraumatic Stress Disorder and Depression Symptoms: Findings From the Detroit Neighborhood Health Study Horesh D, Lowe SR, Galea S, Uddin M, Koenen KC. Depress Anxiety. 2014.
Posttraumatic stress disorder (PTSD) and depression are known to be highly comorbid. However, previous findings regarding the nature of this comorbidity have been inconclusive. This study prospectively examined whether PTSD and depression are distinct constructs in an epidemiologic sample, as well as assessed the directionality of the PTSD-depression association across time. Nine hundred and forty-two Detroit residents (males: n = 387; females: n = 555) were interviewed by phone at three time points, 1 year apart. At each time point, they were assessed for PTSD (using the PCL-C), depression (PHQ-9), trauma exposure, and stressful life events. First, a confirmatory factor analysis showed PTSD and depression to be two distinct factors at all three waves of assessments (W1, W2, and W3). Second, chi-square analysis detected significant differences between observed and expected rates of comorbidity at each time point, with significantly more no-disorder and comorbid cases, and significantly fewer PTSD only and depression only cases, than would be expected by chance alone. Finally, a cross-lagged analysis revealed a bidirectional association between PTSD and depression symptoms across time for the entire sample, as well as for women separately, wherein PTSD symptoms at an early wave predicted later depression symptoms, and vice versa. For men, however, only the paths from PTSD symptoms to subsequent depression symptoms were significant. Across time, PTSD and depression are distinct, but correlated, constructs among a highly-exposed epidemiologic sample. Women and men differ in both the risk of these conditions, and the nature of the long-term associations between them.

Borderline Personality Features In Childhood: The Role Of Subtype, Developmental Timing, and Chronicity Of Child Maltreatment Hecht KF, Cicchetti D, Rogosch FA, Crick NR. Dev Psychopathol. 2014; 26(3): 805-815.
Child maltreatment has been established as a risk factor for borderline personality disorder (BPD), yet few studies consider how maltreatment influences the development of BPD features through childhood and adolescence. Subtype, developmental timing, and chronicity of child maltreatment were examined as factors in the development of borderline personality features in childhood. Children (M age = 11.30, SD = 0.94), including 314 maltreated and 285 nonmaltreated children from comparable low socioeconomic backgrounds, provided self-reports of developmentally salient borderline personality traits. Maltreated children had higher overall borderline feature scores, had higher scores on each individual subscale, and were more likely to be identified as at high risk for development of BPD through raised scores on all four subscales. Chronicity of maltreatment predicted higher overall borderline feature scores, and patterns of onset and recency of maltreatment significantly predicted whether a participant would meet criteria for the high-risk group. Implications of findings and recommendations for intervention are discussed.

Sources Of Pharmaceutical Opioids For Non-medical Use Among Young Adults Daniulaityte R, Falck R, Carlson RG. J Psychoactive Drugs. 2014; 46(3): 198-207.
The study uses qualitative and quantitative data to describe sources of pain pills for illicit use among young adult (18- to 23-year-old) users. Respondent-driven sampling was used to recruit 383 individuals in the Columbus, Ohio, area. The sample was almost 50% Caucasian and about 55% male. Qualitative interview participants (n = 45) were selected from the larger sample. Qualitative data suggest that pharmaceutical opioid availability was so pervasive that most individuals did not have to venture outside of their immediate social networks to find people who sold or shared pills. Participants emphasized differences between those who are actively involved in obtaining pills and those who play a more passive role. Active involvement was described as going out searching for pills and paying money to obtain them. In contrast, passive role included obtaining pills when somebody offered or shared them free of charge. Multiple logistic regression analysis indicates that a more active role in obtaining pharmaceutical opioids was related to being White, more frequent use of pharmaceutical opioids, extended-release oxycodone use, and using pharmaceutical opioids to get high, as opposed to self-treating a health problem. The study results can help inform drug use epidemiology, interventions, and policy.

Moderation Of Maltreatment Effects On Childhood Borderline Personality Symptoms By Gender and Oxytocin Receptor and FK506 Binding Protein 5 Genes Cicchetti D, Rogosch FA, Hecht KF, Crick NR; Hetzel S. Dev Psychopathol. 2014; 26(3): 831-849.
In this investigation, gene-environment-gender interaction effects in predicting child borderline personality disorder symptomatology among maltreated and nonmaltreated low-income children (N = 1,051) were examined. In the context of a summer research camp, adult-, peer-, and self-report assessments of borderline precursor indicators were obtained, as well as child self-report on the Borderline Personality Features Scale for Children. Genetic variants of the oxytocin receptor genotype and the FK506 binding protein 5 gene CATT haplotype were investigated. Children who self-reported high levels of borderline personality symptomatology were differentiated by adults, peers, and additional self-report on indicators of emotional instability, conflictual relationships with peers and adults, preoccupied attachment, and indicators of self-harm and suicidal ideation. Maltreated children also were more likely to evince many of these difficulties relative to nonmaltreated children. A series of analyses of covariance, controlling for age and ancestrally informative markers, indicated significant Maltreatment Gene Gender three-way interactions.

Consideration of the maltreatment parameters of subtype, onset, and recency expanded understanding of variation among maltreated children. The three-way interaction effects demonstrated differential patterns among girls and boys. Among girls, the gene-environment interaction was more consistent with a diathesis-stress model, whereas among boys a differential-sensitivity interaction effect was indicated. Moreover, the genetic variants associated with greater risk for higher borderline symptomatology, dependent on maltreatment experiences, were opposite in girls compared to boys. The findings have important implications for understanding variability in early predictors of borderline personality pathology.

Firearm Homicide and Other Causes Of Death In Delinquents: A 16-year Prospective Study
Teplin LA, Jakubowski JA, Abram KM, Olson ND, Stokes ML, Welty LJ. Pediatrics. 2014; 134(1): 63-73.
Delinquent youth are at risk for early violent death after release from detention. However, few studies have examined risk factors for mortality. Previous investigations studied only serious offenders (a fraction of the juvenile justice population) and provided little data on females. The Northwestern Juvenile Project is a prospective longitudinal study of health needs and outcomes of a stratified random sample of 1829 youth (657 females, 1172 males; 524 Hispanic, 1005 African American, 296 non-Hispanic white, 4 other race/ethnicity) detained between 1995 and 1998. Data on risk factors were drawn from interviews; death records were obtained up to 16 years after detention. We compared all-cause mortality rates and causes of death with those of the general population. Survival analyses were used to examine risk factors for mortality after youth leave detention. Delinquent youth have higher mortality rates than the general population to age 29 years ($P < .05$), irrespective of gender or race/ethnicity. Females died at nearly 5 times the general population rate ($P < .05$); Hispanic males and females died at 5 and 9 times the general population rates, respectively ($P < .05$). Compared with the general population, significantly more delinquent youth died of homicide and its subcategory, homicide by firearm ($P < .05$). Among delinquent youth, racial/ethnic minorities were at increased risk of homicide compared with non-Hispanic whites ($P < .05$). Significant risk factors for external-cause mortality and homicide included drug dealing (up to 9 years later), alcohol use disorder, and gang membership (up to a decade later).Delinquent youth are an identifiable target population to reduce disparities in early violent death.

A Comparison Of Nicotine Biomarkers and Smoking Patterns In Daily and Nondaily Smokers
Shiffman S, Dunbar MS, Benowitz NL. Cancer Epidemiol Biomarkers Prev. 2014; 23(7): 1264-1272.
Nondaily or intermittent smokers (ITS) are increasingly common, but how much nicotine, if any, ITS take in and how quickly they metabolize it has not yet been studied. The authors compared carbon monoxide (CO), urinary cotinine, and nicotine metabolism [nicotine metabolite ratio (NMR): 3-hydroxycotinine:cotinine] in 224 ITS and 222 daily smokers (DS). Effects of gender and ethnicity were examined.DS had higher cotinine concentrations than ITS (1,39669 vs. 47844 ng/mL), attributable to higher cigarettes per day (CPD). In both groups, cotinine rose more slowly as CPD increased. There were no differences in cotinine between White (WH) and African American (AA) DS; among ITS, AA cotinine was over twice that of WH. Among DS, CO was significantly higher among WH than AA smokers, but significantly lower among WH IT'S than AA ITS. Although AA ITS smoked more than WH ITS (CPD: 4.13 0.55 vs. 3.31 0.41), this did not account for the observed cotinine nor CO differences. There were no differences in NMR by group or race, nor any gender effects. At comparable CPD, DS; and ITS; intake of nicotine per cigarette was similar, as were their rates of nicotine metabolism. Among ITS, AA smokers smoke more and

take in more nicotine per cigarette than WH ITS, consistent with the view of ITS as a heterogeneous group. Differences in nicotine intake per cigarette and metabolism likely cannot account for differences in DS and ITS smoking. Future studies should explore ethnic differences in ITS smoking.

Age Of Onset and Course Of Major Depressive Disorder: Associations With Psychosocial Functioning Outcomes In Adulthood Wilson S, Hicks BM, Foster KT, McGue M, Iacono WG. Psychol Med. 2014; 1-10.
Major depressive disorder (MDD) that onsets by adolescence is associated with various deficits in psychosocial functioning. However, adolescent-onset MDD often follows a recurrent course that may drive its associated impairment. To tease apart these two clinical features, the authors examined the relative associations of age of onset (adolescent versus adult) and course (recurrent versus single episodes) of MDD with a broad range of psychosocial functioning outcomes assessed in early adulthood. Participants comprised a large, population-based sample of male and female twins from the Minnesota Twin Family Study (MTFS; n=1252) assessed prospectively from ages 17 to 29 years. A recurrent course of MDD predicted impairment in several psychosocial domains in adulthood, regardless of whether the onset was in adolescence or adulthood. By contrast, adolescent-onset MDD showed less evidence of impairment in adulthood after accounting for recurrence. Individuals with both an adolescent onset and recurrent episodes of MDD represented a particularly severe group with pervasive psychosocial impairment in adulthood. The negative implications of adolescent-onset MDD for psychosocial functioning in adulthood seem to be due primarily to its frequently recurrent course, rather than its early onset, per se. The results highlight the importance of considering both age of onset and course for understanding MDD and its implications for functioning, and also in guiding targeted intervention efforts.

Effects Of A Summer Treatment Program On Functional Sports Outcomes In Young Children With ADHD O'Connor BC, Fabiano GA, Waschbusch DA, Belin PJ, Gnagy EM; Pelham WE, Greiner AR, Roemmich JN. J Abnorm Child Psychol. 2014; 42(6): 1005-1017.
Participation in youth sports can be very beneficial, but children with Attention Deficit Hyperactivity Disorder (ADHD) may participate less often and less successfully. The current study evaluated functional sports outcomes for children with ADHD who attended an intensive behavioral treatment program that included a sports training component, and it compared outcomes to children with ADHD who did not attend the program. Results suggest that treatment resulted in significant improvements in many aspects of children sports functioning, including knowledge of game rules, in vivo game performance, and fundamental skill tasks (motor proficiency, ability to trap a soccer ball appropriately, reduced handball penalties in soccer, and improved ability to catch a baseball). Parents also reported improved sports skills and good sportsmanship in the treatment group. No differences between groups were evident on additional skill tasks evaluating accurately kicking a soccer ball, throwing a baseball, or hitting a baseball off a tee. These results suggest intensive behavioral intervention that includes sports training can significantly improve functional sports outcomes for young children with ADHD.

Influences Of Motivational Contexts On Prescription Drug Misuse and Related Drug Problems Kelly BC, Rendina HJ, Vuolo M, Wells BE, Parsons JT. J Subst Abuse Treat. 2014.
Prescription drug misuse has emerged as a significant problem among young adults. While the effects of motivational contexts have been demonstrated for illicit drugs, the role of motivational contexts in prescription drug misuse remains understudied. Using data from 400 young adults recruited via time-space sampling, we examined the role of motivational contexts in the frequency

of misuse of three prescription drug types as well as drug-related problems and symptoms of dependency. Both negative and positive motivations to use drugs are associated with increases in prescription drug misuse frequency. Only negative motivations are associated directly with drug problems and drug dependence, as well as indirectly via prescription pain killer misuse. Addressing positive and negative motivational contexts of prescription drug misuse may not only provide a means to reduce misuse and implement harm reduction measures, but may also inform the content of treatment plans for young adults with prescription drug misuse problems.

Implications Of Marijuana Legalization For Adolescent Substance Use Hopfer C. Subst Abus. 2014.

Marijuana that is legally available for adults has multiple implications for adolescent substance use. One potential effect that legalization may have is an increase in adolescent use to due increased availability, greater social acceptance, and possibly lower prices. Legalization may also facilitate the introduction of new formulations of marijuana (edible, vaporized) and with potentially higher potencies. It is unknown what adolescent consumption patterns will be if marijuana is widely available and marketed in different forms, or what effects different patterns of adolescent use will have on cognition, the development of marijuana use disorders, school performance, and the development of psychotic illnesses. Also unclear is whether adolescent users will be experiencing higher levels of THC compared with previous generations of users due to higher potencies. While previous studies of the effects of adolescent marijuana use provide some guidance for current policy and public health recommendations, many new studies will be needed that answer questions in the context of use within a legal adult environment. Claims that marijuana has medicinal benefits create additional challenges for adolescent prevention efforts as they contrast with messages of its harmfulness. Prevention and treatment approaches will need to address perceptions of the safety of marijuana, claims of its medicinal use, and consider family-wide effects as older siblings and parents may increasingly openly consume and advocate for marijuana use. Guidance for primary care physicians will be needed regarded screening and counseling. Widespread legalization and acceptance of marijuana implies that as law enforcement approaches for marijuana control decline, public health, medical, and scientific efforts to understand and reduce negative consequences of adolescent marijuana use need to be substantially increased to levels commensurate with those efforts for tobacco and alcohol.

Internalizing and Externalizing Problem Behavior and Early Adolescent Substance Use: A Test Of A Latent Variable Interaction And Conditional Indirect Effects Scalco MD, Colder CR, Hawk LW, Read JP, Wieczorek WF, Lengua L. J. Psychol Addict Behav. 2014; 28(3): 828-840.

Externalizing problem behavior is a robust predictor of early adolescent substance use (SU); however, findings regarding internalizing problems have been mixed, suggesting that there may be important moderators of the relationship between internalizing problems and SU. The present study used a community sample (mean age was 12.1 at the first assessment, 55% women, 83% White) to test a longitudinal latent variable interaction structural equation model to examine whether externalizing problems moderated the relationship between internalizing problems and SU. Peer delinquency was tested as a mediator in the model and prior levels of the mediator and outcome were controlled at each wave to establish temporal precedence. Results suggested that (1) internalizing problems were protective against associating with deviant peers, but only at high levels of externalizing symptomatology, (2) higher levels of peer delinquency were associated with increases in SU, and (3) peer delinquency mediated the effect of the problem behavior interaction on SU. These findings suggest that the impact of internalizing problems on peer delinquency and

SU needs to be considered in the context of externalizing problems. Moreover, developmental models involving internalizing symptoms should consider that internalizing symptoms are generally protective against substance use in early adolescence.

Civilian Stressors Associated With Alcohol Use Disorders In The National Guard Cerda M, Richards C, Cohen GH, Calabrese JR, Liberzon I, Tamburrino M, Galea S, Koenen KC. Am J Prev Med. 2014; 47(4): 461-466.
Alcohol use disorders are a serious public health concern among soldiers. Although deployment-related exposures have been linked with alcohol use disorders in soldiers, less is understood about the link between modifiable, civilian stressors and post-deployment alcohol use disorders The objectives of this study were to (1) compare the influence of civilian stressors and deployment-related traumatic events and stressors on post-deployment alcohol use disorders among Army National Guardsmen primarily deployed to Afghanistan and Iraq; and (2) evaluate whether civilian stressors influence a different set of alcohol use disorder phenotypes than deployment-related traumatic events and stressors. A cohort of Ohio National Guard soldiers was recruited in 2008-2009 and interviewed three times over 3 years. The analytic sample included Ohio National Guard soldiers who had been deployed by 2008-2009, had participated in at least one follow-up wave, had reported consuming at least one alcoholic drink in their lifetime, and had non-missing data on alcohol use disorders (n=1,095). Analyses were conducted in 2013.In a model including measures of civilian stressors and deployment-related traumatic events, only civilian stressors (OR=2.07, 95% CI=1.46, 2.94) were associated with subsequent alcohol use disorder. The effects of civilian stressors were only present among people with no history of alcohol use disorder. Independent of deployment-related exposures, post-deployment civilian stressors are associated with the onset of alcohol use disorder among reserve-component soldiers. Concerted investment to address daily civilian difficulties associated with reintegration into civilian life may be needed to prevent new cases of alcohol use disorders among returning military personnel.

Sensation Seeking Predicting Growth In Adolescent Problem Behaviors Byck GR, Swann G, Schalet B, Bolland J, Mustanski B. Child Psychiatry Hum Dev. 2014.
There is limited literature on the relationship between sensation seeking and adolescent risk behaviors, particularly among African Americans. The authors tested the association between psychometrically-derived subscales of the Zuckerman Sensation Seeking Scale and the intercepts and slopes of individual growth curves of conduct problems, sexual risk taking, and substance use from ages 13 to 18years by sex. Boys and girls had different associations between sensation seeking and baseline levels and growth of risk behaviors. The Pleasure Seeking scale was associated with baseline levels of conduct problems in boys and girls, baseline substance use in boys, and growth in sexual risk taking and substance use by girls. Girls had the same pattern of associations with the Danger/Novelty scale as the Pleasure Seeking scale. Knowledge about the relationships between adolescent risk taking and sensation seeking can help in the targeted design of prevention and intervention programs for the understudied population of very low-income, African American adolescents.

Global Epidemiology Of HIV Among Female Sex Workers: Influence Of Structural Determinants Shannon K, Strathdee SA, Goldenberg SM, Duff P, Mwangi P, Rusakova M, Reza-Paul S, Lau J, Deering K, Pickles MR, Boily M-C. Lancet. 2014.
Female sex workers (FSWs) bear a disproportionately large burden of HIV infection worldwide. Despite decades of research and programme activity, the epidemiology of HIV and the role that structural determinants have in mitigating or potentiating HIV epidemics and access to care for

FSWs is poorly understood. The authors reviewed available published data for HIV prevalence and incidence, condom use, and structural determinants among this group. Only 87 (43%) of 204 unique studies reviewed explicitly examined structural determinants of HIV. Most studies were from Asia, with few from areas with a heavy burden of HIV such as sub-Saharan Africa, Russia, and eastern Europe. To further explore the potential effect of structural determinants on the course of epidemics, we used a deterministic transmission model to simulate potential HIV infections averted through structural changes in regions with concentrated and generalized epidemics, and high HIV prevalence among FSWs. This modelling suggested that elimination of sexual violence alone could avert 17% of HIV infections in Kenya (95% uncertainty interval [UI] 1-31) and 20% in Canada (95% UI 3-39) through its immediate and sustained effect on non-condom use) among FSWs and their clients in the next decade. In Kenya, scaling up of access to antiretroviral therapy among FSWs and their clients to meet WHO eligibility of a CD4 cell count of less than 500 cells per *L could avert 34% (95% UI 25-42) of infections and even modest coverage of sex worker-led outreach could avert 20% (95% UI 8-36) of infections in the next decade. Decriminalization of sex work would have the greatest effect on the course of HIV epidemics across all settings, averting 33-46% of HIV infections in the next decade. Multipronged structural and community-led interventions are crucial to increase access to prevention and treatment and to promote human rights for FSWs worldwide.

Prevalence and Correlates Of Nonmedical Prescription Opioid Use Among A Cohort Of Sex Workers In Vancouver, Canada Argento E, Chettiar J, Nguyen P, Montaner J, Shannon K. Int J Drug Policy. 2014.

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

The Impact Of Childhood Parental Loss On Risk For Mood, Anxiety and Substance Use Disorders In A Population-based Sample Of Male Twins Otowa T, York TP, Gardner CO, Kendler KS, Hettema JM. Psychiatry Res. 2014. .

Previous studies have identified the relationship between parental loss and psychopathology later in life. However, this relationship varied depending on the kind of loss, the parent involved, and the type of psychopathology. In the present study, the authors examined the association between parental loss (any loss, death, and separation) during childhood and lifetime risk for seven common psychiatric and substance use disorders in a sample of 2605 male twins from the Virginia population-based twin registry. Using structural equation modeling (SEM), the authors also examined the extent to which the influence of parental loss contributes to adult psychopathology. Parental separation was associated with a wide range of adult psychopathology, whereas parental death was specifically associated with phobia and alcohol dependence. Maternal and paternal separations were almost equally associated with most forms of psychopathology. SEM suggested that parental loss accounted for about 10% of the variance of adult psychopathology, of which parental separation had the strongest impacts on risk for depression and drug abuse/dependence (11% of the total variance). Findings suggest that early parental separation has stronger and wider effects on adult psychopathology than parental death.

Psychosocial Vulnerability and HIV-Related Sexual Risk Among Men Who Have Sex With Men and Women In the United States Dyer TP, Regan R, Pacek LR, Acheampong A, Khan MR. Arch Sex Behav. 2014.

In the U.S., HIV is concentrated among men who have sex with men (MSM), some of whom have had female partners (MSMW). MSMW are disproportionately impacted by psychosocial vulnerabilities, like depression and substance use that increase sexually transmitted infection (STI) and HIV risk. Research on psychosocial vulnerability and HIV-related sexual risk among MSMW is warranted to reduce infection transmission among MSM and to prevent bridging to female partners. The authors analyzed data from Wave IV (2007-2008) of the National Longitudinal Study of Adolescent Health to assess psychosocial vulnerability and HIV risk-taking among MSMW. Using lifetime and past year sexual activity, we classified men as ever having sex with: women only (MSW), men only (MSMO) or MSMW, with further refined categorization of MSMW with male only partners in the past 12months, only female partners in the past 12months, and both male and female partners in the past 12months (N=6,945). He authors compared psychosocial vulnerability characteristics and HIV-related risk behaviors among the five categories of men. MSMW were more likely to report depression, suicidality, substance use, and incarceration than MSW and MSMO. Compared to MSW, MSMW with current female partners had greater odds of unprotected sex, exchange sex, and STI. MSMW with male partners in the past year had greater odds of multiple or concurrent partners in the past year. HIV risk and psychosocial vulnerability factors are elevated among MSMW, a priority population for HIV risk reduction. HIV risk reduction interventions should address this and heterogeneity of sexual partnerships among MSMW.

Changes In Exposure To Neighborhood Characteristics Are Associated With Sexual Network Characteristics In A Cohort Of Adults Relocating From Public Housing Cooper HLF, Linton S, Haley DF, Kelley ME, Dauria EF, Karnes CC, Ross Z, Hunter-Jones J, Renneker KK, Del Rio C, Adimora A, Wingood G, Rothenberg R, Bonney LE. AIDS Behav. 2014.

Ecologic and cross-sectional multilevel analyses suggest that characteristics of the places where people live influence their vulnerability to HIV and other sexually-transmitted infections (STIs). Using data from a predominately substance-misusing cohort of African-American adults relocating from US public housing complexes, this multilevel longitudinal study tested the hypothesis that

participants who experienced greater post-relocation improvements in economic disadvantage, violent crime, and male: female sex ratios would experience greater reductions in perceived partner risk and in the odds of having a partner who had another partner (i.e., indirect concurrency). Baseline data were collected from 172 public housing residents before relocations occurred; three waves of post-relocation data were collected every 9months. Participants who experienced greater improvements in community violence and in economic conditions experienced greater reductions in partner risk. Reduced community violence was associated with reduced indirect concurrency. Structural interventions that decrease exposure to violence and economic disadvantage may reduce vulnerability to HIV/STIs.

Examining the Relationship Between the Physical Availability Of Medical Marijuana and Marijuana Use Across Fifty California Cities Freisthler B, Gruenewald P. J. Drug Alcohol Depend. 2014; 143: 244-250.
The purpose of the current study is to assess statistical associations between individual demographic and personality characteristics, the city-level physical availability of medical marijuana (as measured through densities per roadway mile of storefront dispensaries and delivery services), and the incidence and prevalence of marijuana use. Individual level data on marijuana use were collected during a telephone survey of 8853 respondents living in 50 mid-size cities in California. Data on medical marijuana dispensaries and delivery services were obtained via six different websites and official city lists. Three outcome variables pertaining to lifetime, past year use, and frequency of past year use were analyzed using random effects logistic models (for lifetime and past year use) and random effects to bit models (for frequency of past 365-day use).The current study finds that the total physical availability of medical marijuana through dispensaries and delivery services per roadway mile at the city-level is positively related to current marijuana use and greater frequency of use, controlling for a variety of demographic and personality characteristics. As expected, current physical availability of medical marijuana was unrelated to lifetime use. Regulations on the number and densities of marijuana outlets may be a sufficient means to restrain overall levels of marijuana use within cities. However, alternative use of delivery services may also provide easy access to marijuana and mitigate these effects.

Correlates Of Hospital Use In Homeless and Unstably Housed Women: The Role Of Physical Health and Pain Doran KM, Shumway M, Hoff RA, Blackstock OJ, Dilworth SE, Riley ED. Women's Health Issues. 2014; 24(5): 535-541.
The objective of this study was to examine correlates of emergency department (ED) use and hospitalizations in a community-based cohort of homeless and unstably housed women, with a focus on the role of physical health and pain. The authors conducted a cross-sectional analysis of baseline survey results from a study of homeless and unstably housed women in San Francisco. Primary outcomes were any self-reported ED visit and inpatient hospitalization over the prior 6 months. Primary independent variables of interest were self-reported physical health status, as measured by the Short Form-12 (SF-12), and bodily pain. Other potential covariates were organized using the Gelberg-Andersen Behavioral Model for Vulnerable Populations. Standard bivariate and multivariable logistic regression techniques were used. Three hundred homeless and unstably housed women were included in the study, of whom 37.7% reported having an ED visit and 23.0% reported being hospitalized in the prior 6 months. Mean SF-12 physical health scores indicated poorer than average health compared with the U.S. norm. Most women (79.3%) reported at least some limitation in their daily activities owing to pain. In adjusted analyses, moderate and high levels of bodily pain were significantly correlated with ED visits (odds ratio [OR], 2.92 and OR, 2.57) and hospitalizations (OR, 6.13 and OR, 2.49). As SF-12 physical health scores decreased,

indicating worse health, the odds of ED use increased. Predisposing, enabling, and additional need factors did not mediate these associations. Physical health and bodily pain are important correlates of ED visits and hospitalizations among homeless and unstably housed women. Interventions to reduce ED use among women who are homeless should address the high levels of pain in this population.

Human Mate Selection and Addiction: A Conceptual Critique Heath AC, Waldron MC, Martin NG, Nelson EC, Bucholz KK, Madden PAF. Behav Genet. 2014; 44(5): 419-426.
The authors review past work on modeling human mate selection, and suggest, using illustrations from existing literature on the impact of alcoholism on relationship formation and dissolution and reproduction, that the challenges of adequately characterizing human mate selection have not yet been overcome. Some paths forwards are suggested.

A Typology Of Prescription Drug Misuse: A Latent Class Approach To Differences and Harms Kelly BC, Rendina HJ, Vuolo M, Wells BE, Parsons JT. Drug Alcohol Rev. 2014. .
Prescription drug misuse is a considerable problem among young adults, and the identification of types of misuse among this population remains important for prevention and intervention efforts. The authors use latent class analysis to identify possible distinct latent groups of prescription drug misusers across multiple prescription drug types (pain killers, sedatives and stimulants). These data are comprised of a sample of 404 young adults recruited from nightlife scenes via time-space sampling. Through the specification of a zero-inflated Poisson latent class analysis, the authors evaluate differences in class membership by various demographic factors as well as assess the relationship between class membership and health outcomes, including indications of dependence, problems associated with substance use and mental health. Their assessment of fit indices led to a four-class solution (dabblers, primary stimulant users, primary downers users and extensive regulars). No demographic differences existed between latent classes. The extensive regular class report the greatest number of symptoms related to dependence, greatest number of problems related to misuse and the greatest mental health problems. The dabblers report the fewest problems and symptoms, while the other two classes experiences problems and symptoms in between the classes on the extremes. Prevention efforts should take into account that young adults who misuse prescription drug have different profiles of misuse, and there may be a need for varied interventions to target these different types of misuse.

A New Approach To Researching The Etiology Of Cannabis Use Disorder: Integrating Transmissible And Non-Transmissible Risk Within A Developmental Framework Tarter R, Kirisci L, Reynolds M. Subst Abus. 2014.
Rapidly occurring changes in law enforcement and licensing of retail outlets to sell marijuana raises the prospect that the population of consumers will expand and accordingly the prevalence of cannabis use disorder (CUD) will increase. This report presents a novel approach to researching CUD etiology joining multivariate and ontogenetic perspectives. CUD is conceptualized as a developmental outcome consisting of transmissible (intergenerational) and non-transmissible components. Partitioning the liability for CUD into these two dimensions enables implementing interventions targeted at the particular source and severity of risk. In addition, results showing that infant temperament disturbances predict transmissible risk leading to CUD two decades later underscore the importance of implementing early prevention.

Neighborhood Characteristics and Sexual Intimate Partner Violence Against Women Among Low-income, Drug-involved New York City Residents: Results From the IMPACT Studies Frye V, Blaney S, Cerda M, Vlahov D, Galea S, Ompad DC. Violence Against Women. 2014; 20(7): 799-824.
The authors assessed relations among neighborhood characteristics and sexual intimate partner violence against women (SIPVAW), among low-income, drug-involved, women (n = 360) and men (n = 670) in New York City between 2005 and 2009. Six percent of women (n = 22) and 5% of men (n = 33) reported experiencing and perpetrating SIPVAW in the past year with a main partner. In adjusted mixed models among women, neighborhood ethnic heterogeneity was significantly negatively associated with SIPVAW victimization. In adjusted logistic models among men, neighborhood collective efficacy was significantly positively associated with SIPVAW perpetration. Novel theoretical frameworks are needed to guide research on neighborhoods and partner violence.

Trajectories Of Marijuana Use Beginning In Adolescence Predict Tobacco Dependence In Adulthood Brook JS, Lee JY, Brook DW. Subst Abus. 2014.
Although the "stage theory" suggests that marijuana use occurs after the initiation of tobacco smoking, substantial evidence exists that they often occur concurrently, and that the use of marijuana may influence the use of tobacco. This study uses trajectory analysis to examine the relationship between marijuana use beginning in adolescence and adult tobacco dependence in a 5-wave longitudinal study (mean ages in each wave: 14, 19, 24, 29, and 32). The sample consisted of 816 participants (52% African Americans, 48% Puerto Ricans), of whom 60% were females. Logistic regression analyses were conducted to predict later tobacco dependence from earlier trajectories of marijuana use. Results: A higher Bayesian posterior probability (BPP) for the chronic marijuana use trajectory group (OR = 10.93, p<.001; AOR = 10.40, p<.001), for the increasing marijuana use trajectory group (OR = 6.94, p<.001; AOR = 6.73, p<.001), and for the moderate marijuana use trajectory group (OR = 3.13, p<.001; AOR = 3.18, p<.001) was associated with an increased likelihood of being dependent on tobacco compared with the BPP of the no or low marijuana use trajectory group. Conclusions: The results underscore the value of considering multiple patterns of marijuana use within a person-centered approach. Thus, it would be appropriate for marijuana cessation programs to incorporate the prevention, assessment, and cessation of tobacco use in their health promotion strategies.

Nonmedical Stimulant Use Among Young Asian-Americans, Native Hawaiians/Pacific Islanders, and Mixed-race Individuals Aged 12-34 Years In the United States Wu L-T, Swartz MS, Brady KT, Blazer DG, Hoyle RH; NIDA AAPI Workgroup. J Psychiatr Res. 2014.
There are concerns over nonmedical use of prescription stimulants among youths, but little is known about the extent of use among young Asian-Americans, Native Hawaiians/Pacific Islanders (NHs/PIs), and mixed-race individuals-the fastest growing segments of the U.S. population. The authors examined prevalence's and correlates of nonmedical stimulant use (NMSU) and disorder (StiUD) for these under recognized groups. Whites were included as a comparison. Data were from young individuals aged 12-34 years in the 2005-2012 National Surveys on Drug Use and Health. The authors used logistic regression to estimate odds of past-year NMSU status. Significant yearly increases in lifetime NMSU prevalence were noted in Whites only. NHs/PIs (lifetime 7.33%, past-year 2.72%) and mixed-race individuals (10.20%, 2.82%) did not differ from Whites in NMSU prevalence (11.68%, 3.15%). Asian-Americans (lifetime 3.83%, past-year 0.90%) had lower prevalence's than Whites. In each racial/ethnic group, "Methamphetamine/Desoxyn/Methedrine or Ritalin" was more commonly used than other stimulant groups; "got them from a friend/relative for

free" and "bought them from a friends/relative" were among the most common sources. Females had greater odds than males of NMSU (among White, NH/PI, mixed-race individuals) and StiUD (among mixed-race individuals). Young adults (aged 18-25) had elevated odds of NMSU (White, NH/PI); adolescents had elevated odds of StiUD (White, mixed-race). Other substance use (especially marijuana, other prescription drugs) increased odds of NMSU and StiUD. NHs/PIs and mixed-race individuals were as likely as Whites to misuse stimulants. Research is needed to delineate health consequences of NMSU and inform prevention efforts for these understudied, rapidly-growing populations.

Does Perceived Racial Discrimination Predict Changes In Psychological Distress and Substance Use Over Time? An Examination Among Black Emerging Adults Hurd NM, Varner FA, Caldwell CH, Zimmerman MA. Dev Psychol. 2014; 50(7): 1910-1918.
The authors assessed whether perceived discrimination predicted changes in psychological distress and substance use over time and whether psychological distress and substance use predicted change in perceived discrimination over time. They also assessed whether associations between these constructs varied by gender. The sample included 607 Black emerging adults (53% female) followed for 4 years. Participants reported the frequency with which they had experienced racial hassles during the past year, symptoms of anxiety and depression during the past week, and cigarette and alcohol use during the past 30 days. The authors estimated a series of latent growth models to test our study hypotheses. They found that the intercept of perceived discrimination predicted the linear slopes of anxiety symptoms, depressive symptoms, and alcohol use. They did not find any associations between the intercept factors of our mental health or substance use variables and the perceived discrimination linear slope factor. The authors found limited differences across paths by gender. Their findings suggest a temporal ordering in the associations among perceived racial discrimination, psychological distress, and alcohol use over time among emerging adults. Further, their findings suggest that perceived racial discrimination may be similarly harmful among men and women.

Assessing Differences In Groups Randomized By Recruitment Chain In A Respondent-driven Sample Of Seattle-area Injection Drug Users Burt RD, Thiede H. Ann Epidemiol. 2014.
Respondent-driven sampling (RDS) is a form of peer-based study recruitment and analysis that incorporates features designed to limit and adjust for biases in traditional snowball sampling. It is being widely used in studies of hidden populations. The authors report an empirical evaluation of RDS consistency and variability, comparing groups recruited contemporaneously, by identical methods and using identical survey instruments. They randomized recruitment chains from the RDS-based 2012 National HIV Behavioral Surveillance survey of injection drug users in the Seattle area into two groups and compared them in terms of sociodemographic characteristics, drug-associated risk behaviors, sexual risk behaviors, human immunodeficiency virus (HIV) status and HIV testing frequency. The two groups differed in five of the 18 variables examined (P.001): race (e.g., 60% white vs. 47%), gender (52% male vs. 67%), area of residence (32% downtown Seattle vs. 44%), an HIV test in the previous 12ýýmonths (51% vs. 38%). The difference in serologic HIV status was particularly pronounced (4% positive vs. 18%). In four further randomizations, differences in one to five variables attained this level of significance, although the specific variables involved differed. The authors found some material differences between the randomized groups. Although the variability of the present study was less than has been reported in serial RDS surveys, these findings indicate caution in the interpretation of RDS results.

HIV, Drugs and the Legal Environment Strathdee SA, Beletsky L, Kerr T. Int J Drug Policy. 2014.
A large body of scientific evidence indicates that policies based solely on law enforcement without taking into account public health and human rights considerations increase the health risks of people who inject drugs (PWIDs) and their communities. Although formal laws are an important component of the legal environment supporting harm reduction, it is the enforcement of the law that affects PWIDs; behavior and attitudes most acutely. This commentary focuses primarily on drug policies and policing practices that increase PWIDs; risk of acquiring HIV and viral hepatitis, and avenues for intervention. Policy and legal reforms that promote public health over the criminalization of drug use and PWID are urgently needed. This should include alternative regulatory frameworks for illicit drug possession and use. Changing legal norms and improving law enforcement responses to drug-related harms requires partnerships that are broader than the necessary bridges between criminal justice and public health sectors. HIV prevention efforts must partner with wider initiatives that seek to improve police professionalism, accountability, and transparency and boost the rule of law. Public health and criminal justice professionals can work synergistically to shift the legal environment away from one that exacerbates HIV risks to one that promotes safe and healthy communities.

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

Familiarity Of Addiction and Its Developmental Mechanisms In Girls Kirillova G, Reynolds M, Kirisci L, Mosovsky S, Ridenour T, Tarter R, Vanyukov M. Drug Alcohol Depend. 2014; 143: 213-218.
Drug use disorders (DUD) have been theorized to share sources of risk variation with other consummatory behaviors. The authors hypothesized that common mechanisms exist for familial risk for DUD, physiological maturation and nutritional status in girls. Whereas body fat content must exceed a threshold to enable adrenarche and gonadarche, nutritional status may also be a behavior risk indicator. Impaired psychological self-regulation associated with DUD risk may manifest in early overeating, which could in turn accelerate reproductive maturation, resulting in a greater likelihood of affiliation with deviant/older peers and drug use. The sample consisted of

families ascertained through the father who either had (N=95) or did not have (N=130) a DUD, and who had a 10-12 year old daughter and her mother available for study. Correlation, survival and path analyses of three consecutive assessments evaluated the relationships between parental DUD (number of affected parents, NAP), nutritional status (NS, subscapular skinfold measurements and body mass index), sexual maturation (Tanner stage), peer delinquency, and the daughters lifetime DUD diagnosis. NAP was positively related to the girls; nutritional status. Longitudinal path analysis indicated mediation of the relationship between NAP and peer delinquency by sexual maturation. The relationship between NAP and sexual maturation is mediated by NS. The effect of sexual maturation at age 11 on the girls; DUD risk is mediated by peer delinquency. The data are consistent with mediation of intergenerational transmission of DUD risk in females by elevated nutrition, leading to accelerated maturation, and affiliation with deviant peers.

High Risk and Little Knowledge: Overdose Experiences and Knowledge Among Young Adult Nonmedical Prescription Opioid Users Frank D, Mateu-Gelabert P, Guarino H, Bennett A, Wendel T, Jessell L, Teper A. Int J Drug Policy. 2014.
Opioid-involved overdoses in the United States have dramatically increased in the last 15 years, largely due to a rise in prescription opioid (PO) use. Yet few studies have examined the overdose knowledge and experience of nonmedical PO users. In depth, semi-structured, audio-recorded interviews were conducted with 46 New York City young adults (ages 18-32) who reported using POs nonmedically within the past 30 days. Verbatim interview transcripts were coded for key themes in an analytic process informed by grounded theory. Despite significant experience with overdose (including overdose deaths), either personally or within opioid-using networks, participants were relatively uninformed about overdose awareness, avoidance and response strategies, in particular the use of naloxone. Overdose experiences typically occurred when multiple pharmaceuticals were used (often in combination with alcohol) or after participants had transitioned to heroin injection. Participants tended to see themselves as distinct from traditional heroin users, and were often outside of the networks reached by traditional opioid safety/overdose prevention services. Consequently, they were unlikely to utilize harm reduction services, such as syringe exchange programs (SEPs) that address drug users; health and safety. These findings suggest that many young adult nonmedical PO users are at high risk of both fatal and non-fatal overdose. There is a pressing need to develop innovative outreach strategies and overdose prevention programs to better reach and serve young PO users and their network contacts. Prevention efforts addressing risk for accidental overdose, including opioid safety/overdose reversal education and naloxone distribution, should be tailored for and targeted to this vulnerable group.

Patterns Of Opioid Use For Chronic Noncancer Pain In The Veterans Health Administration From 2009 To 2011 Edlund MJ, Austen MA, Sullivan MD, Martin BC, Williams JS, Fortney JC, Hudson T. J. Pain. 2014..
Although opioids are frequently prescribed for chronic noncancer pain (CNCP) among Veterans Health Administration (VHA) patients, little has been reported on national opioid prescribing patterns in the VHA. The authors' objective was to better characterize the dosing and duration of opioid therapy for CNCP in the VHA. They analyzed national VHA administrative and pharmacy data for fiscal years 2009 to 2011. For individuals with CNCP diagnoses and any opioid use in the fiscal year, they calculated the distribution of individual mean daily opioid dose, individual total days covered with opioids in a year, and individual total opioid dose in a year. They also investigated the factors associated with being in the top 5% of individuals for total opioid dose in a year, which we term receipt of high-volume opioids. About half of the patients with CNCP received opioids in a given fiscal year. The median daily dose was 21mg morphine equivalents.

Approximately 4.5% had a mean daily dose higher than 120mg morphine equivalents. The median days covered in a year was 115 to 120days in these years for those receiving opioids. Fifty-seven percent had at least 90days covered with opioids per year. Major depression and posttraumatic stress disorder were positively associated with receiving high-volume opioids, but nonopioid substance use disorders were not. Among VHA patients with CNCP, chronic opioid therapy occurs frequently, but for most patients, the average daily dose is modest. Doses and duration of therapy were unchanged from 2009 to 2011.

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. 2014.
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 girls; 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 semi parametric group-based model was used to identify trajectories of disruptive behavior in 1,513 girls from age 6 to 12ýýyears. 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.

An ADH1B Variant and Peer Drinking In Progression To Adolescent Drinking Milestones: Evidence Of A Gene-by-Environment Interaction Olfson E, Edenberg HJ, Nurnberger Jr., J, Agrawal A, Bucholz KK, Almasy LA, Chorlian D, Dick DM, Hesselbrock VM, Kramer JR, Kuperman S, Porjesz B, Schuckit MA; Tischfield JA, Wang J-C, Wetherill L, Foroud TM, Rice J, Goate A, Bierut LJ. Alcohol Clin Exp Res. 2014..
Adolescent drinking is an important public health concern, one that is influenced by both genetic and environmental factors. The functional variant rs1229984 in alcohol dehydrogenase 1B (ADH1B) has been associated at a genome-wide level with alcohol use disorders in diverse adult populations. However, few data are available regarding whether this variant influences early drinking behaviors and whether social context moderates this effect. This study examines the interplay between rs1229984 and peer drinking in the development of adolescent drinking milestones. One thousand five hundred and fifty European and African American individuals who had a full drink of alcohol before age 18 were selected from a longitudinal study of youth as part of the Collaborative Study on the Genetics of Alcoholism (COGA). Cox proportional hazards regression, with GE product terms in the final models, was used to study 2 primary outcomes during adolescence: age of first intoxication and age of first DSM-5 alcohol use disorder symptom. The minor A allele of rs1229984 was associated with a protective effect for first intoxication (HR=0.56, 95% CI 0.41 to 0.76) and first DSM-5 symptom (HR=0.45, 95% CI 0.26 to 0.77) in the final models. Reporting that most or all best friends drink was associated with a hazardous effect for first intoxication (HR=1.81, 95% CI 1.62 to 2.01) and first DSM-5 symptom (HR=2.17, 95% 1.88 to 2.50) in the final models. Furthermore, there was a significant GE interaction for first intoxication (p=0.002) and first DSM-5 symptom (p=0.01). Among individuals reporting none or few best

friends drinking, the ADH1B variant had a protective effect for adolescent drinking milestones, but for those reporting most or all best friends drinking, this effect was greatly reduced. Our results suggest that the risk factor of best friends drinking attenuates the protective effect of a well-established ADH1B variant for 2 adolescent drinking behaviors. These findings illustrate the interplay between genetic and environmental factors in the development of drinking milestones during adolescence.

Confidence Interval Estimation In R-DAS Vsevolozhskaya OA, Anthony JC. Drug Alcohol Depend. 2014; 143: 95-104.
Roughly 25 years ago, the United States National Institute on Drug Abuse (US NIDA) initiated the creation of public use datasets for its National Household Survey on Drug Abuse, since re-named the National Survey on Drug Use and Health (NSDUH). The Substance Abuse and Mental Health Services Administration (SAMHSA), which assumed responsibility for the survey in 1992, has continued and expanded this effort to make the survey data available to researchers. During 2012, SAMHSA created a "Restricted-Use Data Analysis System" (R-DAS) to provide researchers with the capability to create tabulations using restricted NSDUH variables not otherwise available on the public-use files. This methods focused article is intended to help potential users of R-DAS-like online data analysis systems by (i) clarifying statistical issues involving approximation of confidence intervals (CI), (ii) providing a way to estimate CI when tabular output is suppressed with an error message; based on confidentiality restrictions, and (iii) showing how to make pairwise comparisons of estimates not otherwise allowed. For illustration purposes, some empirical estimates are presented on a topic of continuing of public health concern in the US namely, extra-medical use of pain relievers (generally opioids), where the drugs are being used to get high and otherwise outside the boundaries intended by prescribing clinicians. The R-DAS makes it possible to derive state-level estimates of male-female and age-related differences in incidence of extra-medical prescription pain reliever (EMPPR) use, not previously reported in peer-reviewed articles, and not available without research approaches described here.

PREVENTION RESEARCH

Preventing Weight Gain and Obesity: Indirect Effects Of The Family Check-Up In Early Childhood Smith JD, Montano Z, Dishion TJ, Shaw DS, Wilson MN. Prev Sci. 2014.
The early signs of obesity are observable in early childhood. Although the most promising prevention approaches are family-centered, few relevant early prevention programs exist. This study evaluated the effects of an evidence-based, home-visiting intervention, the Family Check-Up (FCU), on the trajectory of children weight gain. The FCU was designed to prevent the development of behavior problems by improving family management practices; children weight has not been an explicit target. On the basis of previous research and conceptual models, we hypothesized that intervention effects on parenting practices, specifically caregivers'use of positive behavior support (PBS) strategies in toddlerhood, would mediate improvements in children weight trajectories. A total of 731 indigent caregiver-child dyads from a multisite randomized intervention trial were examined. Observational assessment of parenting and mealtime behaviors occurred from age 2-5years. The child body mass index (BMI) was assessed yearly from age 5-9.5years. Path analysis with a latent growth model revealed a significant indirect effect of the FCU on the trajectory of BMI in later childhood. Improvements in caregivers; PBS in toddlerhood, which was related to the nutritional quality of the meals caregivers served to the child during the mealtime task, served as the intervening process. Furthermore, findings indicate that the FCU prevents progression to overweight and obese status amongst at-risk children. These study results add to existing evidence that has demonstrated that family-based interventions aimed at improving general family management skills are effective at preventing weight gain. Future directions are discussed.

Youth Tobacco Use Type and Associations With Substance Use Disorders Cavazos-Rehg PA, Krauss MJ, Spitznagel EL, Grucza RA, Bierut LJean. Addiction. 2014; 109(8): 1371-1380.
The objective of this study was to examine the associations between youth poly-tobacco use and substance use disorders. This was an analysis of data from the 2007-2011 US National Survey on Drug Use and Health. Participants wewre randomly selected, household-dwelling adolescents from the non-institutionalized, civilian population of the United States. Subjects included a total of 91,152 adolescents (aged 12-17 years). Logistic regression models were used to examine the associations between type of tobacco user (non-user, users of alternative tobacco products only, users of cigarettes only and users of cigarettes plus alternative tobacco products) with past year alcohol, marijuana or other illicit drug use disorders, adjusting for demographic and social variables. Compared with non-users of tobacco, the greatest risk for substance use disorders was among users of cigarettes plus alternative tobacco products [alcohol disorder adjusted odds ratio (aOR)=18.3, 95% confidence interval (CI)=16.2-20.6; marijuana disorder aOR=37.2, 95% CI=32.5-42.7; other drug disorder aOR=18.4, 95% CI=15.4-21.8], followed by users of cigarettes only (alcohol disorder aOR=9.6, 95% CI=8.8-10.6; marijuana disorder a OR=20.4, 95% CI=18.1-23.0; other drug disorder aOR=9.4, 95% CI=7.8-11.4), then users of alternative tobacco products only (alcohol disorder aOR=8.1, 95% CI=6.7-9.6; marijuana disorder aOR=9.2, 95% CI=7.5-11.4; other drug disorder aOR=3.2, 95% CI=2.4-4.3).Tobacco use in adolescence is associated with higher rates of substance use disorders across all tobacco users, especially among those who use cigarettes plus other tobacco products.

Who Uses A Prescription Drug Monitoring Program and How? Insights From A Statewide Survey Of Oregon Clinicians Irvine JM, Hallvik SE, Hildebran C, Marino M, Beran T, Deyo RA. J Pain. 2014; 15(7): 747-755.
Prescription drug monitoring programs (PDMPs) are relatively new but potentially useful tools to enhance prudent prescribing of controlled substances. However, little is known about the types of clinicians who make the most use of PDMPs, how these programs are incorporated into clinicians'work flow, or how clinicians and patients respond to the information. The authors therefore surveyed a random sample of Oregon providers, with 1,065 respondents. Clinicians in emergency medicine, primary care, and pain and addiction specialties were the largest number of registrants, but many frequent prescribers of controlled substances were not registered to use the PDMP. Among users, 95% reported accessing the PDMP when they suspected a patient of abuse or diversion, but fewer than half would check it for every new patient or every time they prescribe a controlled drug. Nearly all PDMP users reported that they discuss worrisome PDMP data with patients; 54% reported making mental health or substance abuse referrals, and 36% reported sometimes discharging patients from the practice. Clinicians reported frequent patient denial or anger and only occasional requests for help with drug dependence. More research is needed to optimize how clinicians use PDMPs across settings and how clinicians and patients respond to the data. This study examined differences between PDMP users and nonusers and how clinicians in various specialties use PDMPs in practice. A better understanding of effective PDMP use will facilitate access to treatment for patients with pain while curbing the prescription drug epidemic and may ultimately reduce abuse, misuse, and overdose death.

Catecholamine Levels and Delay Discounting Forecast Drug Use Among African American Youths Brody GH, Yu T, MacKillop J, Miller GE, Chen E, Obasi EM, Beach SRH. Addiction. 2014; 109(7): 1112-1118.
The aim of this study was to test hypotheses about the contributions of the catecholamine's epinephrine and norepinephrine [which serve as biological markers of life stress through sympathetic nervous system (SNS) activation], delay discounting and their interaction to the prediction of drug use among young African American adults. This was a 1-year prospective study that involved assessment of SNS activity and collection of self-report data involving delay discounting and drug use. The study setting was rural communities in the southeastern United States. Participants were a total of 456 African Americans who were 19 years of age at the beginning of the study. At age 19, participants provided overnight urine voids that were assayed for epinephrine and norepinephrine. Participants were also assessed for hyperbolic temporal discounting functions (k) and drug use. At age 20, the participants again reported their drug use. Linear regression analyses revealed that (i) catecholamine levels at age 19 forecast increases in drug use [B0.087, P0.01, 95% confidence interval (CI)0.025, 0.148] and (ii) among young men, catecholamine levels interacted positively with delay discounting to forecast increases in drug use (simple slope 0.113, P0.001, 95% CI 0.074, 0.152). Higher urinary catecholamine concentrations in their adulthood predict higher levels of drug use a year later among young African American men in the United States who engage in high, but not low, levels of delay discounting.

Juvenile Justice Girls' Depressive Symptoms and Suicidal Ideation 9 Years After Multidimensional Treatment Foster Care Kerr DCR, DeGarmo DS, Leve LD, Chamberlain P. J Consult Clin Psychol. 2014; 82(4): 684-693.
Multidimensional Treatment Foster Care (MTFC) has been found to reduce delinquency among girls in juvenile justice through 2-year follow-up. Given that such girls are at elevated risk for suicide and depression into adulthood, the authors tested MTFC effects on long-term trajectories of

suicidal ideation and depressive symptoms. Girls (N = 166; mean [SD] age = 15.3 [1.2] years; 68% White) with a recent criminal referral who were mandated to out-of-home care were enrolled in 2 sequential cohorts. Girls were randomized to receive MTFC (n = 81) or group care (GC) treatment as usual (TAU; n = 85); the second MTFC cohort also received modules targeting substance use and risky sexual behavior. Depressive symptoms and suicidal ideation were assessed repeatedly through early adulthood (mean [SD] follow-up = 8.8 [2.9] years). Suicide attempt history was assessed in early adulthood. Girls assigned to MTFC showed significantly greater decreases in depressive symptoms across the long-term follow-up than GC girls (= -.86, $p < .05$). Decreases in suicidal ideation rates were slightly stronger in MTFC than in GC as indicated by a marginal main effect (odds ratio [OR] = .92, $p < .10$) and a significant interaction that favored MTFC in the second cohort relative to the first (OR = .88, $p < .01$). There were no significant MTFC effects on suicide attempt.MTFC decreased depressive symptoms and suicidal thinking beyond the decreases attributable to time and TAU. Thus, MTFC has further impact on girls' lives than originally anticipated.

Effect Of Home Visiting By Nurses On Maternal and Child Mortality: Results Of A 2-decade Follow-up Of A Randomized Clinical Trial Olds DL, Kitzman H, Knudtson MD, Anson E, Smith JA, Cole R. JAMA Pediatr. 2014; 168(9): 800-806.
Mothers and children living in adverse contexts are at risk of premature death. The purpose of this study was to determine the effect of prenatal and infant/toddler nurse home visiting on maternal and child mortality during a 2-decade period (1990-2011).A randomized clinical trial was designed originally to assess the home visiting program effect on pregnancy outcomes and maternal and child health through child age 2 years. The study was conducted in a public system of obstetric and pediatric care in Memphis, Tennessee. Participants included primarily African American women and their first live-born children living in highly disadvantaged urban neighborhoods, who were assigned to 1 of 4 treatment groups: treatment 1 (transportation for prenatal care [n = 166]), treatment 2 (transportation plus developmental screening for infants and toddlers [n = 514]), treatment 3 (transportation plus prenatal/postpartum home visiting [n = 230]), and treatment 4 (transportation, screening, and prenatal, postpartum, and infant/toddler home visiting [n = 228]). Treatments 1 and 3 were included originally to increase statistical power for testing pregnancy outcomes. For determining mortality, background information was available for all 1138 mothers assigned to all 4 treatments and all but 2 live-born children in treatments 2 and 4 (n = 704). Inclusion of children in treatments 1 and 3 was not possible because background information was missing on too many children. Nurses sought to improve the outcomes of pregnancy, children health and development, and mothers' health and life-course with home visits beginning during pregnancy and continuing through child age 2 years. All-cause mortality in mothers and preventable-cause mortality in children (sudden infant death syndrome, unintentional injury, and homicide) derived from the National Death Index. The mean (SE) 21-year maternal all-cause mortality rate was 3.7% (0.74%) in the combined control group (treatments 1 and 2), 0.4% (0.43%) in treatment 3, and 2.2% (0.97%) in treatment 4. The survival contrast of treatments 1 and 2 combined with treatment 3 was significant (P = .007); the contrast of treatments 1 and 2 combined with treatment 4 was not significant (P = .19), and the contrast of treatments 1 and 2 combined with treatments 3 and 4 combined was significant (post hoc P = .008). At child age 20 years, the preventable-cause child mortality rate was 1.6% (0.57%) in treatment 2 and 0.0% (SE not calculable) in treatment 4; the survival contrast was significant (P = .04).Prenatal and infant/toddler home visitation by nurses is a promising means of reducing all-cause mortality among mothers and preventable-cause mortality in their first-born children living in highly disadvantaged settings clinicaltrials.gov Identifier: NCT00708695.

Computer-Based Video To Increase HIV Testing Among Emergency Department Patients Who Decline Aronson ID, Marsch LA, Rajan S, Koken J, Bania TC. AIDS Behav. 2014
The Centers for Disease Control and Prevention recommend routine HIV screening in clinical settings, including emergency departments (EDs), because earlier diagnosis enables treatment before symptoms develop and delivery of interventions to reduce continued transmission. However, patients frequently decline testing. This study delivered a 16-min video-based intervention to 160 patients who declined HIV tests in a high volume, urban ED. One third of participants (n =53) accepted an HIV test post-intervention. Interviews with a subset of participants (n =40) show that before the video, many were unaware HIV testing could be conducted without drawing blood, or that results could be delivered in 20min.

Negative Relational Schemas Predict the Trajectory Of Coercive Dynamics During Early Childhood Smith JD; Dishion TJ, Shaw DS, Wilson MN. J Abnorm Child Psychol. 2014..
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 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 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.

The Role Of Social Impact Bonds In Pediatric Health Care Crowley DM. Pediatrics. 2014; 134(2): e331-333.
In 2010, the United Kingdom's Ministry of Justice entered into an agreement with a nonprofit known as Social Finance to prevent reoffending by juvenile offenders released from prison in Peterborough, England. What made this contract unique is that the government payments to Social Finance were not based on delivery of services but instead on the level of government cost aversion from reduced recidivism. To cover the upfront cost of funding this prevention effort, Social Finance raised $5 million from private investors. If the effort successfully reduces recidivism 7.5% by 2016, then they will receive back their initial investment plus a performance bonus—totaling up to $8 million. This contract, now commonly known as a social impact bond (SIB), represents an innovative financing strategy that leverages private investment to move public services upstream to prevent greater costs in the future. Interim results from the Peterborough SIB indicated that recidivism has dropped 6% compared with the rest of England.1 Since its implementation, new SIBs are being developed to target a wide array of public problems (eg, reducing recidivism, preterm births, and special education). These bonds are attracting substantial interest and support

from the private sector. These bonds are attracting substantial interest and support from the private sector. For instance, Goldman Sachs is supporting a $9.6 million SIB to reduce recidivism on Rikers Island in New York City. In addition, they are supporting, along with the J.B. and M.K. Pritzker Family Foundation, a $7 million bond in Salt Lake City, Utah, to reduce special education needs. Goldman Sachs has also recently announced the development of a $250 million social impact financing accelerator to promote new bonds. Furthermore, Morgan Stanley has founded the Institute of Sustainable Investing with a goal of attracting more than $10 billion in client funds for investing in social finance.

Evaluation Of Two Implementation Strategies In 51 Child County Public Service Systems In Two States: Results Of A Cluster Randomized Head-to-head Implementation Trial Brown C, Chamberlain P, Saldana L, Padgett C, Wang W, Cruden G. Implement Sci. 2014; 9(1): 134.
Much is to be learned about what implementation strategies are the most beneficial to communities attempting to adopt evidence-based practices. This paper presents outcomes from a randomized implementation trial of Multidimensional Treatment Foster Care (MTFC) in child public service systems in California and Ohio, including child welfare, juvenile justice, and mental health. Fifty-one counties were assigned randomly to one of two different implementation strategies (Community Development Teams (CDT) or independent county implementation strategy (IND)) across four cohorts after being matched on county characteristics. The authors compared these two strategies on implementation process, quality, and milestone achievements using the Stages of Implementation Completion (SIC) (Implement Sci 6(1):18, 2011). Composite score for each county, combining the final implementation stage attained, the number of families served, and quality of implementation, was used as the primary outcome. No significant difference between CDT and IND was found for the composite measure. Additional analyses showed that there was no evidence that CDT increased the proportion of counties that started-up programs (i.e., placed at least one family in MTFC). For counties that did implement MTFC, those in the CDT condition served over twice as many youth during the study period as did IND. Of the counties that successfully achieved program start-up, those in the CDT condition completed the implementation process more thoroughly, as measured by the SIC. The authors found no significant differences by implementation condition on the time it took for first placement, achieving competency, or number of stages completed. This trial did not lead to higher rates of implementation or faster implementation but did provide evidence for more robust implementation in the CDT condition compared to IND implementation once the first family received MTFC services. This trial was successful from a design perspective in that no counties dropped out, even though this study took place during an economic recession. The authors believe that this methodological approach of measurement utilizing the SIC, which is comprised of the three dimensions of quality, quantity, and timing, is appropriate for a wide range of implementation and translational studies. Trial registration Trial ID: NCT00880126 (ClinicalTrials.gov).

Adolescent Deviant Peer Clustering As An Amplifying Mechanism Underlying the Progression From Early Substance Use To Late Adolescent Dependence Van Ryzin MJ, Dishion TJ. J Child Psychol Psychiatry. 2014; 55(10): 1153-1161.
Early substance use co-occurs with youths' self-organization into deviant peer groups in which substance use is central to social interaction. The authors hypothesized that the social dynamics of deviant peer groups amplify the risk of progressing from early use to later dependence, and that this influence occurs over and above escalations in use that typically accompany early substance use and membership in deviant groups. This study used a longitudinal, multimethod dataset consisting of 998 adolescents and their families. Participants were recruited from middle schools in a large metropolitan area in the Pacific Northwest. The sample was 47.3% female and ethnically diverse

(42.3% European American, 29.1% African American, and 28.6% other, including biracial). The authors examined deviant peer clustering as a mediator between early substance use and later dependence, controlling for proximal levels of use, SES, early antisocial behavior, and parental monitoring. Tobacco, alcohol, and marijuana use were assessed at ages 12, 13, and 16-17. Past-year nicotine, alcohol, and marijuana dependence (DSM-IV) was assessed at age 19. Youth and parent reports and observational data were used to assess deviant peer clustering at age 16-17, and youth reported on antisocial behavior and parental monitoring at ages 12 and 13. Early substance use predicted increased likelihood of dependence on tobacco, alcohol, and marijuana by late adolescence. Deviant peer affiliation mediated these links, even when accounting for proximal levels of substance use. Early substance use not only promotes escalations in use across adolescence but also provides entry into a deviant social context that contributes to increased risk of dependence. These results emphasize the importance of identifying and intervening in early substance use before it becomes an organizing factor in friendship selection and interaction. Deviant peer clusters are clearly an important avenue for intervention when seeking to interrupt the progression to substance dependence.

How Clinicians Use Prescription Drug Monitoring Programs: A Qualitative Inquiry
Hildebran C, Cohen DJ, Irvine JM, Foley C, O'Kane N, Beran T, Deyo RA. Pain Med. 2014; 15(7): 1179-1186.
Prescription drug monitoring programs (PDMPs) are now active in most states to assist clinicians in identifying potential controlled drug misuse, diversion, or excessive prescribing. Little is still known about the ways in which they are incorporated into workflow and clinical decision making, what barriers continue to exist, and how clinicians are sharing PDMP results with their patients. Qualitative data were collected through online focus groups and telephone interviews. Clinicians from pain management, emergency and family medicine, psychiatry/behavioral health, rehabilitation medicine, internal medicine and dentistry participated. Thirty-five clinicians from nine states participated. The authors conducted two online focus groups and seven telephone interviews. A multidisciplinary team then used a grounded theory approach coupled with an immersion-crystallization strategy for identifying key themes in the resulting transcripts. Some participants, mainly from pain clinics, reported checking the PDMP with every patient, every time. Others checked only for new patients, for new opioid prescriptions, or for patients for whom they suspected abuse. Participants described varied approaches to sharing PDMP information with patients, including openly discussing potential addiction or safety concerns, avoiding discussion altogether, and approaching discussion confrontationally. Participants described patient anger or denial as a common response and noted the role of patient satisfaction surveys as an influence on prescribing. Routines for accessing PDMP data and how clinicians respond to it vary widely. As PDMP use becomes more widespread, it will be important to understand what approaches are most effective for identifying and addressing unsafe medication use.

Comparison Of Text Messaging and Paper-and-Pencil For Ecological Momentary Assessment Of Food Craving and Intake Berkman ET; Giuliani NR, Pruitt AK. Appetite. 2014; 81: 131-137.
Electronic devices such as mobile phones are quickly becoming a popular way to gather participant reports of everyday thoughts, feelings, and behaviors, including food cravings and intake. Electronic devices offer a number of advantages over alternative methods such as paper-and-pencil (PNP) assessment including automated prompts, on-the-fly data transmission, and participant familiarity with and ownership of the devices. However, only a handful of studies have systematically compared compliance between electronic and PNP methods of ecological momentary assessment (EMA), and none have examined eating specifically. Existing comparisons

generally find greater compliance for electronic devices than PNP, but there is variability in the results across studies that may be accounted for by differences across research domains. Here, the authors compared the two EMA methods in an unexamined domain - eating - in terms of response rate and response latency, and their sensitivity to individual difference variables such as body mass index (BMI). Forty-four participants were randomly assigned to report on their food craving, food intake, and hunger four times each day for 2 weeks using either a PNP diary (N=19) or text messaging (TXT; N=25). Response rates were higher for TXT than PNP (96% vs. 70%) and latencies were faster (29min vs. 79min), and response rate and latency were less influenced by BMI in the TXT condition than in the PNP condition. These results support the feasibility of using text messaging for EMA in the eating domain, and more broadly highlight the ways that research domain-specific considerations (e.g., the importance of response latency in measuring short-lived food craving) interact with assessment modality during EMA.

Dopamine Receptor Gene D4 Polymorphisms and Early Sexual Onset: Gender and Environmental Moderation In A Sample Of African-American Youth Kogan SM, Lei M-K, Beach SRH, Brody GH, Windle M, Lee S MacKillop J, Chen Y-F. J Adolesc Health. 2014; 55(2): 235-240.
Early sexual onset and its consequences disproportionately affect African-American youth, particularly male youth. The dopamine receptor D4 gene (DRD4) has been linked to sexual activity and other forms of appetitive behavior, particularly for male youth and in combination with environmental factors (gene environment [GE] effects). The differential susceptibility perspective suggests that DRD4 may exert this effect by amplifying the effects of both positive and negative environments. The authors hypothesized that DRD4 status would amplify the influence of both positive and negative neighborhood environments on early sexual onset among male, but not female, African-Americans. Hypotheses were tested with self-report, bio specimen, and census data from five prospective studies of male and female African-American youth in rural Georgia communities, N=1,677. Early sexual onset was defined as intercourse before age14.No significant GE findings emerged for female youth. Male youth with a DRD4 long allele were more likely than those with two DRD4 short alleles to report early sexual onset in negative community environments and not to report early onset in positive community environments. Dopaminergic regulation of adolescent sexual behaviors may operate differently by gender. DRD4 operated as an environmental amplification rather than a vulnerability factor.

Effects Of the Communities That Care System On Cross-sectional Profiles Of Adolescent Substance Use and Delinquency Van Horn ML, Fagan AA, Hawkins JD, Oesterle S. Am J Prev Med. 2014; 47(2): 188-197.
Adolescent substance use and delinquency are major public health problems. Although community-based prevention strategies have been recommended to produce population-level reductions in rates of substance use and delinquency, few models show evidence of effectiveness. The objective of this study was to test the efficacy of a community-based prevention system, Communities That Care (CTC), in reducing community rates of problem behaviors, particularly effects on specific profiles of adolescent substance use and delinquency in eighth- and tenth-graders. Twenty-four communities were randomized to CTC intervention or control groups. Data were collected from 14,099 8th- and 10th-grade students in these communities using anonymous cross-sectional surveys in 2004 and 2010 and analyzed in 2012. Outcomes were four different profiles of self-reported substance use and delinquency in 8th grade and five profiles in 10th grade. In the cross-sectional 2010 data, there was no intervention effect on the probability of experimenting with substances or of substance use coupled with delinquent activities for either grade. However, tenth-graders in intervention

communities were significantly less likely to be alcohol users than those in control communities (OR=0.69, CI=0.48, 1.00).Cross-sectional population surveys showed evidence of CTC effects in reducing tenth-grade alcohol users but not experimenters. A community-wide reduction in adolescent alcohol use is important because alcohol is the most commonly used illicit substance during adolescence, and early initiation of alcohol use has been associated with alcohol-related disorders in adulthood. Failure to find hypothesized effects on experimenters qualifies these results.

Mindfulness Training Targets Neurocognitive Mechanisms Of Addiction At The Attention-Appraisal-Emotion Interface Garland EL, Froeliger B, Howard MO; Front Psychiatry; 2014 Jan 10; 173 (4): 1664-0640.
Prominent neuroscience models suggest that addictive behavior occurs when environmental stressors and drug-relevant cues activate a cycle of cognitive, affective, and psychophysiological mechanisms, including dysregulated interactions between bottom-up and top-down neural processes, that compel the user to seek out and use drugs. Mindfulness-based interventions (MBIs) target pathogenic mechanisms of the risk chain linking stress and addiction. This review describes how MBIs may target neurocognitive mechanisms of addiction at the attention-appraisal-emotion interface. Empirical evidence is presented suggesting that MBIs ameliorate addiction by enhancing cognitive regulation of a number of key processes, including: clarifying cognitive appraisal and modulating negative emotions to reduce perseverative cognition and emotional arousal; enhancing metacognitive awareness to regulate drug-use action schema and decrease addiction attentional bias; promoting extinction learning to uncouple drug-use triggers from conditioned appetitive responses; reducing cue-reactivity and increasing cognitive control over craving; attenuating physiological stress reactivity through parasympathetic activation; and increasing savoring to restore natural reward processing. Treatment and research implications of our neurocognitive framework are presented. The authors conclude by offering a temporally sequenced description of neurocognitive processes targeted by MBIs through a hypothetical case study. Their neurocognitive framework has implications for the optimization of addiction treatment with MBIs.

Effects Of Mindfulness-Oriented Recovery Enhancement On Reward Responsiveness and Opioid Cue-reactivity Garland EL, Froeliger B, Howard MO. Psychopharmacology (Berl). 2014; 231(16): 3229-3238.
Dysregulated reward processing is a hallmark feature of drug addiction; however, scant research has evaluated restructuring reward processing in the context of addiction treatment. The authors examined effects of Mindfulness-Oriented Recovery Enhancement (MORE) on reward responsiveness (RR) and opioid cue-reactivity in a sample of chronic pain patients with opioid use problems. The authors previously reported that MORE decreased pain, opioid misuse, and craving relative to a social support control group (SG). Here, they examined whether these outcomes were linked to changes in RR in a subset of participants. Participants were chronic pain patients (71% women, age 46.613.9) who received MORE (n=20) or SG (n=29). RR was measured before and after 8weeks of treatment via heart rate (HR) and heart rate variability (HRV) responses during a dot probe task that included opioid-related, pain-related, and natural reward stimuli, as well as craving ratings. The MORE group, who reported decreased opioid misuse and opioid craving during treatment, evidenced less subjective opioid cue-reactivity, greater HR decelerations, and greater increases in HRV to all cues after treatment compared to the SG; HR and HRV effects were most pronounced for natural reward cues. Within the MORE group, HR deceleration to natural reward cues was correlated with increased subjective arousal to the cues, whereas HR deceleration to opioid cues was correlated with decreased subjective arousal. Effects of MORE on craving were mediated by enhanced RR.Results suggest that during treatment with MORE, cardiac-autonomic

responsiveness to non-drug reward increases, while reactivity to opioid reward decreases. Studies are needed to discern whether changes in RR were a result or a determinant of reductions in opioid misuse and craving. RR may play a role in addiction treatment.

Replicating Cluster Subtypes For the Prevention Of Adolescent Smoking and Alcohol Use Babbin SF, Velicer WF, Paiva AL, Brick LAD, Redding CA. Addict Behav. 2014; 40C: 57-65.
Substance abuse interventions tailored to the individual level have produced effective outcomes for a wide variety of behaviors. One approach to enhancing tailoring involves using cluster analysis to identify prevention subtypes that represent different attitudes about substance use. This study applied this approach to better understand tailored interventions for smoking and alcohol prevention. Analyses were performed on a sample of sixth graders from 20 New England middle schools involved in a 36-month tailored intervention study. Most adolescents reported being in the Acquisition Precontemplation (aPC) stage at baseline: not smoking or not drinking and not planning to start in the next six months. For smoking (N=4059) and alcohol (N=3973), each sample was randomly split into five subsamples. Cluster analysis was performed within each subsample based on three variables: Pros and Cons (from Decisional Balance Scales), and Situational Temptations. Across all subsamples for both smoking and alcohol, the following four clusters were identified: (1) Most Protected (MP; low Pros, high Cons, low Temptations); (2) Ambivalent (AM; high Pros, average Cons and Temptations); (3) Risk Denial (RD; average Pros, low Cons, average Temptations); and (4) High Risk (HR; high Pros, low Cons, and very high Temptations).Finding the same four clusters within aPC for both smoking and alcohol, replicating the results across the five subsamples, and demonstrating hypothesized relations among the clusters with additional external validity analyses provide strong evidence of the robustness of these results. These clusters demonstrate evidence of validity and can provide a basis for tailoring interventions.

Opioid Attentional Bias and Cue-elicited Craving Predict Future Risk Of Prescription Opioid Misuse Among Chronic Pain Patients Garland EL, Howard MO. Drug Alcohol Depend. 2014.
Some chronic pain patients receiving long-term opioid analgesic pharmacotherapy are at risk for misusing opioids. Like other addictive behaviors, risk of opioid misuse may be signaled by an attentional bias (AB) towards drug-related cues. The purpose of this study was to examine opioid AB as a potential predictor of opioid misuse among chronic pain patients following behavioral treatment. Chronic pain patients taking long-term opioid analgesics (n=47) completed a dot probe task designed to assess opioid AB, as well as self-report measures of opioid misuse and pain severity, and then participated in behavioral treatment. Regression analyses examined opioid AB and cue-elicited craving as predictors of opioid misuse at 3-month post treatment follow-up. Patients who scored high on a measure of opioid misuse risk following treatment exhibited significantly greater opioid AB scores than patients at low risk for opioid misuse. Opioid AB for 200ms cues and cue-elicited craving significantly predicted opioid misuse risk 20 weeks later, even after controlling for pre-treatment opioid dependence diagnosis, opioid misuse, and pain severity (Model R(2)=.50).Biased initial attentional orienting to prescription opioid cues and cue-elicited craving may reliably signal future opioid misuse risk following treatment. These measures may therefore provide potential prognostic indicators of treatment outcome.

Changing Implicit Attitudes Toward Smoking: Results From A Web-based Approach-avoidance Practice Intervention Macy JT, Chassin L, Presson CC, Sherman JW. J Behav Med. 2014.
Implicit attitudes have been shown to predict smoking behaviors. Therefore, an important goal is the development of interventions to change these attitudes. This study assessed the effects of a web-

based intervention on implicit attitudes toward smoking and receptivity to smoking-related information. Smokers (N=284) were recruited to a two-session web-based study. In the first session, baseline data were collected. Session two contained the intervention, which consisted of assignment to the experimental or control version of an approach-avoidance task and assignment to an anti-smoking or control public service announcement (PSA), and post-intervention measures. Among smokers with less education and with plans to quit, implicit attitudes were more negative for those who completed the approach-avoidance task. Smokers with more education who viewed the anti-smoking PSA and completed the approach-avoidance task spent more time reading smoking-related information. An approach-avoidance task is a potentially feasible strategy for changing implicit attitudes toward smoking and increasing receptivity to smoking-related information.

Treating Chronic Pain: The Need For Non-opioid Options Garland EL. Expert Rev Clin Pharmacol. 2014; 7(5): 545-550.
Chronic pain is a prevalent problem that exacts a significant toll on society. The medical system has responded to this issue by implementing pain management services centered on opioid pharmacotherapy. However, for many chronic pain patients, the analgesic efficacy of long-term opioids is limited. Moreover, chronic exposure to opioids can result in opioid misuse, addiction, and risk of overdose. As such, non-opioid treatment options are needed. This article first provides a selective review of cognitive, affective, and psychophysiological mechanisms implicated in chronic pain to be targeted by novel non-opioid treatments. Next, it briefly details one such treatment approach, Mindfulness-Oriented Recovery Enhancement, and describes evidence suggesting that this intervention can disrupt the risk chain linking chronic pain to prescription opioid misuse.

Commentary--Project Towards No Drug Abuse: An Evidence-based Drug Abuse Prevention Program Sussman S, Valente TW, Rohrbach LA, Dent CW, Sun P. J Prim Prev. 2014; 35(4): 233-237.
Project Towards No Drug Abuse (Project TND) is a research-based program that has been examined over seven group-randomized controlled trials. In all trials, an effect has been found on hard drug use. An effect has been found on alcohol use in four trials, and on cigarettes and marijuana in two trials. (Arguably, an effect is found on marijuana in three trials.) Program effects on violence-related behavior were established in earlier trials, though such effects were not assessed in later trials. Certainly, as in most scientific studies, there are limitations in the interpretation of the effects obtained, particularly regarding cigarette and marijuana use and violence-related behavior, and more empirical work is needed. For Project TND, however, numerous trial replications have been completed, and the effects within each trial could not have been obtained by chance alone more than 10 % of the time (two-tailed). These results suggest that Project TND is indeed evidence-based. To be evidence-based means that evidence has accumulated to suggest that the program is likely to work, at least under conditions that are comparable to those in which it has been tested.

Clarifying the Neural Basis For Incentive Salience Of Tobacco Cues In Smokers Gray JC, Amlung MT, Acker J, Sweet LH, Brown CL, MacKillop J. Psychiatry Res. 2014; 223(3): 218-225.
In functional magnetic resonance imaging (fMRI) studies, smoking cues have been found to elicit increases in brain activity in regions associated with processing rewarding and emotional stimuli. However, most smoking cue studies to date have reported effects relative to neutral control stimuli with no incentive properties, making it unclear whether the observed activation pertains to value in general or the value of cigarettes in particular. The current fMRI study sought to clarify the neural activity reflecting tobacco-specific incentive value versus domain-general incentive value by examining smoking cues, neutral cues, and a third set of cues, monetary cues, which served as an

active control condition. Participants were 42 male daily smokers. Compared to neutral cues, significantly greater activation was found in the left ventral striatum in response to tobacco and money cues. Monetary cues also elicited significantly increased activation in the right inferior frontal gyrus and cuneus compared to the other two cue types. Overall, the results suggest that the salience of monetary cues was the highest and, as a result, might have reduced the incentive salience of tobacco cues.

A Mixed Methods Approach To Network Data Collection Rice E, Holloway IW, Barman-Adhikari A, Fuentes D, Brown C H, Palinkas LA. Field Methods. 2014; 26(3): 252-268.
There is a growing interest in examining network processes with a mix of qualitative and quantitative network data. Research has consistently shown that free recall name generators entail recall bias and result in missing data that affects the quality of social network data. This study describes a mixed methods approach for collecting social network data, combining a free recall name generator in the context of an online survey with network relations data coded from transcripts of semi-structured qualitative interviews. The combined network provides substantially more information about the network space, both quantitatively and qualitatively. While network density was relatively stable across networks generated from different data collection methodologies, there were noticeable differences in centrality and component structure across networks. The approach presented here involved limited participant burden and generated more complete data than either technique alone could provide. The authors make suggestions for further development of this method.

Feasibility Of Providing Interventions For Injection Drug Users In Pharmacy Settings: A Case Study Among San Francisco Pharmacists Rose VJ, Lutnick A, Kral AH. J Psychoactive Drugs. 2014; 46(3): 226-232.
In addition to syringe exchange programs, pharmacies are important venues where injection drug users (IDUs) can access non-prescription syringes and other prevention interventions. This study assessed the feasibility of providing a range of interventions for IDUs in pharmacy settings. Semi-structured qualitative interviews were conducted with 23 participants (policy makers, owner/managers, dispensing pharmacists, and pharmacy staff) from independent and chain/retail pharmacies in San Francisco, California, USA. The highest level of support was for a coupon syringe program and educational materials. Several overarching themes illustrate challenges to implementing pharmacy-based preventive interventions: time, space, sufficient staff, pharmacist training, legal considerations, pharmacist attitudes toward IDUs, and cost and reimbursement issues. This study provides concrete examples of the types of preventive services that pharmacists support and consider feasible, and illustrates that pharmacists welcome the opportunity to broaden their role as critical partners in public health matters related to injection drug use.

A Multiple Imputation Strategy For Sequential Multiple Assignment Randomized Trials Shortreed SM, Laber E, Scott ST, Pineau J, Murphy SA. Stat Med. 2014; 33(24): 4202-4214.
Sequential multiple assignment randomized trials (SMARTs) are increasingly being used to inform clinical and intervention science. In a SMART, each patient is repeatedly randomized over time. Each randomization occurs at a critical decision point in the treatment course. These critical decision points often correspond to milestones in the disease process or other changes in a patient health status. Thus, the timing and number of randomizations may vary across patients and depend on evolving patient-specific information. This presents unique challenges when analyzing data from a SMART in the presence of missing data. This paper presents the first comprehensive discussion of missing data issues typical of SMART studies: we describe five specific challenges and propose a

flexible imputation strategy to facilitate valid statistical estimation and inference using incomplete data from a SMART. To illustrate these contributions, we consider data from the Clinical Antipsychotic Trial of Intervention and Effectiveness, one of the most well-known SMARTs to date. Copyright 2014 John Wiley & Sons, Ltd.

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. 2014.
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.

Sexual Esteem In Emerging Adulthood: Associations With Sexual Behavior, Contraception Use, and Romantic Relationships Maas MK, Lefkowitz ES. J Sex Res. 2014; 1-12.
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.

Temporal Associations Between Substance UseaAnd Delinquency Among Youth With A First Time Offense Hunter SB, Miles JNV, Pedersen ER, Ewing BA; D'Amico EJ. Addict Behav. 2014 Jun; 39(1081-6): 1873-2327
Substance use and delinquency among adolescents have been shown to be positively associated; however, the temporal relationship is not well understood. Examining the association between delinquency and substance use is especially relevant among adolescents with a first-time substance use related offense as they are at-risk for future problems. Data from 193 adolescents at time of diversion program entry and six months later was examined using cross-lagged path analysis to determine whether substance use and related consequences were associated with other types of delinquency across time. Results demonstrated that delinquency at program entry was related to subsequent reports of heavy drinking and alcohol consequences, but not marijuana use or its consequences. In contrast, alcohol and marijuana use at program entry were not related to future reports of delinquency. Findings emphasize the need to build in comprehensive assessments and interventions for youth with a first time offense in order to prevent further escalation of substance use and criminal behaviors.

Disrupting the Downward Spiral Of Chronic Pain and Opioid Addiction With Mindfulness-Oriented Recovery Enhancement: A Review Of Clinical Outcomes and Neurocognitive Targets Garland EL. J Pain Palliat Care Pharmacother. 2014 Jun; 28(122-9): 1536-1539.
Prescription opioid misuse and addiction among chronic pain patients are problems of growing medical and social significance. Chronic pain patients often require intervention to improve their well-being and functioning, and yet, the most commonly available form of pharmacotherapy for chronic pain is centered on opioid analgesics--drugs that have high abuse liability. Consequently, health care and legal systems are often stymied in their attempts to intervene with individuals who suffer from both pain and addiction. As such, novel, nonpharmacologic interventions are needed to complement pharmacotherapy and interrupt the cycle of behavioral escalation. The purpose of this paper is to describe how the downward spiral of chronic pain and prescription opioid misuse may be targeted by one such intervention, Mindfulness-Oriented Recovery Enhancement (MORE), a new behavioral treatment that integrates elements from mindfulness training, cognitive-behavioral therapy, and positive psychology. The clinical outcomes and neurocognitive mechanisms of this intervention are reviewed with respect to their effects on the risk chain linking chronic pain and prescription opioid misuse. Future directions for clinical and pharmacologic research are discussed.

Web-based Screening and Brief Intervention For Student Marijuana Use In A University Health Center: Pilot Study To Examine the Implementation Of ECHECKUP TO GO In Different Contexts Palfai TP, Saitz R, Winter M, Brown TA, Kypri K, Goodness TM; O'Brien LM; Lu J. Addict Behav. 2014; 39(9): 1346-1352.
This pilot study sought to test the feasibility of procedures to screen students for marijuana use in Student Health Services (SHS) and test the efficacy of a web-based intervention designed to reduce marijuana use and consequences. Students were asked to participate in voluntary screening of health behaviors upon arrival at SHS. One hundred and twenty-three students who used marijuana at least monthly completed assessments and were randomized to one of four intervention conditions in a 2 (intervention: Marijuana eCHECKUP TO GO vs. control) 2 (site of intervention: on-site vs. off-site) between-groups design. Follow-up assessments were conducted online at 3 and 6 months. Latent growth modeling was used to provide effect size estimates for the influence of intervention on outcomes. One thousand and eighty undergraduate students completed screening. The intervention did not influence marijuana use frequency. However, there was evidence of a small overall intervention effect on marijuana-related consequences and a medium effect in stratified

analyses in the on-site condition. Analyses of psychological variables showed that the intervention significantly reduced perceived norms regarding peer marijuana use. These findings demonstrate that it is feasible to identify marijuana users in SHS and deliver an automated web-based intervention to these students in different contexts. Effect size estimates suggest that the intervention has some promise as a means of correcting misperceptions of marijuana use norms and reducing marijuana-related consequences. Future work should test the efficacy of this intervention in a full scale randomized controlled trial.

Taking A Life Course Approach To Studying Substance Use Treatment Among A Community Cohort Of African American Substance Users Evans-Polce RJ, Doherty EE, Ensminger ME. Drug Alcohol Depend. 2014; 142: 216-223.
Life course theory emphasizes the need to examine a wide variety of distal factors along with proximal factors, longitudinally. Yet research on who obtains substance use treatment is generally cross-sectional and limited to examining developmentally proximal factors (e.g., substance use severity) and demographic factors. To investigate treatment within a life-course framework, the authors studied 522 drug and/or alcohol users from a community cohort of African Americans followed prospectively from age 6. Developmentally distal factors of childhood and adolescent social behavior, family environment, academic achievement, mental health, and substance use along with the key proximal factors of substance use severity and socioeconomic status were examined using regression analyses to assess their impact on obtaining adult substance use treatment. One-fifth of the study population obtained treatment for substance use by age 32 (20.5%). Although adult socioeconomic status was not associated with substance use treatment in adulthood in the multivariable model, the proximal factor of substance use severity was a strong predictor of obtaining substance use treatment, as expected. After including several developmentally distal factors in the model, childhood aggression also had an independent effect on adult substance use treatment, above and beyond substance use severity. These findings emphasize the importance of using a life course framework when exploring predictors of treatment; early life characteristics are important influences beyond the more proximal factors in adulthood. Research should continue to take a life course approach to better understand pathways to substance use treatment.

The Mediating Role Of Avoidance Coping Between IPV Victimization, Mental Health, and Substance Abuse Among Women Experiencing Bidirectional IPV Flanagan JC, Jaquier V, Overstreet N, Swan SC, Sullivan TP. Psychiatry Res. 2014.
Avoidance coping is consistently linked with negative mental health outcomes among women experiencing intimate partner violence (IPV). This study extended the literature examining the potentially mediating role of avoidance coping strategies on both mental health and substance use problems to a highly generalizable, yet previously unexamined population (i.e., women experiencing bidirectional IPV) and examined multiple forms of IPV (i.e., psychological, physical, and sexual) simultaneously. Among a sample of 362 women experiencing bidirectional IPV, four separate path models were examined, one for each outcome variable. Avoidance coping mediated the relationships between psychological and sexual IPV victimization and the outcomes of PTSD symptom severity, depression severity, and drug use problems. Findings indicate nuanced associations among IPV victimization, avoidance coping, and mental health and substance use outcomes.

Describing and Predicting Developmental Profiles Of Externalizing Problems From Childhood To Adulthood Petersen IT, Bates JE, Dodge KA, Lansford JE, Pettit GS. Dev Psychopathol. 2014; 1-28.
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.

Regularly Drinking Alcohol Before Sex In The United States: Effects Of Relationship Status And Alcohol Use Disorders Thompson Jr, RG; Eaton NR, Hu M-C, Grant BF, Hasin DS. Drug Alcohol Depend. 2014; 141: 167-170.
Drinking alcohol before sex increases the likelihood of engaging in sexual risk behaviors and risk for HIV infection. Relationship status (single versus partnered) and alcohol use disorders (AUD) are associated with each other and sexual risk behaviors, yet have not been examined as predictors of drinking alcohol before sex, using national data. This study examined whether relationship status and AUD increased the likelihood of regularly drinking alcohol before sex in a nationally representative sample. The main and additive interaction effects of relationship status and AUD on regularly drinking alcohol before sex were analyzed among sexually active drinkers (N=17,491) from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Regularly drinking alcohol before sex was defined as drinking alcohol most or all of the time before sex. After adjustment for controls, relationship status (AOR=3.51; CI=2.59-4.75) and AUD (AOR=6.24; CI=5.16-7.53) increased the likelihood of regularly drinking alcohol before sex and interacted to differentially increase this risk, with the effect of being single on the likelihood of regularly drinking alcohol before sex increased among participants with AUD (p<.001).This study reinforces the importance of relationship status and AUD to the risk for regularly drinking alcohol before sex. Public health efforts should target alcohol and HIV prevention messages to single adults, particularly those with AUD, highlighting their risk for regularly drinking alcohol before sex.

Effects Of A Couple-based Intervention To Reduce Risks For HIV, HCV, and STIs Among Drug-involved Heterosexual Couples In Kazakhstan: A Randomized Controlled Trial El-Bassel N, Gilbert L, Terlikbayeva A, Beyrer C, Wu E, Chang M, Hunt T, Ismayilova L, Shaw SA, Primbetova S, Rozental Y, Zhussupov B, Tukeyev M. J Acquir Immune Defic Syndr. 2014; 67(2): 196-203.
Project Renaissance is a randomized controlled trial of an HIV/hepatitis C virus (HCV)/sexually transmitted infection (STI) prevention intervention conducted in Almaty, Kazakhstan. The authors

hypothesized that couples assigned to the intervention of interest will have lower incidence of HIV, HCV, STIs, rates of unprotected sex, and unsafe injection over the 12-month follow-up period compared with those assigned to an attention control arm.A total of 300 couples (600 participants) where one or both partners reported injecting drugs in the past 90 days were randomized to 1 of 2 arms: (1) a 5-session HIV/HCV/STI prevention intervention (risk reduction: RR) or (2) a 5-session Wellness Promotion (WP) intervention. Over the 12-month follow-up period, assignment to RR compared with WP significantly lowered the incidence of HCV infection by 69% [incidence rate ratios (IRR) = 0.31, 95% (CI) confidence interval: 0.10 to 0.90, P = 0.031]. Although differences were not statistically significant, RR participants had a lower incidence of HIV infection by 51% (IRR = 0.49, 95% CI: 0.16 to 1.48, P = 0.204) and any STI by 37% (IRR = 0.63, 95% CI: 0.21 to 1.93, P = 0.418) than WP participants. RR participants reported significantly fewer numbers of unprotected vaginal sex acts with their study partners (IRR = 0.58, 95% CI: 0.36 to 0.93, P = 0.024) and more consistent condom use (odds ratios = 2.30, 95% CI: 1.33 to 4.00, P = 0.003) over the entire follow-up period compared with WP participants. Project Renaissance demonstrated a significant effect for biological and behavioral endpoints. Findings draw attention to an HIV/HCV/STI prevention intervention strategy that can be scaled up for drug-involved couples in harm reduction programs, drug treatment, and criminal justice settings.

Identifying the Facets Of Impulsivity That Explain the Relation Between ADHD Symptoms and Substance Use In A Nonclinical Sample Roberts W, Peters JR, Adams ZW, Lynam DR, Milich R. Addict Behav. 2014; 39(8): 1272-1277.
Adults with attention-deficit/hyperactivity disorder (ADHD) are at higher risk to use substances than their nonclinical peers. Increased levels of impulsivity are generally thought to contribute to their increased levels of risk. Impulsivity is a multifaceted construct, however, and little research to date has attempted to identify which facets of impulsivity contribute to the increased rates of substance abuse among individuals with ADHD. The current study examined the relation among ADHD symptom clusters (i.e., hyperactivity/impulsivity and inattention), substance use rates (i.e., alcohol use, nicotine use, and marijuana use), and personality processes associated with impulsive behavior in a group of young adults. Participants were 361 undergraduate students. Both symptom clusters were positively associated with rates of substance use. Specifically, hyperactive/impulsive symptoms were associated with alcohol and nicotine use, and inattentive symptoms were associated with alcohol use. Several pathways from hyperactive/impulsive symptoms to alcohol, nicotine, and marijuana use via specific facets of impulsivity were identified. These findings have implications for understanding the relation between ADHD symptoms and substance use, as well as clinical implications for preventing and treating substance use problems in individuals with symptoms of ADHD.

Effect Of A Primary Care Based Brief Intervention Trial Among Risky Drug Users On Health-related Quality Of Life Baumeister SE, Gelberg L, Leake BD, Yacenda-Murphy J, Vahidi M, Andersen RM. Drug Alcohol Depend. 2014; 142: 254-261.
Improvement in quality of life (QOL) is a long term goal of drug treatment. Although some brief interventions have been found to reduce illicit drug use, no trial among adult risky (moderate non-dependent) drug users has tested effects on health-related quality of life. A single-blind randomized controlled trial of patients enrolled from February 2011 to November 2012 was conducted in waiting rooms of five federally qualified health centers. 413 adult primary care patients were identified as risky drug users using the WHO-ASSIST and 334 (81% response; 171 intervention, 163 control) consented to participate in the trial. Three-month follow-ups were completed by 261 patients (78%). Intervention patients received the QUIT intervention of brief clinician advice and up

to two drug-use health telephone sessions. The control group received usual care and information on cancer screening. Outcomes were three-month changes in the Short Form Health Survey (SF-12) mental health component summary score (MCS) and physical health component summary score (PCS).The average treatment effect (ATE) was non-significant for MCS (0.2 points, p-value=0.87) and marginally significant for PCS (1.7 points, p-value=0.08). The average treatment effect on the treated (ATT) was 0.1 (p-value=0.93) for MCS and 1.9 (p-value=0.056) for PCS. The effect on PCS was stronger at higher (above median) baseline number of drug use days: ATE=2.7, p-value=0.04; ATT=3.21, p-value=0.02.The trial found a marginally significant effect on improvement in PCS, and significant and stronger effect on the SF-12 physical component among patients with greater frequency of initial drug use.

Improving Youth Mental Health Through Family-Based Prevention In Family Homeless Shelters Lynn CJ, Acri MC, Goldstein L, Bannon W, Beharie N, McKay MM. Child Youth Serv Rev. 2014; 44: 243-248.
This exploratory study examines changes in suicidal ideation among a sample (N = 28) of homeless youth, ages 11-14, residing within family shelters in a large metropolitan area. Changes in suicidal ideation from pretest to posttest are compared across two group approaches to delivering HIV prevention. Youth and their families participating in the HOPE Family Program, incorporating a family strengthening approach, are compared to those receiving a traditional health education-only approach. Multivariate analyses reveal that youth in the HOPE Family Program were 13 times more likely to report a decrease of suicidal ideation. These findings indicate that health education programs integrating a family strengthening approach hold promise for positively impacting mental health outcomes for vulnerable youth.

Peer Rejection, Affiliation With Deviant Peers, Delinquency, and Risky Sexual Behavior Lansford JE, Dodge KA, Fontaine RG, Bates JE, Pettit GS. J Youth Adolesc. 2014; 43(10): 1742-1751.
Risky sexual behavior poses significant health risks by increasing sexually transmitted infections and unintended pregnancies. Previous research has documented many factors related to risky sexual behavior. This study adds to the literature by proposing a prospective, developmental model of peer factors related to risky sexual behavior. Developmental pathways to risky sexual behavior were examined in a sample of 517 individuals (51% female; 82% European American, 16% African American, 2% other) followed from age 5-27. Structural equation models examined direct and indirect effects of peer rejection (assessed via peer nominations at ages 5, 6, 7, and 8), affiliation with deviant peers (assessed via self-report at ages 11 and 12), and delinquency (assessed via maternal report at ages 10 and 16) on risky sexual behavior (assessed via self-report at age 27). More peer rejection during childhood, affiliation with deviant peers during pre- adolescence, and delinquency in childhood and adolescence predicted more risky sexual behavior through age 27, although delinquency at age 16 was the only risk factor that had a significant direct effect on risky sexual behavior through age 27 above and beyond the other risk factors. Peer rejection was related to subsequent risk factors for girls but not boys. Peer risk factors as early as age 5 shape developmental pathways through childhood and adolescence and have implications for risky sexual behavior into adulthood.

Phylogenetic Clustering Of Hepatitis C Virus Among People Who Inject Drugs In Vancouver, Canada Jacka B, Applegate T, Krajden M, Olmstead A, Harrigan PR, Marshall BDL, DeBeck K, Milloy M-J, Lamoury F, Pybus OG, Lima VD, Magiorkinis G, Montoya V, Montaner J, Joy J, Woods C, Dobrer S, Dore GJ, Poon AFY, Grebely J. Hepatology. 2014.

Little is known about factors associated with hepatitis C virus (HCV) transmission among people who inject drugs (PWID). Phylogenetic clustering and associated factors were evaluated among PWID in Vancouver, Canada. Data were derived from the Vancouver Injection Drug Users Study. Participants who were HCV antibody-positive at enrolment and those with HCV antibody seroconversion during follow-up (1996 to 2012) were tested for HCV RNA and sequenced (Core-E2 region). Phylogenetic trees were inferred using maximum likelihood analysis and clusters were identified using ClusterPicker (90% bootstrap threshold, 0.05 genetic distance threshold). Factors associated with clustering were assessed using logistic regression. Among 655 eligible participants, HCV genotype prevalence was: G1a: 48% (n=313), G1b: 6% (n=41), G2a: 3% (n=20), G2b: 7% (n=46), G3a: 33% (n=213), G4a: <1% (n=4), G6a: 1% (n=8), G6e: <1% (n=1), and unclassifiable: 1% (n=9). The mean age was 36 years, 162 (25%) were female, and 164 (25%) were HIV+. Among 501 participants with HCV G1a and G3a, 31% (n=156) were in a pair/cluster. Factors independently associated with phylogenetic clustering included: age <40 (versus age 40, adjusted odds ratio [AOR]=1.64; 95% confidence interval [CI] 1.03, 2.63), human immunodeficiency virus (HIV) infection (AOR=1.82; 95% CI 1.18, 2.81), HCV seroconversion (AOR=3.05; 95% CI 1.40, 6.66), and recent syringe borrowing (AOR 1.59; 95% CI 1.07, 2.36). In this sample of PWID, one-third demonstrated phylogenetic clustering. Factors independently associated with phylogenetic clustering included younger age, recent HCV seroconversion, prevalent HIV infection, and recent syringe borrowing. Strategies to enhance the delivery of prevention and/or treatment strategies to those with HIV and recent HCV seroconversion should be explored, given an increased likelihood of HCV transmission in these subpopulations.

Relations Between Trait Impulsivity, Behavioral Impulsivity, Physiological Arousal, and Risky Sexual Behavior Among Young Men Derefinko KJ, Peters JR, Eisenlohr-Moul TA, Walsh EC, Adams ZW, Lynam DR. Arch Sex Behav. 2014; 43(6): 1149-1158.
The current study examined how impulsivity-related traits (negative urgency, sensation seeking, and positive urgency), behavioral measures of risk taking and reward seeking, and physiological reactivity related to three different risky sexual behaviors in sexually active undergraduate men (N = 135). Regression analyses indicated that sensation seeking and behavioral risk-taking predicted unique variance in number of sexual partners. These findings suggest that, for young men, acquisition of new partners is associated with need for excitement and reward and willingness to take risks to meet those needs. Sensation seeking, behavioral risk-taking, and skin conductance reactivity to arousing stimuli was related to ever having engaged in sex with a stranger, indicating that, for men, willingness to have sex with a stranger is related not only to the need for excitement and risk-taking but also with innate responsiveness to arousing environmental triggers. In contrast, regression analyses indicated that young men who were impulsive in the context of negative emotions were less likely to use condoms, suggesting that emotion-based impulsivity may be an important factor in negligent prophylactic use. This study adds to the current understanding of the divergence between the correlates of risky sexual behaviors and may lend utility to the development of individualized HIV prevention programming.

Impact Of Intimate Partner Forced Sex On HIV Risk Factors In Physically Abused African American and African Caribbean Women Draughon JE, Lucea MB, Campbell JC, Paterno MT, Bertrand DR, Sharps PW, Campbell DW, Stockman JK. J Immigr Minor Health. 2014.
The authors examined associations between intimate partner forced sex (IPFS) and HIV sexual risk behaviors among physically abused Black women. Women aged 18-55 in intimate relationships were interviewed in health clinics in Baltimore, MD and St. Thomas and St. Croix, US Virgin Islands (USVI). Of 426 physically abused women, 38% experienced IPFS; (Baltimore=44 and

USVI=116). USVI women experiencing IPFS were more likely to have 3+ past-year sex partners (AOR 2.06, 95% CI 1.03-4.14), casual sex partners (AOR 2.71, 95% CI 1.42-5.17), and concurrent sex partners (AOR 1.94, 95% CI 1.01-3.73) compared to their counterparts. Baltimore women reporting IPFS were more likely to have exchanged sex (AOR 3.57, 95% CI 1.19-10.75). Women experiencing IPFS were more likely to report their abuser having other sexual partners in Baltimore (AOR 3.30, 95% CI 1.22-8.88) and USVI (AOR 2.03, 95% CI 1.20-3.44). Clinicians should consider the influence of IPFS on individual and partnership HIV sexual risk behaviors.

Daily Physical Activity And Alcohol Use Across the Adult Lifespan Conroy DE, Ram N, Pincus AL, Coffman DL, Lorek AE, Rebar AL, Roche M. J. Health Psychol. 2014.
In contrast to proposals that physical activity (PA) can be a substitute for alcohol use, people who engage in greater overall PA generally consume more alcohol on average than less-active peers. Acknowledging that both PA and alcohol use vary considerably from day-to-day, this study evaluated whether established associations reflect daily behavioral coupling within-person, are an artifact of procedures that aggregate behavior over time, or both. Methods: A life span sample of 150 adults (aged 19-89 years) completed three 21-day measurement bursts of a daily diary study. At the end of each day, they reported on their PA and alcohol consumption. Data were analyzed in a negative binomial multilevel regression. As expected, both behaviors exhibited limited between-person variation. After controlling for age, gender, and seasonal and social calendar influences, daily deviations in PA were significantly associated with daily total alcohol use. Once the within-person process linking PA and alcohol use was controlled, usual PA and total alcohol use were not associated. The authors conclude that the established between-person association linking PA and alcohol use reflects the aggregation of a daily process that unfolds within-people over time. Further work is needed to identify mediators of this daily association and to evaluate causality, as well as to investigate these relations in high-risk samples.

Parental Psychopathology Moderates the Influence Of Parental Divorce On Lifetime Alcohol Use Disorders Among Israeli Adults Thompson Jr. RG, Shmulewitz D, Meyers JL, Stohl M, Aharonovich E, Spivak B, Weizman A, Frisch A, Grant BF, Hasin DS. Drug Alcohol Depend. 2014; 141: 85-91.
Parental divorce and psychopathology are well-documented risk factors for alcohol use disorders (AUD) in the United States and other countries where divorce is common and per capita total alcohol consumption is moderate to high. However, little is known about these relationships in countries where divorce and alcohol problems are less common, such as Israel. Israeli adult household residents (N=797) age 21-45 were interviewed in person between 2007 and 2009. Logistic regression models were used to examine main and additive interaction effects of parental divorce and psychopathology on lifetime DSM-IV AUD, adjusting for age, gender, and ethnicity. Parental divorce (OR=2.18, p0.001) and parental psychopathology (OR=1.61, p0.01) were independently associated with lifetime AUD and, when considered together, showed significant interaction (p=0.026). Specifically, the effect of divorce on AUD was only significant among those who also reported parental psychopathology. This is the first study showing the influence of parental divorce and psychopathology on risk for AUD among Israeli adults, where both divorce and AUD are less common than in the United States. Alcohol prevention and treatment professionals should recognize that children who experience parental divorce and/or psychopathology could be more vulnerable to later developing AUD than those whose parents remain together and without psychopathology.

Optimization Of Remotely Delivered Intensive Lifestyle Treatment For Obesity Using the Multiphase Optimization Strategy: Opt-IN Study Protocol Pellegrini CA, Hoffman SA, Collins LM, Spring B. Contemp Clin Trials. 2014; 38(2): 251-259.
Obesity-attributable medical expenditures remain high, and interventions that are both effective and cost-effective have not been adequately developed. The Opt-IN study is a theory-guided trial using the Multiphase Optimization Strategy (MOST) to develop an optimized, scalable version of a technology-supported weight loss intervention. Opt-IN aims to identify which of 5 treatment components or component levels contribute most meaningfully and cost-efficiently to the improvement of weight loss over a 6 month period. Five hundred and sixty obese adults (BMI 30-40 kg/m(2)) between 18 and 60 years old will be randomized to one of 16 conditions in a fractional factorial design involving five intervention components: treatment intensity (12 vs. 24 coaching calls), reports sent to primary care physician (No vs. Yes), text messaging (No vs. Yes), meal replacement recommendations (No vs. Yes), and training of a participant self-selected support buddy (No vs. Yes). During the 6-month intervention, participants will monitor weight, diet, and physical activity on the Opt-IN smartphone application downloaded to their personal phone. Weight will be assessed at baseline, 3, and 6 months. The Opt-IN trial is the first study to use the MOST framework to develop a weight loss treatment that will be optimized to yield the best weight loss outcome attainable for $500 or less.

"When You Get Old Like This You Don't Run Those Risks Anymore": Influence Of Age On Sexual Risk Behaviors and Condom Use Attitudes Among Methamphetamine-Using Heterosexual Women With A History Of Partner Violence Ludwig-Barron N, Wagner KD, Syvertsen JL, Ewald IJ, Patterson TL, Semple SJ, Stockman JK. Women’s Health Issues. 2014.
Drug use and partner violence affect older women, yet few studies highlight age-specific HIV risks and prevention strategies. This study compares sexual risk behaviors, condom use attitudes, and HIV knowledge between midlife/older women (ages 45+) and younger women (ages 18-44) reporting methamphetamine use and partner violence in San Diego, California. This mixed methods study used themes from a qualitative sub study (n=18) to inform logistic regression analysis of baseline data from an HIV behavioral intervention trial (n=154). Age-related qualitative themes included physiologic determinants, HIV knowledge, and "dodging the bullet," referring to a lifetime of uncertainty surrounding HIV serostatus after engaging in unsafe drug and sex practices. Midlife/older age was associated with never being married (24.2% vs. 51.2; p=.03), having less than a high school education/GED (12.1% vs. 34.7%; p=.04), lower condom use self-efficacy (2.87 vs. 3.19; p=.03), lower positive outcome expectancies (1.9 vs. 2.1; p=.04), and lower HIV knowledge (85.3% vs. 89.7%; p=.04); however, sexual risk behaviors were not associated with age group. In the multivariate analysis, midlife/older age remained independently associated with lower condom use self-efficacy (adjusted odds ratio, 0.49; 95% CI, 0.27-0.87) and lower HIV knowledge (adjusted odds ratio, 0.96; 95% CI, 0.93-0.99). Midlife/older methamphetamine-using women with experiences of partner violence present similar sexual risk profiles, but possess different HIV-related knowledge and attitudes toward prevention methods compared with their younger counterparts. Clinicians and public health practitioners can have a positive impact on this overlooked population by assessing HIV risks during routine screenings, encouraging HIV testing, and providing age-appropriate HIV prevention education.

Uptake and Repeat Use Of Postexposure Prophylaxis In A Community-based Clinic In Los Angeles, California Beymer MR, Bolan RK, Flynn RP, Kerrone DR, Pieribone DL, Kulkarni SP, Stitt JC, Mejia E, Landovitz RJ. AIDS Res Hum Retroviruses. 2014; 30(9): 848-855.
Postexposure prophylaxis (PEP) has become an important tool for HIV prevention in the men who have sex with men (MSM) communities within Los Angeles County. However, it is unclear as to whether the most sexually at-risk MSM populations are accessing PEP services. Furthermore, it is unclear what behavioral risk factors differentiate individuals who utilize PEP once (single PEP) versus those who utilize it multiple times (re-PEP). Data were collected between May 2011 and December 2012 on all clients enrolled in the Los Angeles LGBT Center (the Center) PEP-LA program as well as on all sexually transmitted infection (STI) screening clients visiting the Center. Multivariate logistic regression models were used to analyze results. PEP clients had greater odds of having a history of gonorrhea in the past year when compared to high-risk, non-PEP clients (OR: 1.71; CI: 1.25-2.35). Furthermore, they had greater odds of using methamphetamines (OR: 1.71; CI: 1.30-2.24) and inhaled nitrates (OR: 1.62; CI: 1.30-2.01) in the past 12 months when compared to high-risk, non-PEP clients. Re-PEP clients had greater odds of methamphetamine use than single PEP clients (OR: 2.80; CI: 1.65-4.75). There were no significant differences by race/ethnicity between high-risk, non-PEP clients and PEP clients in either the entire cohort or MSM only sample. However, African Americans made up 8.5% of persons accessing PEP services but 16.7% of persons who tested HIV positive. Similar proportions of PEP use by race/ethnicity are problematic considering the disproportionate burden of HIV infections in the African American community. Although uptake among the highest risk populations has been brisk (n=649), inequities based upon race/ethnicity suggest the need for increased outreach.

Changing Attitudes Toward Smoking and Smoking Susceptibility Through Peer Crowd Targeting: More Evidence From A Controlled Study Moran MB, Sussman S. Health Commun. 2014; 1-4.
Peer crowd identification consistently predicts an adolescent smoking behavior. As such, several interventions have targeted adolescents and young adults based on their identification with a specific crowd (e.g., Hipsters). This study uses a controlled experimental design to isolate and test the effect of peer crowd targeting in an antismoking ad on antismoking attitudes and smoking susceptibility. Two hundred and thirty-nine adolescents, age 13-15 years, completed a baseline survey and then viewed an antismoking ad targeting one of eight crowds; 1 week later they completed a posttest. Participants were assessed on antismoking attitudes and smoking susceptibility. Adolescents who strongly identified with the crowd targeted by the ad reported stronger antismoking attitudes and lower levels of smoking susceptibility. Those who disidentified with the crowd targeted in the ad exhibited not statistically significant increases in smoking susceptibility and weaker antismoking attitudes at posttest. These findings indicate that targeting youths based on their peer crowd is a useful strategy for antismoking interventions. Additional research should further examine whether youths who disidentify with the targeted crowd in an ad exhibit reactance against the message.

Designing Adaptive Intensive Interventions Using Methods From Engineering Lagoa CM, Bekiroglu K, Lanza ST, Murphy SA. J Consult Clin Psychol. 2014; 82(5): 868-878.
Adaptive intensive interventions are introduced, and new methods from the field of control engineering for use in their design are illustrated. A detailed step-by-step explanation of how control engineering methods can be used with intensive longitudinal data to design an adaptive intensive intervention is provided. The methods are evaluated via simulation. Simulation results illustrate how the designed adaptive intensive intervention can result in improved outcomes with

less treatment by providing treatment only when it is needed. Furthermore, the methods are robust to model misspecification as well as the influence of unobserved causes. These new methods can be used to design adaptive interventions that are effective yet reduce participant burden.

Who Benefits Most From Head Start? Using Latent Class Moderation To Examine Differential Treatment Effects Cooper BR, Lanza ST. Child Dev. 2014.
Head Start (HS) is the largest federally funded preschool program for disadvantaged children. Research has shown relatively small impacts on cognitive and social skills; therefore, some have questioned its effectiveness. Using data from the Head Start Impact Study (3-year-old cohort; N=2,449), latent class analysis was used to (a) identify subgroups of children defined by baseline characteristics of their home environment and caregiver and (b) test whether the effects of HS on cognitive, and behavioral and relationship skills over 2 years differed across subgroups. The results suggest that the effectiveness of HS varies quite substantially. For some children there appears to be a significant, and in some cases, long-term, positive impact. For others there is little to no effect.

Advancing Methods For Reliably Assessing Motivational Interviewing Fidelity Using the Motivational Interviewing Skills Code Lord SP, Can D, Yi M, Marin R, Dunn CW, Imel ZE, Georgiou P, Narayanan S, Steyvers M, Atkins DC. J Subst Abuse Treat. 2014.
The current paper presents novel methods for collecting MISC data and accurately assessing reliability of behavior codes at the level of the utterance. The MISC 2.1 was used to rate MI interviews from five randomized trials targeting alcohol and drug use. Sessions were coded at the utterance-level. Utterance-based coding reliability was estimated using three methods and compared to traditional reliability estimates of session tallies. Session-level reliability was generally higher compared to reliability using utterance-based codes, suggesting that typical methods for MISC reliability may be biased. These novel methods in MI fidelity data collection and reliability assessment provided rich data for therapist feedback and further analyses. Beyond implications for fidelity coding, utterance-level coding schemes may elucidate important elements in the counselor-client interaction that could inform theories of change and the practice of MI.

Changes In Substance Use-related Health Risk Behaviors On the Timeline Follow-back Interview As A Function Of Length Of Recall Period Buu A, Li R, Walton MA, Yang H, Zimmerman MA, Cunningham RM. Subst Use Misuse. 2014; 49(10): 1259-1269.
The timeline follow-back (TLFB) interview was adopted to collect retrospective data on daily substance use and violence from 598 youth seeking care in an urban Emergency Department in Flint, Michigan during 2009-2011. Generalized linear mixed models with flexible smooth functions of time were employed to characterize the change in risk behaviors as a function of the length of recall period. Results suggest that the 1-week recall period may be more effective for capturing atypical or variable patterns of risk behaviors, whereas a recall period longer than 2 weeks may result in a more stable estimation of a typical pattern.

Anxiety Symptomatology and Perceived Health In African American Adults: Moderating Role Of Emotion Regulation Carter SE, Walker RL. Cultur Divers Ethnic Minor Psychol. 2014; 20(3): 307-315.
Although emotional health has been theoretically and empirically linked to physical health, the anxiety-physical health association in particular is not well understood for African American adults. This study examined anxiety as a specific correlate of perceived health in addition to testing the potential moderating role of emotion regulation, an index of how and when individuals modulate emotions, in the association for anxiety to perceived health. Study participants were 151

community-based African American adults who completed measures of anxiety symptomatology and emotion regulation in addition to responding to a self-report question of perceived health. Results showed that higher levels of anxiety symptomatology were associated with poorer health ratings for those who reported more limited access to emotion regulation strategies but not those who reported having more emotion regulation strategies. The findings suggest that anxiety-related distress and health problems may be interrelated when emotion regulation strategies are limited.

Sexual Sensation Seeking, Transactional Sex, and Rural African American Cocaine Users Gullette D, Booth BM, Wright PB, Montgomery BE, Stewart KE. J Assoc Nurses AIDS Care. 2014; 25(4): 289-296.
The purpose of this study was to explore correlates of sexual sensation seeking (SSS) in a sample of rural African American cocaine users. Respondent-driven sampling was used to recruit 251 participants from two impoverished rural counties in eastern Arkansas. Consistent with previous investigations, SSS scores were associated with being younger, being male, having more sexual partners, and having more unprotected sexual encounters in the previous 30 days. Multiple regression revealed that SSS was correlated with a number of oral sex acts, transactional sex (exchanging sex for food, shelter, drugs, money, or other commodities), and Addiction Severity Index drug composite. SSS continues to demonstrate a strong association with sexual risk behaviors in diverse populations, including vulnerable groups like this community. Interventions to reduce unsafe sexual behaviors among high-risk groups, including drug users and individuals who engage in transactional sex, should incorporate approaches that include high sensation seekers' needs for novelty and variety.

Testing Demographic Differences For Alcohol Use Initiation Among Adolescents For the Decisional Balance And Situational Temptation Prevention Inventories Sillice MA, Paiva AL, Babbin SF, McGee HA, Rossi JS, Redding CA, Meier KS, Oatley K, Velicer WF. Addict Behav. 2014; 39(9): 1367-1371.
Alcohol use by middle school-aged students is a public health concern because of the numerous adverse social, health and psychological outcomes. Prevention programs attempt to intervene before alcohol use begins. A tailored, computer-delivered program for the prevention of alcohol use and a series of new trans theoretical model measures were developed, including decisional balance (Pros and Cons) of alcohol use and Situational Temptations to Try Alcohol. This study investigated if there were any demographic differences on these measures in a sample of 6th grade middle school students from 20 schools (N=4151) at baseline. Three factorial analysis of variance tests were conducted to explore the impact of race (whites vs. non-whites), ethnicity (Hispanics vs. Non-Hispanics) and gender (males vs. females). A significant two-way interaction effect was found between gender and ethnicity for Pros of Alcohol Use. A significant three-way interaction effect was found between gender, race and ethnicity for Cons of Alcohol Use. Main effects were found for the three demographic factors for Situational Temptations to Try Alcohol. However, the effect sizes for the interaction effects and main effects were very small (all below (2)=.01), suggesting that race/ethnicity and gender alone may not be highly influential factors in the Decisional Balance for the Prevention of Alcohol and Situational Temptations to Try Alcohol in adolescence. The implications for these results and alcohol use prevention among this group are discussed.

A Comparative Study Of Self-report, Urinalysis and Hair Analysis In the Detection Of Methamphetamine In Yaba Users Junkuy A, Aramrattana A, Sribanditmongkol P. J Med Assoc Thai. 2014; 97(7): 776-784.

Three diagnostic methods have dominated drug-abuse research: self-report, urinalysis and hair analysis. Previous studies have compared detection rates for various drugs, but none has focused a three-pronged concordance study on the use of methamphetamine (MA). The aim of this study was to determine and compare the rates of MA detection in urine and hair of subjects who reported consuming MA in the form of Yaba. Self-reports of Yaba use, as well as biological specimens for chemical analyses, were collected from paid volunteers participating in a larger project studying risk-taking behavior of young adults in northern Thailand. All subjects in the present study reported using Yaba within 90 days of enrollment. Hair analysis for MA followed a validated protocol that coupled solid phase micro extraction (SPME) with gas chromatography-mass spectrometry (GC-MS). Preliminary urinalysis was by means of REMEDi-HS. Positive urine was confirmed for MA by the SPME/GC-MS protocol. The MA detection rate by hair analysis (34.3%, n = 172) was significantly higher than by urinalysis (19.1%, n = 96) ($p < 0.01$; McNemar test). All subjects with MA-positive urine samples reported using Yaba within 30 days of testing, while hair analysis gave positive results for self-reports up to 90 days. Urinalysis showed greater concordance with self-report than hair analysis if testing occurred within seven days of most recent admitted Yaba use. The reverse was true after 14 days. Agreement of laboratory findings with self-reports increased if test results for the two biological matrices were combined. There was no strong agreement between hair analysis and urinalysis for subjects reporting most recent use within 30 days of testing (kappa = 0.131; 95% CI = 0.022-0.240).For the Yaba users in the present study, urinalysis for MA significantly detected more positives than hair analysis if the most recent use reportedly occurred within seven days of testing. Hair analysis yielded better results after an interval of 14 days, with its window of detection extending up to three months. There were no urine positive samples for reported use after 30 days. Combining urinalysis and hair analysis increased the probability of detecting recent MA use. Both urinalysis and hair analysis significantly under-detected MA in the biological samples collected. The combined detection rate was 44.4%. This discrepancy might have resulted from over-reporting of Yaba use due to social/psychological factors and/or insufficient MA consumption causing test results to fall below cutoff levels.

Control Systems Engineering For Optimizing A Prenatal Weight Gain Intervention To Regulate Infant Birth Weight Savage JS, Downs DS, Dong Y, Rivera DE. Am J Public Health. 2014; 104(7): 1247-1254.

The authors used dynamical systems modeling to describe how a prenatal behavioral intervention that adapts to the needs of each pregnant woman may help manage gestational weight gain and alter the obesogenic intrauterine environment to regulate infant birth weight. This approach relies on integrating mechanistic energy balance, theory of planned behavior, and self-regulation models to describe how internal processes can be impacted by intervention dosages, and reinforce positive outcomes (e.g., healthy eating and physical activity) to moderate gestational weight gain and affect birth weight. A simulated hypothetical case study from MATLAB with Simulink showed how, in response to our adaptive intervention, self-regulation helps adjust perceived behavioral control. This, in turn, changes the woman's intention and behavior with respect to healthy eating and physical activity during pregnancy, affecting gestational weight gain and infant birth weight. This article demonstrates the potential for real-world applications of an adaptive intervention to manage gestational weight gain and moderate infant birth weight. This model could be expanded to examine the long-term sustainable impacts of an intervention that varies according to the participant needs on maternal postpartum weight retention and child postnatal eating behavior.

A Longitudinal Examination Of Mothers' and Fathers' Social Information Processing Biases and Harsh Discipline In Nine Countries Lansford JE, Woodlief D, Malone PS, Oburu P, Pastorelli C, Skinner AT, Sorbring E, Tapanya S, Tirado LMU, Zelli A, Al-Hassan SM, Alampay LP, Bacchini D, Bombi AS, Bornstein MH, Chang L, Deater-Deckard K, Di Giunta L, Dodge KA. Dev Psychopathol. 2014; 26(3): 561-573.
This study examined whether parents' social information processing was related to their subsequent reports of their harsh discipline. Interviews were conducted with mothers (n = 1,277) and fathers (n = 1,030) of children in 1,297 families in nine countries (China, Colombia, Italy, Jordan, Kenya, the Philippines, Sweden, Thailand, and the United States), initially when children were 7 to 9 years old and again 1 year later. Structural equation models showed that parents' positive evaluations of aggressive responses to hypothetical childrearing vignettes at Time 1 predicted parents' self-reported harsh physical and nonphysical discipline at Time 2. This link was consistent across mothers and fathers, and across the nine countries, providing support for the universality of the link between positive evaluations of harsh discipline and parents' aggressive behavior toward children. The results suggest that international efforts to eliminate violence toward children could target parents' beliefs about the acceptability and advisability of using harsh physical and nonphysical forms of discipline.

Local Support For Alcohol Control Policies and Perceptions Of Neighborhood Issues In Two College Communities Fairlie AM, DeJong W, Wood MD. Subst Abuse 2014.
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 two college communities, the present study: 1) measured public support for local alcohol control policies to stem underage drinking and alcohol over-service 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 ages 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. The authors conclude that 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.

Vulnerabilities Faced By the Children Of Sex Workers In Two Mexico-US Border Cities: A Retrospective Study On Sexual Violence, Substance Use and HIV Risk Servin AE, Strathdee S, Munoz FA, Vera A, Rangel G, Silverman JG. AIDS Care. 2015 Jan; 27(1-5): 1360-1451.
Most studies of female sex workers (FSWs) conducted in the Mexico-US border region have focused on individual HIV risk, centered on sexual behaviors and substance abuse patterns. Little

attention has been drawn to the reality that sex workers are often parents whose children potentially face vulnerabilities unique to their family situation. The objective of the present study was to identify the vulnerabilities faced by the children of FSWs in two Mexican-US border cities. From 2008 to 2010, 628 FSW-injection drug users underwent interviewer-administered surveys and HIV/STI testing. Approximately one in five participants (20%) reported having a parent involved in sex work and majority referred it was their mother (88%). Close to one-third of participants (31%) reported first injecting drugs <18 years of age, and 33% reported they began working regularly as a prostitute <18 years of age. First drinking alcohol <18 years old (AOR = 1.87, 95%CI: 1.13-3.08), lifetime cocaine use (AOR = 1.76, 95%CI: 1.09-2.84), ever being forced or coerced into non-consensual sex as a minor (<18 years of age; AOR = 1.54, 95%CI: 1.01-2.35), and injecting drugs with used syringes in the prior month (AOR = 1.63, 95%CI: 1.07-2.49) were the factors associated with having had a parent involved in sex work. These findings begin to lay the groundwork for understanding the potential vulnerabilities faced by the children of sex workers. Understanding these potential needs is necessary for creating relevant, evidence-based interventions focused on supporting these women.

Transitions in Gambling Participation During Late Adolescence And Young Adulthood Bray BC, Lee GP, Liu W, Storr CL, Ialongo NS, Martins SS. J Adolesc Health. 2014; 55(2): 188-194.
The purpose of this study was to examine transitions in gambling participation from late adolescence into emerging adulthood and to identify factors (i.e., gender, race, intervention status, lunch status, conduct disorder, parental monitoring, neighborhood environment, and substance use) that might influence these transitions. Markov modeling was used to describe the movement between past-year gambling states (i.e., nongambling and gambling) across 5 years. Annual data on the past-year gambling behavior and substance use were collected from 515 young men and women starting at the age of 17 years. Past-year gambling declined from 51% prevalence at the age of 17 years to 21% prevalence at the age of 22 years. Participants who reported no past-year gambling at a particular annual assessment had more than an 80% probability of also reporting no past-year gambling at the following assessment. Men were 1.07-2.82 times more likely than women to transition from past-year nongambling to gambling year to year, and women were 1.27-5.26 times more likely than men to transition from past-year gambling to nongambling year to year. In addition, gender and past-year tobacco use interacted such that men who used tobacco were most likely (and men who did not use tobacco least likely) to gamble at baseline. Transition rates between gambling states appear to be relatively stable over time from late adolescence into emerging adulthood; however, men and those who engage in substance use may be at an increased risk of gambling participation.

Does DSM-5 Nomenclature For Inhalant Use Disorder Improve Upon DSM-IV? Ridenour TA, Halliburton AE, Bray BC. Psychol Addict Behav. 2014.
Among drug classes, substance use disorder (SUD) consequent to using inhalants (SUD-I) has perhaps the smallest evidence base. This study compared DSM-IV versus DSM-5 nomenclatures, testing whether 4 traditional categories of inhalants (aerosols, gases, nitrites, solvents) are manifestations of a single pathology, obtaining item parameters of SUD-I criteria, and presenting evidence that SUD can result from using nitrites. An urban, Midwestern, community sample of 162 inhalant users was recruited. Participants were 2/3 male, nearly 85% White, and had a mean age of 20.3 years (SD = 2.4 years), spanning the ages of greatest incidence of SUD and slightly older than the primary ages of inhalants use initiation. Analyses consisted of bivariate associations, principle components analysis, and item response theory analysis. Validity was demonstrated for SUD-I consequent to each inhalant type as well as for aggregating all inhalant types into a single drug

class. Results supported DSM-5 nomenclature over DSM-IV in multiple ways except that occurrence of diagnostic orphans was not statistically smaller using DSM-5. (PsycINFO Database Record (c) 2014 APA, all rights reserved).

Differential Effects Of Mental Health Problems Among Truant Youths Dembo R, Wareham J, Schmeidler J, Briones-Robinson R, Winters KC. J Behav Health Serv Res. 2014.
Research indicates at-risk youth are more likely to experience emotional and psychological problems. Young people who are often truant from school represent a group of at-risk youth, but one for which mental health issues are understudied. This study examined heterogeneity of mental health problems among a sample of 300 truant adolescents using latent class analysis (LCA). LCA indicated the sample of truants was best represented by four latent subgroups of youth with low mental health problems; high depression, low mania; high mania, low depression; and high depression and mania. These subgroups were examined in relation to sociodemographic and psychosocial measures at baseline and after truancy offenses. Results indicated general and unique differences in these covariates across the four latent classes. Service and practice implications of better understanding mental health issues of truant youth are discussed.

Antibiotic Resistance: A Primer and Call To Action Smith RA, M'ikanatha NM, Read AF. Health Commun. 2014; 1-6.
During the past century, discoveries of microorganisms as causes of infections and antibiotics as effective therapeutic agents have contributed to significant gains in public health in many parts of the world. Health agencies worldwide are galvanizing attention toward antibiotic resistance, which is a major threat to public health (Centers for Disease Control and Prevention, 2013; World Health Organization, 2014). Some life scientists believe that we are approaching the post-antibiotic age (Davies & Davies, 2010). The growing threat of antimicrobial resistance is fueled by complex factors with biological, behavioral, and societal aspects. This primer provides an overview of antibiotic resistance and its growing burden on public health, the biological and behavioral mechanisms that increase antibiotic resistance, and examples of where health communication scholars can contribute to efforts to make our current antibiotic drugs last as long as possible. In addition, the authors identify compelling challenges for current communication theories and practices.

Cognitive Performance Profiles By Latent Classes Of Drug Use Harrell PT, Mancha BEE, Martins SS, Mauro PM, Kuo JH, Scherer M, Bolla KI, Latimer WW. Am J Addict. 2014; 23(5): 431-439.
The relationship between substance use and cognitive deficits is complex and requires innovative methods to enhance understanding. The present study is the first to use LCA to examine associations of drug use patterns with cognitive performance. Cocaine/heroin users (N=552) completed questionnaires, and cognitive measures. LCA identified classes based on past-month drug use and adjusted for probabilities of group membership when examining cognitive performance. Latent indicators were: alcohol (ALC), cigarettes (CIG), marijuana (MJ), crack smoking (CS), nasal heroin (NH), injection cocaine (IC), injection heroin (IH), and injection speedball (IS). Age and education were included as covariates in model creation. Bootstrap likelihood ratio test (BLRT) supported a 5-class model. Prevalent indicators (estimated probability of over 50%) for each class are as follows: "Older Nasal Heroin/Crack Smokers" (ONH/CS, n=166.9): ALC, CIG, NH, CS; "Older, Less Educated Polysubstance" (OLEP, n=54.8): ALC, CIG, CS, IH, IC, and IS; "Younger Multi-Injectors" (MI, n=128.7): ALC, CIG, MJ, IH, IC, and IS; "Less Educated Heroin Injectors" (LEHI, n=87.4): CIG, IH; and "More Educated Nasal Heroin" users

(MENH, n=ALC, CIG, NH. In general, all classes performed worse than established norms and older, less educated classes performed worse, with the exception that MENH demonstrated worse cognitive flexibility than YMI. This study demonstrated novel applications of a methodology for examining complicated relationships between polysubstance use and cognitive performance. Education and/or nasal heroin use are associated with reduced cognitive flexibility in this sample of inner city drug users.

Global Response To HIV: Treatment As Prevention, Or Treatment For Treatment? Sigaloff KCE, Lange JMA, Montaner J. Clin Infect Dis. 2014; 59 Suppl 1: S7-S11.
The concept of "treatment as prevention" has emerged as a means to curb the global HIV epidemic. There is, however, still ongoing debate about the evidence on when to start antiretroviral therapy in resource-poor settings. Critics have brought forward multiple arguments against a "test and treat" approach, including the potential burden of such a strategy on weak health systems and a presumed lack of scientific support for individual patient benefit of early treatment initiation. In this article, the authors highlight the societal and individual advantages of treatment as prevention in resource-poor settings. They argue that the available evidence renders the discussion on when to start antiretroviral therapy unnecessary and that, instead, efforts should be aimed at offering treatment as soon as possible.

Injection and Non-injection Drug Use and Infectious Disease In Baltimore City: Differences By Race Keen 2nd L, Khan M, Clifford L, Harrell PT, Latimer WW. Addict Behav. 2014; 39(9): 1325-1328.
The current study examines differences in the prevalence of biologically-confirmed hepatitis C virus (HCV), HIV, and coinfection between Black and White adult cocaine/heroin users across three drug use subgroups identified in previous research (Harrell et al., 2012): non-injection smoking crack/nasal heroin users, heroin injectors, and polydrug injectors.59% of the 482 participants in the study were male. Significant race differences emerged between drug use subgroup memberships. Non-injection smoking crack/nasal heroin users were predominantly Black (75%), while heroin injectors and polydrug injectors were predominantly White (69% and 72%, respectively). Polydrug injectors accounted for nearly three quarters of the HCV positive diagnoses in Whites. Though HIV disease status, stratified by race, did not differ significantly between drug use subgroups, the non-injection smoking crack/nasal heroin subgroup contained over half of the HIV positive diagnoses in the sample and was predominantly Black. Despite much lower rates of injection, Blacks (8%) had a higher prevalence of coinfection than Whites (3%; X(2) (2)=6.18, p=.015).The current findings are consistent with trends in the recent HIV transmission statistics where sexual activity has overtaken injection drug use as a HIV risk factor. The current findings also provide further support to the notion of injection drug use as an exceedingly high-risk behavior for HCV and coinfection, specifically those who are polysubstance injectors.

Causal Inference In Longitudinal Comparative Effectiveness Studies With Repeated Measures Of A Continuous Intermediate Variable Wang C-P, Jo B, Hendricks Brown C. Stat Med. 2014; 33(20): 3509-3527.
The authors propose a principal stratification approach to assess causal effects in nonrandomized longitudinal comparative effectiveness studies with a binary endpoint outcome and repeated measures of a continuous intermediate variable. Their method is an extension of the principal stratification approach originally proposed for the longitudinal randomized study "Prevention of Suicide in Primary Care Elderly: Collaborative Trial" to assess the treatment effect on the continuous Hamilton depression score adjusting for the heterogeneity of repeatedly measured binary

compliance status. The authors' motivation for this work comes from a comparison of the effect of two glucose-lowering medications on a clinical cohort of patients with type 2 diabetes. Here, they consider a causal inference problem assessing how well the two medications work relative to one another on two binary endpoint outcomes: cardiovascular disease-related hospitalization and all-cause mortality. Clinically, these glucose-lowering medications can have differential effects on the intermediate outcome, glucose level over time. Ultimately, the authors want to compare medication effects on the endpoint outcomes among individuals in the same glucose trajectory stratum while accounting for the heterogeneity in baseline covariates (i.e., to obtain principal effects; on the endpoint outcomes). The proposed method involves a three-step model estimation procedure. Step 1 identifies principal strata associated with the intermediate variable using hybrid growth mixture modeling analyses. Step 2 obtains the stratum membership using the pseudo class technique and derives propensity scores for treatment assignment. Step 3 obtains the stratum-specific treatment effect on the endpoint outcome weighted by inverse propensity probabilities derived from Step 2.

Factorial Experiments: Efficient Tools For Evaluation Of Intervention Components Collins LM, Dziak JJ, Kugler KC, Trail JB. Am J Prev Med. 2014; 47(4): 498-504.
An understanding of the individual and combined effects of a set of intervention components is important for moving the science of preventive medicine interventions forward. This understanding can often be achieved in an efficient and economical way via a factorial experiment, in which two or more independent variables are manipulated. The factorial experiment is a complement to the RCT; the two designs address different research questions. To offer an introduction to factorial experiments aimed at investigators trained primarily in the RCT. The factorial experiment is compared and contrasted with other experimental designs used commonly in intervention science to highlight where each is most efficient and appropriate. Several points are made: factorial experiments make very efficient use of experimental subjects when the data are properly analyzed; a factorial experiment can have excellent statistical power even if it has relatively few subjects per experimental condition; and when conducting research to select components for inclusion in a multicomponent intervention, interactions should be studied rather than avoided. Investigators in preventive medicine and related areas should begin considering factorial experiments alongside other approaches. Experimental designs should be chosen from a resource management perspective, which states that the best experimental design is the one that provides the greatest scientific benefit without exceeding available resources.

Age Cohort Differences In Illicit Drug Use And HCV Among African American Substance Users Whitehead NE, Hearn L, Trenz RC, Burrell 2nd LE, Latimer WW. J Addict Dis. 2014.
Identifying prognostic indicator for undiagnosed HCV is crucial to attenuate the negative impact of this disease. This study explored the influence of recent and more distal injection drug use on biologically-confirmed HCV infection among a sample (N = 260) of older and younger African Americans. Data from the baseline assessment of the NEURO-HIV epidemiologic study was analyzed using confounder adjusted regression techniques. Older adults were more likely to test positive for HCV (OR = 2.80, 95% CI = 1.53-5.11) due to lifetime injection drug use (AOR = 5.37, 95% CI = 3.10-9.28). Clinical implications are discussed.

Asymptotics Of Nonparametric L-1 Regression Models With Dependent Data Zhao Z, Wei Y, Lin DKJ. Bernoulli (Andover). 2014; 20(3): 1532-1559.
The authors investigate asymptotic properties of least-absolute-deviation or median quantile estimates of the location and scale functions in nonparametric regression models with dependent data from multiple subjects. Under a general dependence structure that allows for longitudinal data

and some spatially correlated data, we establish uniform Bahadur representations for the proposed median quantile estimates. The obtained Bahadur representations provide deep insights into the asymptotic behavior of the estimates. The authors' main theoretical development is based on studying the modulus of continuity of kernel weighted empirical process through a coupling argument. Progesterone data is used for an illustration.

HIV Prevalence and Risk Behaviors Among African American Women Who Trade Sex For Drugs Versus Economic Resources Dunne EM, Dyer TP, Khan MR, Cavanaugh CE, Melnikov A, Latimer WW. AIDS Behav. 2014; 18(7): 1288-1292.
Trading sex for money, drugs, goods, services, or a place to stay is prevalent among women who use drugs and has been associated with women's risk of HIV acquisition. There is evidence that trading sex for drugs only may be associated with elevated risk of HIV compared with trading sex for money. The purpose of this study was to assess whether HIV risk behaviors and HIV prevalence differ among African American drug using women (N = 92) who traded sex for drugs only, traded sex for economic resources (defined as money, shelter, or other resources) only, or traded sex for both economic resources and drugs. In this study, lower rates of condom use and higher rates of HIV were found among women who traded sex for drugs only compared to women who traded sex for economic resources or for economic resources and drugs. These findings suggest that African American women who trade sex for drugs only represent an understudied yet highly vulnerable group.

Women's Perspectives On Female-initiated Barrier Methods For the Prevention Of HIV In the Context Of Methamphetamine Use and Partner Violence Stockman JK, Syvertsen JL, Robertson AM, Ludwig-Barron NT, Bergmann JN, Palinkas LA. Women's Health Issues. 2014; 24(4): e397-405.
Female-initiated barrier methods for the prevention of HIV may be an effective alternative for drug-using women who are unable to negotiate safe sex, often as a result of physical and/or sexual partner violence. Utilizing a SAVA (substance abuse, violence, and AIDS) syndemic framework, the authors qualitatively examined perspectives on female condoms and vaginal microbicides among 18 women with histories of methamphetamine abuse and partner violence in San Diego, California. Most women were not interested in female condoms owing to perceived discomfort, difficulty of insertion, time-intensive effort, and unappealing appearance. Alternatively, most women viewed vaginal microbicides as a useful method. Positive aspects included convenience, ability to disguise as a lubricant, and a sense of control and empowerment. Concerns included possible side effects, timing of application, and unfavorable characteristics of the gel. Acceptability of female-initiated barrier methods was context dependent (i.e., partner type, level of drug use and violence that characterized the sexual relationship). Findings indicate that efforts are needed to address barriers identified for vaginal microbicides to increase its uptake in future HIV prevention trials and marketing of future Food and Drug Administration-approved products. Strategies should address gender-based inequalities (e.g., partner violence) experienced by drug-using women and promote female empowerment. Education on female-initiated barrier methods is also needed for women who use drugs, as well as health care providers and other professionals providing sexual health care and contraception to women with histories of drug use and partner violence.

Challenges Facing HIV-positive Persons Who Use Drugs and Their Families In Vietnam Lee S-J, Li L, Lin C, Tuan L A. AIDS Care. 2014; 1-5.
It is hypothesized that persons who use drugs (PWUD) in Vietnam who are also HIV-positive may face additional challenges in psychosocial outcomes, and these challenges may extend to their

family members. In this study, the authors examined depressive symptoms, stigma, social support, and caregiver burden of HIV-positive PWUD and their family members, compared to the outcomes of HIV-negative PWUD and their family members. Baseline, 3-month, and 6-month assessment data were gathered from 83 PWUD and 83 family members recruited from four communes in Phu Th Province, Vietnam. For PWUD, although the authors observed a general decline in overall stigma over time for both groups, HIV-positive PWUD consistently reported significantly higher overall stigma for all three periods. Depressive symptoms among family members in both groups declined over time; however, family members of HIV-positive PWUD reported higher depressive symptoms across all three periods. In addition, family members of HIV-positive PWUD reported lower levels of tangible support across all three periods. Caregiver burden among family members of HIV-positive PWUD increased significantly over time, whereas the reported burden among family members of HIV-negative PWUD remained relatively unchanged. The findings highlight the need for future interventions for PWUD and family members, with targeted and culturally specific strategies to focus on the importance of addressing additional stigma experienced by PWUD who are HIV-positive. Such challenges may have direct negative impact on their family members' depressive symptoms, tangible support, and caregiver burden.

Internalized Stigma and Sterile Syringe Use Among People Who Inject Drugs In New York City, 2010-2012 Rivera AV, DeCuir J, Crawford ND, Amesty S, Lewis CF. Drug Alcohol Depend. 2014.
Little is known on the effect of stigma on the health and behavior of people who inject drugs (PWID). PWID may internalize these negative attitudes and experiences and stigmatize themselves (internalized stigma). With previous research suggesting a harmful effect of internalized stigma on health behaviors, the authors aimed to determine socio-demographic characteristics and injection risk behaviors associated with internalized PWID-related stigma in New York City (NYC). Three NYC pharmacies assisted in recruiting PWID. Pharmacy-recruited PWID syringe customers received training in recruiting up to three of their peers. Participants completed a survey on injection behaviors and PWID-related stigma. Among HIV-negative PWID (n=132), multiple linear regression with GEE (to account for peer network clustering) was used to examine associations with internalized PWID-related stigma. Latinos were more likely to have higher internalized stigma, as were those with lower educational attainment. Those with higher internalized stigma were more likely to not use a syringe exchange program (SEP) recently, although no association was found with the recent use of pharmacies for syringes. Lastly, higher internalized stigma was related to less than 100% use of pharmacies or SEPs for syringe needs. These data suggest that PWID with higher internalized stigma are less likely to consistently use sterile syringe sources in urban settings with multiple sterile syringe access points. These results support the need for individual- and structural-level interventions that address PWID-related stigma. Future research is needed to examine why PWID with higher internalized stigma have less consistent use of public syringe access venues.

The Temporal Course Of the Influence Of Anxiety On Fairness Considerations Luo Y, Wu T, Broster LS, Feng C, Zhang D, Gu R, Luo Y-J. Psychophysiology. 2014; 51(9): 834-842.
This study investigated the potential causes of anxious people social avoidance. The classic ultimatum game was utilized in concert with electroencephalogram recording. Participants were divided into two groups according to levels of trait anxiety as identified by a self-report scale. The behavioral results indicate that high-anxious participants were more prone to reject human-proposed than computer-proposed unequal offers compared to their low-anxious counterparts. The event-related potential results indicate that the high-anxious group showed a larger feedback-related negativity when receiving unequal monetary offers than equal ones, and a larger P3 when receiving

human-proposed offers than computer-proposed ones, but these effects were absent in the low-anxious group. The authors suggest anxious people social avoidance results from hypersensitivity to unequal distributions during interpersonal interactions.

Hazardous Drinking and HIV-risk-related Behavior Among Male Clients Of Female Sex Workers In Tijuana, Mexico Goodman-Meza D, Pitpitan EV, Semple SJ, Wagner KD, Chavarin CV, Strathdee SA, Patterson TL. Am J Addict. 2014; 23(5): 502-509.
Male clients of female sex workers (FSWs) are at high risk for HIV. Whereas the HIV risks of alcohol use are well understood, less is known about hazardous alcohol use among male clients of FSWs, particularly in Mexico. The authors sought to identify risk factors for hazardous alcohol use and test associations between hazardous alcohol use and HIV risk behavior among male clients in Tijuana. Male clients of FSWs in Tijuana (n=400) completed a quantitative interview in 2008. The AUDIT was used to characterize hazardous alcohol use. Multivariate logistic regression was used to determine independent associations of demographic and HIV risk variables with hazardous alcohol use (vs. non-hazardous). Forty percent of the sample met criteria for hazardous alcohol use. Variables independently associated with hazardous drinking were reporting any sexually transmitted infection (STI), having sex with a FSW while under the influence of alcohol, being younger than 36 years of age, living in Tijuana, and ever having been jailed. Hazardous drinkers were less likely ever to have been deported or to have shared injection drugs. Hazardous alcohol use is associated with HIV risk, including engaging in sex with FSWs while intoxicated and having an STI among male clients of FSWs in Tijuana. The authors systematically described patterns and correlates of hazardous alcohol use among male clients of FSWs in Tijuana, Mexico. The results suggest that HIV/STI risk reduction interventions must target hazardous alcohol users, and be tailored to address alcohol use.

Modeling Scenarios For the End Of AIDS Lima VD, Thirumurthy H, Kahn JG, Saavedra J, Carceres CF, Whiteside A. Clin Infect Dis. 2014; 59 Suppl 1: S16-20.
At the end of 2012, 3 decades after the human immunodeficiency virus (HIV) was first identified, neither a cure nor a fully preventive vaccine was available. Despite multiple efforts, the epidemic remains an exceptional public health challenge. At the end of 2012, it was estimated that, globally, 35 million people were living with HIV, 2.3 million had become newly infected, and 1.6 million had died from AIDS-related causes. Despite substantial prevention efforts and increases in the number of individuals on highly active antiretroviral therapy (HAART), the epidemic burden continues to be high. Here, the authors provide a brief overview of the epidemiology of HIV transmission, the work that has been done to date regarding HIV modeling in different settings around the world, and how to finance the response to the HIV epidemic. In addition, they suggest discussion topics on how to move forward with the prevention agenda and highlight the role of treatment as prevention (TasP) in curbing the epidemic.

Timing Of Income Assistance Payment and Overdose Patterns At A Canadian Supervised Injection Facility Zlotorzynska M, Milloy M-JS, Richardson L, Nguyen P, Montaner JS, Wood E, Kerr T. Int J Drug Policy. 2014; 25(4): 736-739.
Little is known about the relationship between timing of income assistance provision and health behaviors among injection drug users (IDU). The authors therefore investigated associations between income assistance provision and overdose patterns among IDU utilizing Insite, a supervised injection facility in Vancouver, Canada. Using data collected at Insite between March 2004 and December 2010, they examined trends in overdoses and drugs injected. Data were stratified by proximity to the most recent day of issue of income assistance cheques, based on dates

provided by the province. After adjustment for frequency of use, the risk of overdose for those injecting at Insite on the three days starting with "cheque day" was higher than for those injecting on other days (Odds Ratio OR]=2.06; 95% Confidence Interval [CI]: 1.80-2.36, p<0.001). These associations were also significant when drug-specific overdose rates were considered. The proportion of overdoses involving exclusive opioid use was lower for events occurring around cheque day than on other days (OR=0.63; 95% CI: 0.47-0.84, p=0.002), though we observed no significant association between the proportion of overdoses involving stimulants and cheque timing (p=0.129). The risk of overdose among IDU utilizing Insite was significantly higher on and immediately after cheque day than during other days, and may be associated with reduced tolerance and increases in binge drug use. Alternative models of income assistance administration should be evaluated to reduce overdoses around cheque day.

HIV Treatment Strategies That Can Weather Future Challenges Hogg RS, Anema A, Hogg EA, Montaner JSG. Lancet Infect Dis. 2014; 14(7): 534-535. This is Comment on **Early Versus Delayed Initiation Of Highly Active Antiretroviral Therapy For HIV-Positive Adults With Newly Diagnosed Pulmonary Tuberculosis (TB-HAART): A Prospective, International, Randomised, Placebo-Controlled Trial** [Lancet Infect Dis. 2014]
Early initiation of antiretroviral therapy not only prevents AIDS and extends survival of people with HIV, but also significantly reduces new HIV infections.1 At the core of the treatment-as-prevention strategy is the goal of using safer, simpler, and better tolerated antiretroviral regimens to sustain suppression of viral replication and maintain an undetectable plasma viral load. The goal of treatment as prevention is to achieve immune reconstitution and disease-free survival; as the viral load becomes undetectable in biological fluids (eg, semen, vaginal fluids, blood) the risk of HIV transmission decreases by more than 95%.

BEHAVIORAL AND INTEGRATIVE TREATMENT RESEARCH

Randomized Trial of Telephone-Delivered Acceptance and Commitment Therapy versus Cognitive Behavioral Therapy for Smoking Cessation: A Pilot Study Bricker JB, Bush T, Zbikowski SM, Mercer LD, Heffner JL. Nicotine Tob Res. 2014 Nov;16(11):1446-1454.
The authors conducted a pilot randomized trial of telephone-delivered acceptance and commitment therapy (ACT) versus cognitive behavioral therapy (CBT) for smoking cessation. Participants were 121 uninsured South Carolina State Quitline callers who were adult smokers (at least 10 cigarettes/day) and who wanted to quit within the next 30 days. Participants were randomized to 5 sessions of either ACT or CBT telephone counseling and were offered 2 weeks of nicotine replacement therapy (NRT). ACT participants completed more calls than CBT participants (M = 3.25 in ACT vs. 2.23 in CBT; p = .001). Regarding satisfaction, 100% of ACT participants reported their treatment was useful for quitting smoking (vs. 87% for CBT; p = .03), and 97% of ACT participants would recommend their treatment to a friend (vs. 83% for CBT; p = .06). On the primary outcome of intent-to-treat 30-day point prevalence abstinence at 6 months postrandomization, the quit rates were 31% in ACT versus 22% in CBT (odds ratio [OR] = 1.5, 95% confidence interval [CI] = 0.7-3.4). Among participants depressed at baseline (n = 47), the quit rates were 33% in ACT versus 13% in CBT (OR = 1.2, 95% CI = 1.0-1.6). Consistent with ACT's theory, among participants scoring low on acceptance of cravings at baseline (n = 57), the quit rates were 37% in ACT versus 10% in CBT (OR = 5.3, 95% CI = 1.3-22.0). The authors conclude that ACT is feasible to deliver by phone, is highly acceptable to quitline callers, and shows highly promising quit rates compared with standard CBT quitline counseling. As results were limited by the pilot design (e.g., small sample), a full-scale efficacy trial is now needed.

Substance Use Recovery Outcomes among a Cohort of Youth Participating in a Mobile-Based Texting Aftercare Pilot Program Gonzales R, Ang A, Murphy DA, Glik DC, Anglin MD. J Subst Abuse Treat. 2014 Jul;47(1):20-26.
Project ESQYIR (Educating & Supporting Inquisitive Youth in Recovery) is a pilot study examining the feasibility of a 12-week mobile-based aftercare intervention for youth (ages 12 to 24) transitioning out of community-based substance abuse treatment programs. From January 2012 through July 2013, a total of 80 youth were recruited from outpatient and residential treatment programs, geographically dispersed throughout Los Angeles County, California. Results revealed that youth who participated in the texting mobile pilot intervention were significantly less likely to relapse to their primary compared to the aftercare as usual control condition (OR=0.52, p=0.002) over time (from baseline throughout the 12-week aftercare pilot program to a 90-day follow-up). Participants in the texting aftercare pilot program also reported significantly less substance use problem severity (β=-0.46, p=0.03) and were more likely to participate in extracurricular recovery behaviors (β=1.63, p=0.03) compared to participants in the standard aftercare group. Collectively, findings from this pilot aftercare study suggest that mobile texting could provide a feasible way to engage youth in recovery after substance abuse treatment to aid with reducing relapse and promoting lifestyle behavior change.

Real-Time Mobile Detection of Drug Use with Wearable Biosensors: A Pilot Study Carreiro S, Smelson D, Ranney M, Horvath KJ, Picard RW, Boudreaux ED, Hayes R, Boyer EW. J Med Toxicol. 2014 Oct 21. [Epub ahead of print].
While reliable detection of illicit drug use is paramount to the field of addiction, current methods involving self-report and urine drug screens have substantial limitations that hinder their utility. Wearable biosensors may fill a void by providing valuable objective data regarding the timing and

contexts of drug use. This is a preliminary observational study of four emergency department patients receiving parenteral opioids and one individual using cocaine in a natural environment. A portable biosensor was placed on the inner wrist of each subject, to continuously measure electrodermal activity (EDA), skin temperature, and acceleration. Data were continuously recorded for at least 5 min prior to drug administration, during administration, and for at least 30 min afterward. Overall trends in biophysiometric parameters were assessed. Injection of opioids and cocaine use were associated with rises in EDA. Cocaine injection was also associated with a decrease in skin temperature. Opioid tolerance appeared to be associated with a blunted physiologic response as measured by the biosensor. Laterality may be an important factor, as magnitude of response varied between dominant and nondominant wrists in a single patient with bilateral wrist measurements. Changes in EDA and skin temperature are temporally associated with intravenous administration of opioids and cocaine; the intensity of response, however, may vary depending on history and extent of prior use.

Smoking Cessation Outcomes among Sexual and Gender Minority and Nonminority Smokers in Extended Smoking Treatments Grady ES, Humfleet GL, Delucchi KL, Reus VI, Muñoz RF, Hall SM. Nicotine Tob Res. 2014 Sep;16(9):1207-1215.
Sexual and gender minority individuals (i.e., lesbian, gay, bisexual, and transgender [LGBT]) have a higher smoking prevalence than nonminority individuals. There is limited evidence of smoking abstinence success in nontailored smoking treatments among LGBT smokers. This study is a secondary data analysis comparing the efficacy of extended, nontailored treatments among sexual and gender minority and nonminority smokers. Data from two clinical trials were combined to increase power and generalizability of the findings. Trials began with 12 weeks of counseling, nicotine replacement, and bupropion, after which participants were randomized to an extended treatment. Follow-up occurred at weeks 12, 24, 52, 64, and 104. Of the sample (n = 777), 17% identified as sexual and gender minority and 83% as nonminority. The sample was 75% non-Hispanic White, with 86% completing at least some college, and 68% were employed. Sexual and gender minorities were younger and indicated a greater desire to quit smoking than nonminority smokers. No other differences emerged on demographic, smoking, or mood variables. The average Fagerström Test for Nicotine Dependence score was 4.8, and mean daily cigarettes was 19.8. The generalized estimating equations model revealed no significant differences in abstinence between sexual and gender minority smokers and nonminority smokers at all follow-up assessments. The authors conclude that sexual and gender minority smokers appear as likely to quit or abstain as nonminority smokers in extended, nontailored interventions. However, these findings may not generalize to other geographic areas, where access to treatment is limited or a higher stigma of sexual orientation exists.

Randomized Trial Comparing Mindfulness Training for Smokers to a Matched Control Davis JM, Manley AR, Goldberg SB, Smith SS, Jorenby DE. J Subst Abuse Treat. 2014 Sep;47 (3):213-221.
Smoking continues to take an enormous toll on society, and although most smokers would like to quit, most are unsuccessful using existing therapies. These findings call on researchers to develop and test therapies that provide higher rates of long-term smoking abstinence. The authors report results of a randomized controlled trial comparing a novel smoking cessation treatment using mindfulness training to a matched control based on the American Lung Association's Freedom From Smoking program. Data were collected on 175 low socioeconomic status smokers in 2011-2012 in a medium sized midwestern city. A significant difference was not found in the primary outcome; intent-to-treat biochemically confirmed 6-month smoking abstinence rates were

mindfulness=25.0%, control=17.9% (p=0.35). Differences favoring the mindfulness condition were found on measures of urges and changes in mindfulness, perceived stress, and experiential avoidance. While no significant differences were found in quit rates, the mindfulness intervention resulted in positive outcomes.

Randomized, Controlled Pilot Trial of a Smartphone App for Smoking Cessation using Acceptance and Commitment Therapy Bricker JB, Mull KE, Kientz JA, Vilardaga R, Mercer LD, Akioka KJ, Heffner JL. Drug Alcohol Depend. 2014 Oct 1;143:87-94.
There is a dual need for (1) innovative theory-based smartphone applications for smoking cessation and (2) controlled trials to evaluate their efficacy. Accordingly, this study tested the feasibility, acceptability, preliminary efficacy, and mechanism of behavioral change of an innovative smartphone-delivered acceptance and commitment therapy (ACT) application for smoking cessation vs. an application following US Clinical Practice Guidelines. Adult participants were recruited nationally into the double-blind randomized controlled pilot trial (n=196) that compared smartphone-delivered ACT for smoking cessation application (SmartQuit) with the National Cancer Institute's application for smoking cessation (QuitGuide). The authors recruited 196 participants in two months. SmartQuit participants opened their application an average of 37.2 times, as compared to 15.2 times for QuitGuide participants (p<0001). The overall quit rates were 13% in SmartQuit vs. 8% in QuitGuide (OR=2.7; 95% CI=0.8-10.3). Consistent with ACT's theory of change, among those scoring low (below the median) on acceptance of cravings at baseline (n=88), the quit rates were 15% in SmartQuit vs. 8% in QuitGuide (OR=2.9; 95% CI=0.6-20.7). The authors conclude that ACT is feasible to deliver by smartphone application and shows higher engagement and promising quit rates compared to an application that follows US Clinical Practice Guidelines. As results were limited by the pilot design (e.g., small sample), a full-scale efficacy trial is now needed.

Delay Discounting Rates: A Strong Prognostic Indicator of Smoking Relapse Sheffer CE, Christensen DR, Landes R, Carter LP, Jackson L, Bickel WK. Addict Behav. 2014 Nov;39(11):1682-1689.
Recent evidence suggests that several dimensions of impulsivity and locus of control are likely to be significant prognostic indicators of relapse. One-hundred and thirty-one treatment seeking smokers were enrolled in six weeks of multi-component cognitive-behavioral therapy with eight weeks of nicotine replacement therapy. Cox proportional hazard regressions were used to model days to relapse with each of the following: delay discounting of $100, delay discounting of $1000, six subscales of the Barratt Impulsiveness Scale (BIS), Rotter's Locus of Control (RLOC), Fagerstrom's Test for Nicotine Dependence (FTND), and the Perceived Stress Scale (PSS). Hazard ratios for a one standard deviation increase were estimated with 95% confidence intervals for each explanatory variable. Likelihood ratios were used to examine the level of association with days to relapse for different combinations of the explanatory variables while accounting for nicotine dependence and stress level. These analyses found that the $100 delay discounting rate had the strongest association with days to relapse. Further, when discounting rates were combined with the FTND and PSS, the associations remained significant. When the other measures were combined with the FTND and PSS, their associations with relapse were non-significant. These findings indicate that delay discounting is independently associated with relapse and adds to what is already accounted for by nicotine dependence and stress level. They also signify that delay discounting is a productive new target for enhancing treatment for tobacco dependence. Consequently, adding an intervention designed to decrease discounting rates to a comprehensive treatment for tobacco dependence has the potential to decrease relapse rates.

Natural History of Attempts to Stop Smoking Hughes JR, Solomon LJ, Naud S, Fingar JR, Helzer JE, Callas PW. Nicotine Tob Res. 2014 Sep;16(9):1190-1198.
This study provides a prospective fine-grain description of the incidence and pattern of intentions to quit, quit attempts, abstinence, and reduction in order to address several clinical questions about self-quitting. A total of 152 smokers who planned to quit in the next 3 months called nightly for 12 weeks to an Interactive Voice Response system to report cigarettes/day, quit attempts, intentions to smoke or not in the next day, and so forth. No treatment was provided. Most smokers (60%) made multiple transitions among smoking, reduction, and abstinence. Intention to not smoke or quit often did not result in a quit attempt but were still strong predictors of a quit attempt and eventual abstinence. Most quit attempts (79%) lasted less than 1 day; about one fifth (18%) of the participants were abstinent at 12 weeks. The majority of quit attempts (72%) were not preceded by an intention to quit. Such quit attempts were shorter than quit attempts preceded by an intention to quit (<1 day vs. 25 days). Most smokers (67%) used a treatment, and use of a treatment was nonsignificantly associated with greater abstinence (14 days vs. 3 days). Making a quit attempt and failing early predicted an increased probability of a later quit attempt compared to not making a quit attempt early (86% vs. 67%). Smokers often (17%) failed to report brief quit attempts on an end-of-study survey. The authors conclude that cessation is a more chronic, complex, and dynamic process than many theories or treatments assume.

Effects of Varenicline, Nicotine or Placebo on Depressive Symptoms in Postmenopausal Smokers Avery N, Kenny AM, Kleppinger A, Brindisi J, Litt MD, Oncken CA. Am J Addict. 2014 Sep-Oct;23(5):459-465.
Varenicline carries a black box warning for neuropsychiatric adverse events. The authors examined varenicline use and past history of major depressive disorder (MDD) on depressive symptoms during smoking cessation. This is a secondary analysis of two smoking cessation studies in 152 postmenopausal women who received placebo or nicotine patch, or 78 women who received varenicline with relaxation. Lifetime history of MDD (LH-MDD) was assessed at baseline and women with current MDD were excluded. Center for Epidemiologic Study Depression scale (CESD) measured depressive symptoms at baseline, 6 and 12 weeks. Baseline CESD scores were 5.3 + 4.4. Those with a LH-MDD reported higher CESD scores ($p > .001$). Those taking varenicline reported lower scores over all time periods compared to nicotine or placebo ($p < .01$). The differences between varenicline and the other treatments remained when controlling for LH-MDD, indicating an independent effect. CESD scores were associated with concurrent smoking status ($p < .001$), and with withdrawal symptoms ($p < .001$). CESD score were lower in those receiving varenicline, whether this is due to an anti-depressant effect, subject selection, use of relaxation or another cause is unknown. Varenicline does not increase depressive symptoms during smoking cessation in postmenopausal women without current MDD. Subjects with a LH-MDD are susceptible to developing depressive symptoms during smoking cessation, regardless of pharmacologic aid. Pharmacologic aids did not increase depression symptoms in this select population of postmenopausal women without current depression. Smoking cessation does increase depressive symptoms in those with LH-MDD, though the degree of increase was not clinically meaningful.

Alternate Tobacco Product and Drug Use among Adolescents who Use Electronic Cigarettes, Cigarettes Only, and Never Smokers Camenga DR, Kong G, Cavallo DA, Liss A, Hyland A, Delmerico J, Cummings KM, Krishnan-Sarin S. J Adolesc Health. 2014 Oct;55(4):588-591.
The purpose of this study was to determine whether use of alternative tobacco products (i.e., cigars, blunts, hookah, smokeless tobacco), alcohol, and marijuana differs among adolescents who

currently use (1) electronic cigarettes (e-cigarettes); (2) cigarettes only; and (3) never smokers. This was an analysis of a self-reported survey from four high schools in 2010-2011 (n = 3,102) with a subsample (n = 1,556) surveyed on alcohol and marijuana. Analyses were conducted with multinomial logistic regression models accounting for clustering by schools. The sample contained 2.4% (n = 76) e-cigarette users, 12.4% (n = 386) cigarette smokers, and 85.1% (n = 3,197) never smokers. E-cigarette users were more likely than cigarette-only smokers to report blunt (adjusted odds ratio, 1.81; 95% confidence interval, 1.21-2.71) and hookah use (adjusted odds ratio, 3.12; 95% confidence interval, 1.90-5.13), but not cigar, smokeless tobacco, alcohol, or marijuana use. E-cigarette users are more likely than cigarette smokers to use hookah and blunts.

Loneliness in HIV-Infected Smokers Stanton CA, Moadel AB, Kim RS, Weinberger AH, Shuter J. AIDS Care. 2014 Oct 8:1-5.
Loneliness is common in persons living with HIV (PLWH). Lonely people smoke at higher rates than the general population, and loneliness is a likely contributor to the ongoing smoking epidemic among PLWH. The authors explored factors associated with loneliness in a cohort of 272 PLWH smokers enrolled in two separate tobacco treatment trials. Loneliness was independently associated with lack of a spouse or partner, lower educational attainment, "other or unknown" HIV exposure category, depression, anxiety, recent alcohol consumption, and higher daily cigarette consumption. Referral to group therapy reduced loneliness, whereas referral to an individual web-based tobacco treatment did not.

Clarifying the Neural Basis for Incentive Salience of Tobacco Cues in Smokers Gray JC, Amlung MT, Acker J, Sweet LH, Brown CL, MacKillop J. Psychiatry Res. 2014 Sep 30;223(3):218-225.
In functional magnetic resonance imaging (fMRI) studies, smoking cues have been found to elicit increases in brain activity in regions associated with processing rewarding and emotional stimuli. However, most smoking cue studies to date have reported effects relative to neutral control stimuli with no incentive properties, making it unclear whether the observed activation pertains to value in general or the value of cigarettes in particular. The current fMRI study sought to clarify the neural activity reflecting tobacco-specific incentive value versus domain-general incentive value by examining smoking cues, neutral cues, and a third set of cues, monetary cues, which served as an active control condition. Participants were 42 male daily smokers. Compared to neutral cues, significantly greater activation was found in the left ventral striatum in response to tobacco and money cues. Monetary cues also elicited significantly increased activation in the right inferior frontal gyrus and cuneus compared to the other two cue types. Overall, the results suggest that the salience of monetary cues was the highest and, as a result, might have reduced the incentive salience of tobacco cues.

Varenicline Efficacy and Safety among Methadone Maintained Smokers: A Randomized Placebo-Controlled Trial Nahvi S, Ning Y, Segal KS, Richter KP, Arnsten JH. Addiction. 2014 Sep;109(9):1554-1563.
The aim of this study was to test the efficacy and safety of varenicline as an aid to smoking cessation in methadone-maintained smokers. This was a multicenter, randomized, double-blind, placebo-controlled trial with random assignment to 12 weeks of varenicline 1 mg twice daily (n = 57) or matched placebo (n = 55), with in-person and telephone counseling. The study setting comprised urban methadone programs in the Bronx, New York City, New York, USA. Participants were methadone maintenance patients, smoking ≥5 cigarettes/day, interested in quitting, stable in methadone treatment, without current Axis I psychiatric disorders, suicidal ideation or recent

suicide attempts. Measurements obtained were seven-day point prevalence abstinence verified by expired carbon monoxide (CO) < 8 parts per million at week 12 (primary outcome); carbon monoxide (CO)-verified abstinence, cigarettes/day, incident Axis I psychiatric illness, suicidal ideation or serious adverse events (SAEs) at weeks 2, 4, 8, 12 or 24 (secondary outcomes). Baseline demographic, smoking and clinical factors were similar between groups. Retention at 24 weeks was 90%. Subjects receiving varenicline were more likely than those receiving placebo to achieve abstinence (10.5 versus 0%, P = 0.03; effect size 10.5%, 95% confidence interval (CI) = 4.4-19.3%) and to reduce smoking (median five versus two cigarettes/day, P < 0.001) at 12 weeks. These effects were not maintained after drug treatment ceased. Incident psychiatric illness (OR= 0.84, 95% CI = 0.16, 4.4) and suicidality [odds ratio (OR) = 0.88, 95% CI 0.2, 3.9] were not different between groups. There were no psychiatric or cardiac SAEs. The authors conclude that varenicline can aid short-term smoking abstinence in methadone-maintained smokers.

Feasibility and Preliminary Efficacy of a Web-Based Smoking Cessation Intervention for HIV-Infected Smokers: A Randomized Controlled Trial Shuter J, Morales DA, Considine-Dunn SE, An LC, Stanton CA. J Acquir Immune Defic Syndr. 2014 Sep 1;67(1):59-66. The objective of this study was to evaluate the feasibility and preliminary efficacy of a Web-based tobacco treatment for persons living with HIV (PLWH). This was a prospective, randomized controlled trial conducted in an HIV-care center in the Bronx, New York. Subject eligibility criteria included HIV infection, current tobacco usage, interest in quitting, and access to a computer with internet. One hundred thirty-eight subjects enrolled, and 134 completed the study. The study intervention, Positively Smoke Free on the Web (PSFW), an 8-session, 7-week targeted tobacco treatment program for PLWH, was compared with standard care (brief advice to quit and self-help brochure). All subjects were offered nicotine patches. The main feasibility outcomes were number of sessions logged into, number of Web pages visited, number of interactive clicks, and total time logged in. The main efficacy outcome was biochemically verified, 7-day point prevalence abstinence 3 months after intervention. PSFW subjects logged into a mean of 5.5 of 8 sessions and 26.2 of 41 pages. They executed a mean of 10 interactive clicks during a mean total of 59.8 minutes logged in. Most required reminder phone calls to complete the sessions. Educational level, anxiety score, and home access of the Web site were associated with Web site usage. Ten percent of the PSFW group vs. 4.3% of controls achieved the abstinence end point. Among those who completed all 8 sessions, 17.9% were abstinent, and among women completers, 30.8% were abstinent. The authors concluded that Web-based treatment is a feasible strategy for PLWH smokers, and preliminary findings suggest therapeutic efficacy.

Lost in Translation? Moving Contingency Management and Cognitive Behavioral Therapy into Clinical Practice Carroll KM. Ann N Y Acad Sci. 2014 Oct;1327(1):94-111.
In the treatment of addictions, the gap between the availability of evidence-based therapies and their limited implementation in practice has not yet been bridged. Two empirically validated behavioral therapies, contingency management (CM) and cognitive behavioral therapy (CBT), exemplify this challenge. Both have a relatively strong level of empirical support but each has weak and uneven adoption in clinical practice. This review highlights examples of how barriers to their implementation in practice have been addressed systematically, using the Stage Model of Behavioral Therapies Development as an organizing framework. For CM, barriers such as cost and ideology have been addressed through the development of lower-cost and other adaptations to make it more community friendly. For CBT, barriers such as relative complexity, lack of trained providers, and need for supervision have been addressed via conversion to standardized computer-

assisted versions that can serve as clinician extenders. Although these and other modifications have rendered both interventions more disseminable, diffusion of innovation remains a complex, often unpredictable process. The existing specialty addiction-treatment system may require significant reforms to fully implement CBT and CM, particularly greater focus on definable treatment goals and performance-based outcomes.

A Mechanistic Test of Nicotine Replacement Therapy Sampling for Smoking Cessation Induction Burris JL, Heckman BW, Mathew AR, Carpenter MJ. Psychol. Addict Behav. 2014 Oct 27. [Epub ahead of print].

Studies that explore the mechanisms of treatment effect are needed in the area of smoking cessation induction, the primary goal of which is to promote the occurrence of a quit attempt among individuals who report little interest in smoking cessation. This study tested the mediational effect of 5 psychological variables (motivation to quit, abstinence self-efficacy, knowledge of nicotine replacement therapy (NRT), and both positive and negative attitudes toward NRT) on the relationship between NRT sampling and smoking outcomes. Adults who reported low levels of intention to quit in the next month (n = 593) were recruited for a nationwide randomized clinical trial of NRT sampling. Participants provided self-report data via telephone interview on multiple occasions, with the final follow-up at 6 months. Motivation to quit, and to a lesser degree, abstinence self-efficacy at the end of the 6-week intervention best accounted for the effect of NRT sampling as a promoter of quit attempts, smoking reduction, and 7-day point prevalence abstinence. Providing smokers with free NRT samples, in addition to encouraging them to engage in temporary abstinence, results in meaningful change in motivation and self-efficacy, which in turn influence smoking outcomes. Cessation induction interventions should aim to increase motivation to quit and abstinence self-efficacy, above and beyond any efforts to increase knowledge or prompt attitudinal shifts.

Guidelines for Establishing a Telemental Health Program to Provide Evidence-Based Therapy for Trauma-Exposed Children and Families Jones AM, Shealy K M, Reid-Quiñones K, Moreland AD, Davidson TM, López CM, Barr SC, de Arellano MA. Psychological Services. 2014 Nov; 11(4): 398-409.

Although similar rates of traumatic experiences exist in both rural and urban settings, mental health resources available to those living in rural areas are often scarce. Limited resources pose a problem for children and families living in rural areas, and several barriers to service access and utilization exist including reduced anonymity, few "after hours" services, decreased availability of evidence-based treatments, few specialty clinics, and expenses associated with travel, taking time off work, and provision of childcare. As a solution, the authors discuss the utility, use, and set-up of a telemental health program within an existing community outreach program. Suggestions for establishing a telemental health clinic are presented along with guidelines for the delivery of trauma-focused, cognitive-behavioral therapy (TF-CBT) via telemental health videoconferencing technology. Specific guidelines discussed include (1) establishing and using community partnerships, (2) Memoranda of Understanding (MOU), (3) equipment setup and technological resources, (4) videoconferencing software, (5) physical setup, (6) clinic administration, (7) service reimbursement and start-up costs, (8) therapy delivery modifications, and (9) delivering culturally competent services to rural and remote areas.

Paving the Way to Successful Implementation: Identifying Key Barriers to Use of Technology-Based Therapeutic Tools for Behavioral Health Care Ramsey A, Lord S, Torrey J, Marsch L, Lardiere M. J Behav Health Serv Res. 2014 Sep 6. [Epub ahead of print].
This study aimed to identify barriers to use of technology for behavioral health care from the perspective of care decision makers at community behavioral health organizations. As part of a larger survey of technology readiness, 260 care decision makers completed an open-ended question about perceived barriers to use of technology. Using the Consolidated Framework for Implementation Research (CFIR), qualitative analyses yielded barrier themes related to characteristics of technology (e.g., cost and privacy), potential end users (e.g., technology literacy and attitudes about technology), organization structure and climate (e.g., budget and infrastructure), and factors external to organizations (e.g., broadband accessibility and reimbursement policies). Number of reported barriers was higher among respondents representing agencies with lower annual budgets and smaller client bases relative to higher budget, larger clientele organizations. Individual barriers were differentially associated with budget, size of client base, and geographic location. Results are discussed in light of implementation science frameworks and proactive strategies to address perceived obstacles to adoption and use of technology-based behavioral health tools.

A Systematic Review ofthe Effects of Behavioral Counseling on Sexual Risk Behaviors and H V/STI Prevalence in Low- and Middle-Income Countries Zajac K, Kennedy CE, Fonner VA, Armstrong KS, O'Reilly KR, Sweat MD. AIDS Behav. 2014 Sep 12. [Epub ahead of print].
The purpose of this study was to assess the effectiveness of behavioral counseling interventions in reducing sexual risk behaviors and HIV/STIprevalence in low- and middle-income countries. A systematic review of papers published between 1990 and 2011 was conducted, identifying studies that utilized either a multi-arm or pre-post design and presented post-intervention data. Standardized methods of searching and data abstraction were used, and 30 studies met inclusion criteria. Results are summarized by intervention groups: (a) people living with HIV; (b) people who use drugs and alcohol; (c) serodiscordant couples; (d) key populations for HIV prevention; and (e) people at low to moderate HIV risk. Evidence for the effectiveness of behavioral counseling was mixed, with more rigorously designed studies often showing modest or no effects. Recommendations about the use of behavioral counseling in developing countries are made based on study results and in light of the field's movement towards combination prevention programs.

Paving the Way to Successful Implementation: Identifying Key Barriers to use of Technology-Based Therapeutic Tools for Behavioral Health Care Ramsey A, Lord S, Torrey J, Marsch L, Lardiere M. J Behav Health Serv Res. 2014 Sep 6. [Epub ahead of print]. This study aimed to identify barriers to use of technology for behavioral health care from the perspective of care decision makers at community behavioral health organizations. As part of a larger survey of technology readiness, 260 care decision makers completed an open-ended question about perceived barriers to use of technology. Using the Consolidated Framework for Implementation Research (CFIR), qualitative analyses yielded barrier themes related to characteristics of technology (e.g., cost and privacy), potential end users (e.g., technology literacy and attitudes about technology), organization structure and climate (e.g., budget and infrastructure), and factors external to organizations (e.g., broadband accessibility and reimbursement policies). Number of reported barriers was higher among respondents representing agencies with lower annual budgets and smaller client bases relative to higher budget, larger clientele organizations. Individual barriers were differentially associated with budget, size of client base, and geographic

location. Results are discussed in light of implementation science frameworks and proactive strategies to address perceived obstacles to adoption and use of technology-based behavioral health tools.

Computer-Based Video to Increase HIV Testing among Emergency Department Patients who Decline Aronson ID, Marsch LA, Rajan S, Koken J, Bania TC. AIDS Behav. 2014 Jul 27. [Epub ahead of print].
The Centers for Disease Control and Prevention recommend routine HIV screening in clinical settings, including emergency departments (EDs), because earlier diagnosis enables treatment before symptoms develop and delivery of interventions to reduce continued transmission. However, patients frequently decline testing. This study delivered a 16-min video-based intervention to 160 patients who declined HIV tests in a high volume, urban ED. One third of participants (n = 53) accepted an HIV test post-intervention. Interviews with a subset of participants (n = 40) show that before the video, many were unaware HIV testing could be conducted without drawing blood, or that results could be delivered in 20 min.

Feasibility, Acceptability, and Preliminary Efficacy of a Smartphone Intervention for Schizophrenia Ben-Zeev D, Brenner CJ, Begale M, Duffecy J, Mohr DC, Mueser KT. Schizophr Bull. 2014 Nov; 40(6):1244-1253.
The FOCUS smartphone intervention was developed to provide automated real-time/real-place illness management support to individuals with schizophrenia. The system was specifically designed to be usable by people with psychotic disorders who may have cognitive impairment, psychotic symptoms, negative symptoms, and/or low reading levels. FOCUS offers users both prescheduled and on-demand resources to facilitate symptom management, mood regulation, medication adherence, social functioning, and improved sleep. In this study, 33 individuals with schizophrenia or schizoaffective disorder used FOCUS over a 1-month period in their own environments. Participants were able to learn how to use the intervention independently, and all but one participant completed the trial successfully and returned the smartphones intact. Completers used the system on 86.5% of days they had the device, an average of 5.2 times a day. Approximately 62% of use of the FOCUS intervention was initiated by the participants, and 38% of use was in response to automated prompts. Baseline levels of cognitive functioning, negative symptoms, persecutory ideation, and reading level were not related to participants' use of the intervention. Approximately 90% of participants rated the intervention as highly acceptable and usable. Paired samples t tests found significant reductions in psychotic symptoms, depression, and general psychopathology, after 1 month of FOCUS use. This study demonstrated the feasibility, acceptability, and preliminary efficacy of the FOCUS intervention for schizophrenia and introduces a new treatment model which has promise for extending the reach of evidence-based care beyond the confines of a physical clinic using widely available technologies.

Novel Methods to Collect Meaningful Data from Adolescents for the Development of Health Interventions Hieftje K, Duncan LR, Fiellin LE. Health Promot Pract. 2014 Sep; 15(5):714-722.
Health interventions are increasingly focused on young adolescents, and as a result, discussions with this population have become a popular method in qualitative research. Traditional methods used to engage adults in discussions do not translate well to this population, who may have difficulty conceptualizing abstract thoughts and opinions and communicating them to others. As part of a larger project to develop and evaluate a video game for risk reduction and HIV prevention in young adolescents, the authors were seeking information and ideas from the priority audience that would help us create authentic story lines and character development in the video game. To

accomplish this authenticity, they conducted in-depth interviews and focus groups with young adolescents aged 10 to 15 years and employed three novel methods: Storytelling Using Graphic Illustration, My Life, and Photo Feedback Project. These methods helped provide a thorough understanding of the adolescents' experiences and perspectives regarding their environment and future aspirations, which they translated into active components of the video game intervention. This article describes the processes the authors used and the valuable data they generated using these three engaging methods. These three activities are effective tools for eliciting meaningful data from young adolescents for the development of health interventions.

Vaccine for Cocaine Dependence: A Randomized Double-Blind Placebo-Controlled Efficacy Trial Kosten TR, Domingo CB, Shorter D, Orson F, Green C, Somoza E, Sekerka R, Levin FR, Mariani JJ, Stitzer M,Tompkins DA, Rotrosen J, Thakkar V, Smoak B, Kampman K. Drug Alcohol Depend. 2014 Jul 1; 140:42-47.

The authors evaluated the immunogenicity, efficacy, and safety of succinylnorcocaine conjugated to cholera toxin B protein as a vaccine for cocaine dependence. This 6-site, 24 week Phase III randomized double-blind placebo-controlled trial assessed efficacy during weeks 8 to 16. The authors measured urine cocaine metabolites thrice weekly as the main outcome. The 300 subjects (76% male, 72% African-American, mean age 46 years) had smoked cocaine on average for 13 days monthly at baseline. They hypothesized that retention might be better and positive urines lower for subjects with anti-cocaine IgG levels of ≥42 μg/mL (high IgG), which was attained by 67% of the 130 vaccine subjects receiving five vaccinations. Almost 3-times fewer high than low IgG subjects dropped out (7% vs 20%). Although for the full 16 weeks cocaine positive urine rates showed no significant difference between the three groups (placebo, high, low IgG), after week 8, more vaccinated than placebo subjects attained abstinence for at least two weeks of the trial (24% vs 18%), and the high IgG group had the most cocaine-free urines for the last 2 weeks of treatment (OR=3.02), but neither were significant. Injection site reactions of induration and tenderness differed between placebo and active vaccine, and the 29 serious adverse events did not lead to treatment related withdrawals, or deaths. The vaccine was safe, but it only partially replicated the efficacy found in the previous study based on retention and attaining abstinence.

Co-occurring Prescription Opioid use Problems and Post-Traumatic Stress Disorder Symptom Severity Meier A, Lambert-Harris C, McGovern MP, Xie H, An M, McLeman B. Am J Drug Alcohol Abuse. 2014 Jul; 40(4):304-311.

Prescription opioids are the most rapidly growing category of abused substances, and result in significant morbidity, mortality and healthcare costs. Co-occurring with psychiatric disorders, persons with prescription opioid problems have negative treatment outcomes. Data are needed on the prevalence of co-occurring prescription opioid abuse and specific disorders, such as posttraumatic stress disorder (PTSD), to better inform clinical practice. The objective of this study was to determine prevalence rates of current co-occurring prescription opioid use problems and PTSD symptom severity among patients in community addiction treatment settings. The authors abstracted administrative and chart information on 573 new admissions to three addictive treatment agencies during 2011. Systematic data were collected on PTSD symptoms, substance use, and patient demographics. Prescription opioid use was significantly associated with co-occurring PTSD symptom severity (OR: 1.42, $p<0.05$). Use of prescription opioids in combination with sedatives (OR: 3.81, $p<0.01$) or cocaine (OR: 2.24, $p<0.001$) also were associated with PTSD severity. The odds of having co-occurring PTSD symptoms and prescription opioid use problem were nearly three times greater among females versus males (OR: 2.63, $p<0.001$). Younger patients (18-34 years old) also were at higher risk (OR: 1.86, $p<0.01$). The authors conclude that prescription opioid use

problems are a risk factor for co-occurring PTSD symptom severity. Being female or younger increase the likelihood of this co-morbidity. Further research is needed to confirm these finding, particularly using more rigorous diagnostic procedures. These data suggest that patients with prescription opioid use problems should be carefully evaluated for PTSD symptoms.

Elucidating Dimensions of Post-Traumatic Stress Symptoms and their Functional Correlates in Disaster-Exposed Adolescents Sumner JA, Pietrzak RH, Danielson CK, Adams ZW, Ruggiero KJ. J Psychiatr Res. 2014 Sep 16. [Epub ahead of print].

The aim of this study was to elucidate the dimensional structure of posttraumatic stress disorder (PTSD) and potential moderators and functional correlates of this structure in disaster-affected adolescents. A population-based sample of 2000 adolescents aged 12-17 years (M = 14.5 years; 51% female) completed interviews on post-tornado PTSD symptoms, substance use, and parent-adolescent conflict between 4 and 13 months (M = 8.8, SD = 2.6) after tornado exposure. Confirmatory factor analyses revealed that all models fit well but a 5-factor dysphoric arousal model provided a statistically significantly better representation of adolescent PTSD symptoms compared to 4-factor dysphoria and emotional numbing models. There was evidence of measurement invariance of the dysphoric arousal model across gender and age, although girls and older adolescents aged 15-17 years had higher mean scores than boys and younger adolescents aged 12-14 years, respectively, on some PTSD dimensions. Differential magnitudes of association between PTSD symptom dimensions and functional correlates were observed, with emotional numbing symptoms most strongly positively associated with problematic substance use since the tornado, and dysphoric arousal symptoms most strongly positively associated with parent-adolescent conflict; both correlations were significantly larger than the corresponding correlations with anxious arousal. Taken together, these results suggest that the dimensional structure of tornado-related PTSD symptomatology in adolescents is optimally characterized by five separate clusters of re-experiencing, avoidance, numbing, dysphoric arousal, and anxious arousal symptoms, which showed unique associations with functional correlates. Findings emphasize that PTSD in disaster-exposed adolescents is not best conceptualized as a homogenous construct and highlight potential differential targets for post-disaster assessment and intervention.

SiHLEWeb.com: Development and Usability Testing of an Evidence-Based HIV Prevention Website for Female African-American Adolescents Danielson CK, McCauley JL, Gros KS, Jones AM, Barr SC, Borkman AL, Bryant BG, Ruggiero KJ. Health Informatics J. 2014 Aug 28. [Epub ahead of print].

African-American adolescent girls are at disproportionate risk for HIV infection. Although numerous evidence-based risk-reduction interventions exist, dissemination and implementation resources remain limited, and prevention services remain notably inaccessible to the very populations at highest risk for HIV infection. Internet delivery of HIV risk-reduction programming has promise as a mechanism for extending the reach of existing prevention efforts and overcoming barriers associated with traditional service delivery. This article (1) details the development process for the creation of SiHLEWeb, a web-adapted version of an evidence-based, culturally informed HIV prevention program traditionally delivered to female African-American adolescents via an in-person group format, and (2) presents findings from quantitative and qualitative usability testing conducted among 18 African-American girls (13-18 years). Results suggest that users found the website improved knowledge and learning, was helpful, efficient to use, and generally attractive. Users reported some concerns about website navigation. Implications for Internet delivery of health prevention programming are discussed.

Prevalence and Predictors of PTSD and Depression among Adolescent Victims of the Spring 2011 Tornado Outbreak Adams ZW, Sumner JA, Danielson CK, McCauley JL, Resnick HS, Grös K, Paul LA, Welsh KE, Ruggiero KJ. J Child Psychol Psychiatry. 2014 Sep;55(9):1047-1055.
Relatively few studies have examined prevalence and predictors of posttraumatic stress disorder (PTSD) or major depressive episode (MDE) in disaster-affected adolescents. Fewer still have administered diagnostic measures or studied samples exposed to tornadoes, a common type of disaster. Further, methodologic problems limit the generalizability of previous findings. This study addressed prevalence estimates and risk factors for PTSD and MDE among adolescents exposed to the Spring 2011 tornado outbreak in Alabama and Joplin, Missouri. A large (N = 2000), population-based sample of adolescents and caregivers, recruited randomly from tornado-affected communities, participated in structured telephone interviews. PTSD and MDE prevalence were estimated for the overall sample, by gender, and by age. Hierarchical logistic regression was used to identify risk factors for PTSD and MDE. Overall, 6.7% of adolescents met diagnostic criteria for PTSD and 7.5% of adolescents met diagnostic criteria for MDE since the tornado. Girls were significantly more likely than boys to meet diagnostic criteria for MDE, and older adolescents were more likely than younger adolescents to report MDE since the tornado. Female gender, prior trauma exposure, and an injured family member were associated with greater risk for PTSD and MDE. Specific incident characteristics (loss of services, concern about others' safety) were associated with greater PTSD risk; prior disaster exposure was associated with lower MDE risk. However, most adolescents were resilient following tornado exposure, roughly 1 in 15 developed PTSD, 1 in 13 developed MDE, and many more endorsed subclinical mental health problems. Information regarding specific risk factors can guide early screening, prevention, and intervention efforts in disaster-affected communities.

Substance-Abusing Mothers and Fathers' Willingness to Allow their Children to Receive Mental Health Treatment Kelley ML, D'Lima GM, Henson JM, Cotten C. J Subst Abuse Treat. 2014 Jul;47(1):106-111.
The purpose of this study was to examine attitudes of substance-abusing mothers and fathers entering outpatient treatment toward allowing their children to participate in individual- or family-based interventions. Data were collected from a brief anonymous survey completed by adults at intake into a large substance abuse treatment program in western New York. Only one-third of parents reported that they would be willing to allow their children to participate in any form of mental health treatment. Results of chi-square analyses revealed that a significantly greater proportion of mothers reported that they would allow their children to participate in mental health treatment (41%) compared to fathers (28%). Results of logistic regression analyses revealed even after controlling for child age, mothers were more likely than fathers to indicate their willingness to allow their children to receive mental health treatment; however, type of substance abuse (alcohol versus drug abuse) was not associated with parents' willingness to allow their children to receive treatment. Parental reluctance to allow their children to receive individual or family-based treatment is a significant barrier in efforts to intervene with these at-risk children.

Social Anxiety and Heavy Situational Drinking: Coping and Conformity Motives as Multiple Mediators Terlecki MA, Buckner JD. Addict Behav. 2014 Sep 11;40C:77-83. Individuals with clinically elevated social anxiety are at greater risk for alcohol use disorder, and the relation between social anxiety and drinking problems is at least partially accounted for by drinking more in negative emotional (e.g., feeling sad or angry) and personal/intimate (e.g., before sexual intercourse) situations. Identification of cognitive/motivational factors related to drinking in these high-risk situations could inform the development of treatment and prevention interventions for

these high-risk drinkers. The current cross-sectional study examined the mediating effect of drinking motives on the relationship between social anxiety and drinking these high-risk situations among undergraduates (N=232). Clinically elevated social anxiety was associated with greater coping and conformity motives. Both coping and conformity motives mediated the relation between social anxiety and heavier alcohol consumption in negative emotional and personal/intimate contexts. Multiple mediation analyses indicated that these motives work additively to mediate the social anxiety-drinking situations relationship, such that heavy situational drinking among undergraduates with clinically elevated social anxiety can be jointly attributed to desire to cope with negative affect and to avoid social scrutiny.

Cannabis-Related Impairment: The Impacts of Social Anxiety and Misconceptions of Friends' Cannabis-Related Problems Ecker AH, Richter AA, Buckner JD. Addict Behav. 2014 Dec;39(12):1746-1749.

Socially anxious cannabis users are especially vulnerable to cannabis-related impairment, yet mechanisms underlying this vulnerability remain unclear. Socially anxious persons may use cannabis despite related problems if they believe such problems are common, and thus socially acceptable. Yet no known studies have examined the impact of beliefs regarding others' cannabis-related problems on one's own use-related problems. This study investigated the impact of beliefs about a close friend's experience with cannabis-related problems on the relationship between social anxiety and cannabis-related problems. The sample consisted of 158 (75% female) current (past-month) cannabis-using undergraduates. Believing one's friend experienced more cannabis problems was related to experiencing more cannabis-related problems oneself. In fact, perceived friend's problems accounted for 40% of the unique variance in one's own cannabis problems. Descriptive norms (others' use) and injunctive norms (others' approval of risky use) were unrelated to the number of one's own problems. Social anxiety was related to experiencing more cannabis problems. This relation was moderated by perceived friend's problems such that greater social anxiety was related to more cannabis-related problems among participants who believed their friend experienced more cannabis-related problems. This was not the case among participants who believed their friend experienced fewer problems. Normative beliefs regarding a close friend's cannabis problems were robustly and uniquely related to experiencing more cannabis-related impairment. Beliefs regarding friends' experience with cannabis-related problems may play an especially important role in the experience of cannabis-related problems among socially anxious users.

Robust Impact of Social Anxiety in Relation to Coping Motives and Expectancies, Barriers to Quitting, and Cessation-Related Problems Buckner JD, Zvolensky MJ, Jeffries ER, Schmidt NB. Exp Clin Psychopharmacol. 2014 Aug;22(4):341-347.

Although social anxiety is related to smoking and nicotine dependence, few researchers have sought to identify factors that contribute to these relations. The current study examined whether social anxiety was associated with cognitive vulnerability factors related to smoking: perceived barriers for quitting, cessation-related problems, negative-affect-reduction-outcome expectancies, and negative-affect-reduction motives. Further, the authors tested whether social anxiety was robustly related to these factors after controlling for cigarettes smoked per day, gender, alcohol-use frequency, lifetime cannabis-use status, panic attack frequency, anxiety sensitivity, and negative affectivity. The sample consisted of 580 (38.6% female) treatment-seeking smokers. Social anxiety was associated with perceived barriers for quitting, cessation-related problems, negative-affect-reduction-outcome expectancies, and negative-affect-reduction motives. After controlling for covariates, social anxiety was robustly related to perceived barriers for quitting, cessation-related problems, and negative-affect-reduction-outcome expectancies. Social anxiety was robustly related

to negative-affect-reduction motives among men, but not women. Results indicate that social anxiety is robustly related to cognitive vulnerability factors associated with poorer cessation outcomes, suggesting that social anxiety may be an important therapeutic target during smoking cessation.

A Review of Guidelines on Home Drug Testing Web Sites for Parents Washio Y, Fairfax-Columbo J, Ball E, Cassey H, Arria AM, Bresani E, Curtis BL, Kirby KC. J Addict Med. 2014 Jul-Aug;8(4):258-263. The objectives of this study were to update and extend prior work reviewing Web sites that discuss home drug testing for parents, and assess the quality of information that the Web sites provide, to assist them in deciding when and how to use home drug testing. The authors conducted a worldwide Web search that identified 8 Web sites providing information for parents on home drug testing. They assessed the information on the sites using a checklist developed with field experts in adolescent substance abuse and psychosocial interventions that focus on urine testing. None of the Web sites covered all the items on the 24-item checklist, and only 3 covered at least half of the items (12, 14, and 21 items, respectively). The remaining 5 Web sites covered less than half of the checklist items. The mean number of items covered by the Web sites was 11. Among the Web sites that we reviewed, few provided thorough information to parents regarding empirically supported strategies to effectively use drug testing to intervene on adolescent substance use. Furthermore, most Web sites did not provide thorough information regarding the risks and benefits to inform parents' decision to use home drug testing. Empirical evidence regarding efficacy, benefits, risks, and limitations of home drug testing is needed.

Providing Alcohol for Underage Youth: What Messages Should We be Sending Parents? Kaynak Ö, Winters KC, Cacciola J, Kirby KC, Arria AM. J Stud Alcohol Drugs. 2014 Jul;75(4):590-605.
There have been conflicting findings in the literature concerning the risks to adolescents when parents provide them with alcohol. Studies have examined various ways in which parents directly affect adolescent alcohol consumption through provision (e.g., parental offers, parental allowance/supervision, parental presence while drinking, and parental supply). This review synthesizes findings on the direct ways parental provision can influence a child's alcohol consumption and related problems in an effort to provide parents with science-based guidance. The authors describe potential mechanisms of the relationship between these parental influences and adolescent problems, suggest future directions for research, and discuss implications for parents. Twenty-two studies (a mix of cross-sectional and longitudinal) that empirically examined the association between parental provision and adolescent drinking outcomes were reviewed. Parental provision was generally associated with increased adolescent alcohol use and, in some instances, increased heavy episodic drinking as well as higher rates of alcohol-related problems. Data in support of the view that parental provision serves as a protective factor in the face of other risk factors were equivocal. The nature and extent of the risks associated with parental provision, and the potential mechanisms underlying this association, are complex issues. Although more rigorous studies with longitudinal designs are needed, parents should be aware of potential risks associated with providing adolescents with alcohol and a place to drink. It is recommended that parents discourage drinking until adolescents reach legal age.

Injection Drug Use is Associated with Suicide Attempts but not Ideation or Plans in a Sample of Adolescents with Depressive Symptoms Liu RT, Case BG, Spirito A. J Psychiatr Res. 2014 Sep;56:65-71.
Based on the interpersonal theory of suicide, pain habituation that occurs with injection substance use may raise risk for a suicide attempt. The current study tested whether injection substance use, relative to painless routes of substance administration, was related to greater risk for suicide attempts. The authors also assessed whether this risk was specific to suicide attempts and not suicidal ideation or suicide plans. Data on 2095 substance-using adolescents aged 12-17 who endorsed clinically significant depression symptoms and answered questions on suicidal thoughts and behavior were drawn from the 2004-2011 National Survey on Drug Use and Health, a nationally representative household survey. Logistic regression analyses were conducted to assess the associations between injection substance use and suicidal ideation, plans, and attempts. Injection substance use was associated with suicide attempts (OR = 3.02, 95% CI = 1.75-5.23) but not ideation or plans. These findings were not accounted for by sex, age, race/ethnicity, family income, abuse and dependence symptoms, and depression symptoms. Among ideators, injection substance use was associated with suicide attempts (OR = 2.92, 95% CI = 1.58-5.06), but not plans. Among suicide planners, injection substance use was associated with suicide attempts (OR = 5.16, 95% CI = 1.88-14.17). Consistent with the interpersonal theory of suicide, adolescent injection drug use was associated with specific risk for suicide attempts but not ideation or planning. Hence, consideration of the manner in which adolescents use substances is important in evaluating suicide risk in this population.

Task Importance Affects Event-Based Prospective Memory Performance in Adults with HIV-Associated Neurocognitive Disorders and HIV-Infected Young Adults with Problematic Substance Use Woods SP, Doyle KL, Morgan EE, Naar-King S, Outlaw AY, Nichols SL, Loft S. J Int Neuropsychol Soc. 2014 Jul;20(6):652-662.
Two experiments were conducted to examine the effects of task importance on event-based prospective memory (PM) in separate samples of adults with HIV-associated neurocognitive disorders (HAND) and HIV-infected young adults with substance use disorders (SUD). All participants completed three conditions of an ongoing lexical decision task: (1) without PM task requirements; (2) with PM task requirements that emphasized the importance of the ongoing task; and (3) with PM task requirements that emphasized the importance of the PM task. In both experiments, all HIV+ groups showed the expected increase in response costs to the ongoing task when the PM task's importance was emphasized. In Experiment 1, individuals with HAND showed significantly lower PM accuracy as compared to HIV+ subjects without HAND when the importance of the ongoing task was emphasized, but improved significantly and no longer differed from HIV+ subjects without HAND when the PM task was emphasized. A similar pattern of findings emerged in Experiment 2, whereby HIV+ young adults with SUD (especially cannabis) showed significant improvements in PM accuracy when the PM task was emphasized. Findings suggest that both HAND and SUD may increase the amount of cognitive attentional resources that need to be allocated to support PM performance in persons living with HIV infection.

Association Between Interleukin-6 and Neurocognitive Performance as a Function of Self-Reported Lifetime Marijuana Use in a Community Based Sample of African American Adults Keen L 2nd, Turner AD. J Int Neuropsychol Soc. 2014 Sep;20(8):773-783. The purpose of the current study was to determine if self-reported lifetime marijuana use moderates the relationship between interleukin-6 (IL-6) and neurocognitive performance. Participants included 161 African American adults (50.3% women), with a mean age of 45.24 (SD=11.34). Serum was drawn upon

entry into the study and participants completed a demographic questionnaire, which included drug use history, and a battery of neuropsychological tests. Using multiple regression analyses and adjusting for demographic covariates, the interaction term comprised of IL-6 and self-reported lifetime marijuana use was significantly associated with poorer performance on the Written (β=-.116; SE=.059; p=.049) and Oral trials (β=-.143; SE=.062; p=.022) of the Symbol Digit Modalities Test, as well as the Trail Making Test trial A (β=.157; SE=.071; p=.028). Current findings support previous literature, which presents the inverse relationship between IL-6 and neurocognitive dysfunction. The potential protective properties of marijuana use in African Americans, who are at increased risk for inflammatory diseases, are discussed.

Binge Drinking, Stimulant Use and HIV Risk in a Sample of Illicit Drug Using Heterosexual Black Men Keen L 2nd, Dyer TP, Whitehead NE, Latimer W. Addict Behav. 2014 Sep;39(9):1342-1345.
Relatively little research has examined the effects of binge drinking and HIV risk in heterosexual Black men. Even less research has explored this relationship in illicit drug using heterosexual Black men who are at an elevated risk of contracting and transmitting HIV through various vectors, including risky sexual behavior, in the Black community. The purpose of the current study is to examine the associations between binge drinking, drug use and HIV status in a community-based sample of 127 self-identified heterosexual Black men. Overall, 17% reported binge drinking in the past month. Both stimulant use (AOR 7.29; 95%; CIs, 2.07, 25.70), and binge drinking (AOR=5.28; 95% CIs, 1.34, 20.91) were associated with HIV status. These findings will inform prevention interventions to reduce the HIV risk among Black heterosexual men.

Injection and Non-Injection Drug Use and Infectious Disease in Baltimore City: Differences by Race Keen L 2nd, Khan M, Clifford L, Harrell PT, Latimer WW. Addict Behav. 2014 Sep;39(9):1325-1328.
The current study examines differences in the prevalence of biologically-confirmed hepatitis C virus (HCV), HIV, and coinfection between Black and White adult cocaine/heroin users across three drug use subgroups identified in previous research (Harrell et al., 2012): non-injection smoking crack/nasal heroin users, heroin injectors, and polydrug injectors. 59% of the 482 participants in the study were male. Significant race differences emerged between drug use subgroup memberships. Non-injection smoking crack/nasal heroin users were predominantly Black (75%), while heroin injectors and polydrug injectors were predominantly White (69% and 72%, respectively). Polydrug injectors accounted for nearly three quarters of the HCV positive diagnoses in Whites. Though HIV disease status, stratified by race, did not differ significantly between drug use subgroups, the non-injection smoking crack/nasal heroin subgroup contained over half of the HIV positive diagnoses in the sample and was predominantly Black. Despite much lower rates of injection, Blacks (8%) had a higher prevalence of coinfection than Whites (3%; X(2) (2)=6.18, p=.015). The current findings are consistent with trends in the recent HIV transmission statistics where sexual activity has overtaken injection drug use as a HIV risk factor. The current findings also provide further support to the notion of injection drug use as an exceedingly high-risk behavior for HCV and coinfection, specifically those who are polysubstance injectors.

Self-Reported Lifetime Marijuana Use and Interleukin-6 Levels in Middle-Aged African Americans Keen L 2nd, Pereira D, Latimer W. Drug Alcohol Depend. 2014 Jul 1;140:156-160.
Research examining the relationship between marijuana and cytokine function has been well developed in the biochemical literature. However, scant literature exists regarding this relationship between inflammatory markers and marijuana use in public health or behavioral studies and is

virtually nonexistent in non-neurologically compromised African American samples. The current study examined the differences in serum interleukin-6 (IL-6), a proinflammatory cytokine, between non-drug users (n=78), marijuana only users (n=46) and marijuana plus other drugs users (n=45) in a community-based sample of middle aged African Americans. Participants included 169 African American adults (50.30% female), with a mean age of 45.68 years (SD=11.72 years) from the Washington, DC metropolitan area. Serum was drawn upon entry into the study and the participants completed a demographic questionnaire, which included questions regarding drug use history. After adjusting for demographic and physiological covariates, analysis of covariance revealed a significant difference between the three groups, F(2,158)=3.08, p=0.04). Post hoc analyses revealed lifetime marijuana only users had significantly lower IL-6 levels (M=2.20 pg/mL, SD=1.93) than their lifetime nonuser counterparts (M=3.73 pg/mL, SD=6.28). No other comparisons among the groups were statistically significantly different. The current findings extend previous cellular and biochemical literature, which identifies an inverse association between IL-6 and marijuana use. Examining this relationship in the psychological and behavioral literature could be informative to the development of clinical interventions for inflammatory diseases.

A Pilot Trial of a Videogame-Based Exercise Program for Methadone Maintained Patients. Cutter CJ, Schottenfeld RS, Moore BA, Ball SA, Beitel M, Savant JD, Stults-Kolehmainen MA, Doucette C, Barry DT. J Subst Abuse Treat. 2014 Oct;47(4):299-305.
Few studies have examined exercise as a substance use disorder treatment. This pilot study investigated the feasibility and acceptability of an exercise intervention comprising the Wii Fit Plus™ and of a time-and-attention sedentary control comprising Wii™ videogames. The authors also explored their impact on physical activity levels, substance use, and psychological wellness. Twenty-nine methadone-maintained patients enrolled in an 8-week trial were randomly assigned to either Active Game Play (Wii Fit Plus™ videogames involving physical exertion) or Sedentary Game Play (Wii™ videogames played while sitting). Participants had high satisfaction and study completion rates. Active Game Play participants reported greater physical activity outside the intervention than Sedentary Game Play participants despite no such differences at baseline. Substance use decreased and stress and optimism improved in both conditions. Active Game Play is a feasible and acceptable exercise intervention, and Sedentary Game Play is a promising time-and-attention control. Further investigations of these interventions are warranted.

Examining Educational Attainment, Prepregnancy Smoking Rate, and Delay Discounting as Predictors of Spontaneous Quitting among Pregnant Smokers White TJ, Redner R, Skelly JM, Higgins ST. Exp Clin Psychopharmacol. 2014 Oct;22(5):384-391.
The authors investigated three potential predictors (educational attainment, prepregnancy smoking rate, and delay discounting [DD]) of spontaneous quitting among pregnant smokers. These predictors were examined alone and in combination with other potential predictors using study-intake assessments from controlled clinical trials examining the efficacy of financial incentives for smoking cessation and relapse prevention. Data from 349 pregnant women (231 continuing smokers and 118 spontaneous quitters) recruited from the greater Burlington, VT, area contributed to this secondary analysis, including psychiatric/sociodemographic characteristics, smoking characteristics, and performance on a computerized DD task. Educational attainment, smoking rate, and DD values were each significant predictors of spontaneous quitting in univariate analyses. A model examining those three predictors together retained educational attainment as a main effect and revealed a significant interaction of DD and smoking rate (i.e., DD was a significant predictor at lower but not higher smoking rates). A final model considering all potential predictors, included education, the interaction of DD and smoking rate, and five additional predictors (i.e., stress ratings, the belief that

smoking during pregnancy will "greatly harm my baby," age of smoking initiation, marital status, and prior quit attempts during pregnancy). The study presented here contributes new knowledge on predictors of spontaneous quitting among pregnant smokers with substantive practical implications for reducing smoking during pregnancy.

The Efficacy of Contingency Management for Adolescent Cannabis Use Disorder: A Controlled Study Kaminer Y, Burleson JA, Burke R, Litt MD. Subst Abus. 2014 Jul 10:0. [Epub ahead of print].
To investigate the efficacy of a voucher based reinforcement therapy (VBRT) rewarding drug free urine for adolescents with cannabis use disorder. This was a controlled 10-week study where 59 adolescents age 14-18 years were assigned by cohorts into groups of either an integrated cognitive behavioral therapy (CBT) and VBRT or CBT with attendance-based reward program. Substance use was monitored by twice-weekly urinalysis. Other measures were collected at pre-, post-treatment, and at 3-month follow-up. There was no significant difference in the linear change between conditions for cannabis use either from session one to ten or between end-of -treatment to three-month follow-up. Also, self-efficacy and coping response did no show improvement during treatment.: In this study, the addition of contingency management (CM) to CBT in youth was not found to be more efficacious than similar compensation rewarding attendance only. Continued examination of the efficacy of CM and its interaction with the associated mechanisms of behavior change (MBCs) of CBT in youth is necessary. Examination of the effect of the magnitude of the reward as well as considering the emotional and cognitive developmental differences from adults is warranted.

A Pilot Study of a Distress Tolerance Treatment for Opiate-Dependent Patients Initiating Buprenorphine: Rationale, Methodology, and Outcomes Brown RA, Bloom EL, Hecht J, Moitra E, Herman DS, Stein MD. Behav Modif. 2014 Sep;38(5):730-759.
Buprenorphine, an opioid that is a long-acting partial opiate agonist, is an efficacious treatment for opiate dependence that is growing in popularity. Nevertheless, evidence suggests that many patients will lapse within the first week of treatment and that lapses are often associated with withdrawal-related or emotional distress. Recent research suggests that individuals' reactions to this distress may represent an important treatment target. In the current study, the authors describe the development and outcomes from a preliminary pilot evaluation (N = 5) of a novel distress tolerance (DT) treatment for individuals initiating buprenorphine. This treatment incorporates exposure-based and acceptance-based treatment approaches that the authors have previously applied to the treatment of tobacco dependence. Results from this pilot study establish the feasibility and acceptability of this approach. The authors are now conducting a randomized controlled trial of this treatment that we hope will yield clinically significant findings and offer clinicians an efficacious behavioral treatment to complement the effects of buprenorphine.

RESEARCH ON PHARMACOTHERAPIES FOR DRUG ABUSE

Alpha 2A Adrenergic Receptor Agonist, Guanfacine, Attenuates Cocaine-Related Impairments Of Inhibitory Response Control And Working Memory In Animal Models Terry AV Jr, Callahan PM, Schade R, Kille NJ, Plagenhoef M. Pharmacol Biochem Behav. 2014 Nov;126: 63-72.

There is considerable evidence that centrally acting α2A adrenergic receptor agonists can attenuate impairments in executive function that result from dysfunction of the prefrontal cortex. Such positive effects resulted in the recent approval by the United States Food and Drug Administration (FDA) of the α2A agonists clonidine and guanfacine for the treatment of Attention-Deficit/ Hyperactivity Disorder (ADHD), but also suggest that they could have beneficial effects in substance abuse disorders and other neuropsychiatric conditions. The purpose of this study was to evaluate guanfacine for its ability to attenuate behavioral alterations associated with acute cocaine exposure in rats trained to perform a task of sustained attention, the five choice serial reaction time task (5C-SRTT) and monkeys trained to perform a task of working/short term memory, the delayed match to sample (DMTS) task. In the rodent 5C-SRTT acute intraperitoneal (i.p.) administration of cocaine (3.5-15.0mg/kg) did not affect accuracy, but was associated with dose-dependent increases in premature responses and timeout responses. Guanfacine (0.1-1.0mg/kgi.p.) dose-dependently decreased premature responses and timeout responses associated with cocaine and it attenuated similar deficits in inhibitory response control observed in a variable ITI version of the 5C-SRTT. In the DMTS task in monkeys, acute intramuscular (i.m.) administration of cocaine (4.0mg/kg) was associated with impairments in accuracy at long delay intervals, an effect that was attenuated by guanfacine (0.4mg/kg). These animal studies suggest that guanfacine may have therapeutic potential for treating impairments of executive function that are associated with the abuse of cocaine.

Effects Of Oral And Intravenous Administration Of Buspirone On Food-Cocaine Choice In Socially Housed Male Cynomolgus Monkeys Czoty PW, Nader MA. Neuropsychopharmacology. 2014 Nov 13. [Epub ahead of print].

Drugs acting at D_3 dopamine receptors have been suggested as medications for cocaine dependence. These experiments examined the effects of intravenously and orally administered buspirone, a D2-like receptor antagonist with high affinity for D_3 and D_4 receptors, on the relative reinforcing strength of cocaine in group-housed male cynomolgus monkeys. Use of socially housed monkeys permitted the assessment of whether social status, known to influence D2-like receptor availability, modulates the behavioral effects of buspirone. Buspirone was administered acutely to monkeys self-administering cocaine under a food-drug choice procedure in which a cocaine self-administration dose-effect curve was determined daily. When administered by either route, buspirone significantly decreased cocaine choice in dominant-ranked monkeys. In subordinate monkeys, however, i.v. buspirone was ineffective on average, and oral buspirone increased choice of lower cocaine doses. The effects of buspirone only differed according to route of administration in subordinate monkeys. Moreover, it is noteworthy that the effects of buspirone were similar to those of the D_3-receptor selective antagonist PG01037 and qualitatively different than those of less selective drugs that act at D2-like or serotonin $(5\text{-HT})_{1A}$ receptors, suggesting a D_3- and possibly D_4-receptor mechanism of action for buspirone. Taken together, the data support the utility of drugs targeting D_3/D_4 receptors as potential treatments for cocaine addiction, particularly in combination with enriching environmental manipulations.

Further Characterization Of Quinpirole-Elicited Yawning As A Model Of Dopamine D3 Receptor Activation In Male And Female Monkeys Martelle SE, Nader SH, Czoty PW, John WS, Duke AN, Garg PK, Garg S, Newman AH, Nader MA. J Pharmacol Exp Ther. 2014 Aug;350(2):205-211

The dopamine (DA) D3 receptor (D3R) has been associated with impulsivity, pathologic gambling, and drug addiction, making it a potential target for pharmacotherapy development. Positron emission tomography studies using the D3R-preferring radioligand [(11)C]PHNO ([(11)C](+)-propyl-hexahydro-naphtho-oxazin) have shown higher binding potentials in drug abusers compared with control subjects. Preclinical studies have examined D3R receptor activation using the DA agonist quinpirole and the unconditioned behavior of yawning. However, the relationship between quinpirole-elicited yawning and D3R receptor availability has not been determined. In Experiment 1, eight drug-naive male rhesus monkeys were scanned with [(11)C]PHNO, and the ability of quinpirole (0.01-0.3 mg/kg i.m.) to elicit yawning was examined. Significant positive (globus pallidus) and negative (caudate nucleus, putamen, ventral pallidum, and hippocampus) relationships between D3R receptor availability and quinpirole-induced yawns were noted. Experiment 2 replicated earlier findings that a history of cocaine self-administration (n = 11) did not affect quinpirole-induced yawning and extended this to examine monkeys (n = 3) with a history of methamphetamine (MA) self-administration and found that monkeys with experience self-administering MA showed greater potency and significantly higher quinpirole-elicited yawning compared with controls. Finally, quinpirole-elicited yawning was studied in drug-naive female monkeys (n = 6) and compared with drug-naive male monkeys (n = 8). Sex differences were noted, with quinpirole being more potent and eliciting significantly more yawns in males compared with females. Taken together these findings support the use of quinpirole-elicited yawning as a behavioral tool for examining D3R activation in monkeys and that both drug history and sex may influence individual sensitivity to the behavioral effects of D3R compounds

Environmental Enrichment Reduces Methamphetamine Cue-Induced Reinstatement But Does Not Alter Methamphetamine Reward Or VMAT2 Function Hofford RS, Darna M, Wilmouth CE, Dwoskin LP, Bardo MT. Behav Brain Res. 2014 Aug 15;270:151-158.

Environmental factors influence a variety of health-related outcomes. In general, being raised in an environment possessing social, sensory, and motor enrichment reduces the rewarding effects of various drugs, thus protecting against abuse vulnerability. However, in the case of methamphetamine (METH), which acts at the vesicular monoamine transporter 2 (VMAT2) to enhance dopamine release from the cytosol, previous evidence suggests that METH reward may not be altered by environmental enrichment. This study examined the influence of an enriched environment on measures of METH reward, METH seeking, and VMAT2 function. Rats were raised from weaning to adulthood in either an enriched environment (presence of social cohorts and novel objects) or an isolated environment (no cohorts or novel objects). Rats in these two conditions were subsequently tested for their acquisition of conditioned place preference (CPP), METH self-administration, maintenance of self-administration at various unit doses of METH (0.001-0.5mg/kg/infusion), and cue-induced reinstatement. VMAT2 function in striatum from these two groups also was assessed. No significant environment effects were found in CPP or METH self-administration, which paralleled a lack of effect in VMAT2 function between groups. However, cue-induced reinstatement was reduced by environmental enrichment. Together, these results suggest that environmental enrichment does not alter VMAT2 function involved in METH reward. However, the enrichment-induced decrease in cue-induced reinstatement indicates that enrichment may have a beneficial effect against relapse following a period of extinction via a neural mechanism other than striatal VMAT2 function.

2',6'-Dihalostyrylanilines, Pyridines, and Pyrimidines For The Inhibition Of The Catalytic Subunit Of Methionine S-Adenosyltransferase-2 Sviripa VM, Zhang W, Balia AG, Tsodikov OV, Nickell JR, Gizard F, Yu T, Lee EY, Dwoskin LP, Liu C, Watt DS. Med Chem. 2014 Jul 24;57(14):6083-6091.

Inhibition of the catalytic subunit of the heterodimeric methionine S-adenosyl transferase-2 (MAT2A) with fluorinated N,N-dialkylaminostilbenes (FIDAS agents) offers a potential avenue for the treatment of liver and colorectal cancers where upregulation of this enzyme occurs. A study of structure-activity relationships led to the identification of the most active compounds as those with (1) either a 2,6-difluorostyryl or 2-chloro-6-fluorostyryl subunit, (2) either an N-methylamino or N,N-dimethylamino group attached in a para orientation relative to the 2,6-dihalostyryl subunit, and (3) either an N-methylaniline or a 2-(N,N-dimethylamino)pyridine ring. These modifications led to FIDAS agents that were active in the low nanomolar range, that formed water-soluble hydrochloride salts, and that possessed the desired property of not inhibiting the human hERG potassium ion channel at concentrations at which the FIDAS agents inhibit MAT2A. The active FIDAS agents may inhibit cancer cells through alterations of methylation reactions essential for cancer cell survival and growth.

Casein Kinase 1δ/ε Inhibitor PF-5006739 Attenuates Opioid Drug-Seeking Behavior Wager TT, Chandrasekaran RY, Bradley J, Rubitski D, Berke H, Mente S, Butler T, Doran A, Chang C, Fisher K, Knafels J, Liu S, Ohren J, Marconi M, DeMarco G, Sneed B, Walton K, Horton D, Rosado A, Mead A. ACS Chem Neurosci. 2014 Oct 28. [Epub ahead of print].

Casein kinase 1 delta (CK1δ) and casein kinase 1 epsilon (CK1ε) inhibitors are potential therapeutic agents for a range of psychiatric disorders. The feasibility of developing a CNS kinase inhibitor has been limited by an inability to identify safe brain-penetrant compounds with high kinome selectivity. Guided by structure-based drug design, potent and selective CK1δ/ε inhibitors have now been identified that address this gap, through the design and synthesis of novel 4-[4-(4-fluorophenyl)-1-(piperidin-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine derivatives. PF-5006739 (6) possesses a desirable profile, with low nanomolar in vitro potency for CK1δ/ε (IC50 = 3.9 and 17.0 nM, respectively) and high kinome selectivity. In vivo, 6 demonstrated robust centrally mediated circadian rhythm phase-delaying effects in both nocturnal and diurnal animal models. Further, 6 dose-dependently attenuated opioid drug-seeking behavior in a rodent operant reinstatement model in animals trained to self-administer fentanyl. Collectively, these data support further development of 6 as a promising candidate to test the hypothesis of CK1δ/ε inhibition in treating multiple indications in the clinic.

Effects Of the NOP Agonist SCH221510 On Producing and Attenuating Reinforcing Effects As Measured By Drug Self-Administration In Rats Sukhtankar DD, Lagorio CH, Ko MC. Eur J Pharmacol. 2014 Dec 15;745:182-189.

Nociceptin/orphanin FQ peptide (NOP) receptor agonists attenuate morphine-induced conditioned place preference in rodents. However, it is not known whether NOP agonists have reinforcing properties or can inhibit mu opioid receptor (MOP)-mediated reinforcement as measured by drug self-administration in rodents. Further understanding the behavioral effects of NOP agonists could suggest them as having potential in attenuating reinforcing effects of opioids. In the first part of the study, reinforcing properties of selective NOP agonist SCH221510 were determined and compared with the full MOP agonist remifentanil under fixed-ratio 5 (FR5) and progressive-ratio (PR) schedules of drug self-administration. In the second part, effects of systemic and intracisternal pretreatment of SCH221510 were determined and compared with MOP antagonist naltrexone in attenuating reinforcing effects of remifentanil and a non-drug reinforcer (sucrose pellets).

Remifentanil self-administration (0.3-10µg/kg/infusion) generated a biphasic dose-response curve, characteristic of drugs with reinforcing properties. SCH221510 (3-300µg/kg/infusion) self-administration resulted in flat dose-response curves and early break-points under the PR, indicative of drugs lacking reinforcing value. Intracisternally, but not systemically, administered SCH221510 (0.3-3µg) attenuated remifentanil self-administration, comparable with systemic naltrexone (0.03-0.3mg/kg). SCH221510 (1-3µg), unlike naltrexone (0.03-1mg/kg), attenuated responding for sucrose pellets. Both effects of SCH221510 were reversed by the NOP antagonist J-113397 (0.3-3µg). These results suggest that SCH221510 does not function as a reinforcer in rats, and that it can attenuate the reinforcing value of MOP agonists; therefore, the potential utility of NOP agonists for the treatment of drug addiction warrants further evaluation.

Functional Plasticity Of the N/OFQ-NOP Receptor System Determines Analgesic Properties Of NOP Receptor Agonists Schröder W, Lambert DG, Ko MC, Koch T. Br J Pharmacol. 2014 Aug;171(16):3777-3800.

Despite high sequence similarity between NOP (nociceptin/orphanin FQ opioid peptide) and opioid receptors, marked differences in endogenous ligand selectivity, signal transduction, phosphorylation, desensitization, internalization and trafficking have been identified; underscoring the evolutionary difference between NOP and opioid receptors. Activation of NOP receptors affects nociceptive transmission in a site-specific manner, with antinociceptive effects prevailing after peripheral and spinal activation, and pronociceptive effects after supraspinal activation in rodents. The net effect of systemically administered NOP receptor agonists on nociception is proposed to depend on the relative contribution of peripheral, spinal and supraspinal activation, and this may depend on experimental conditions. Functional expression and regulation of NOP receptors at peripheral and central sites of the nociceptive pathway exhibits a high degree of plasticity under conditions of neuropathic and inflammatory pain. In rodents, systemically administered NOP receptor agonists exerted antihypersensitive effects in models of neuropathic and inflammatory pain. However, they were largely ineffective in acute pain while concomitantly evoking severe motor side effects. In contrast, systemic administration of NOP receptor agonists to non-human primates (NHPs) exerted potent and efficacious antinociception in the absence of motor and sedative side effects. The reason for this species difference with respect to antinociceptive efficacy and tolerability is not clear. Moreover, co-activation of NOP and µ-opioid peptide (MOP) receptors synergistically produced antinociception in NHPs. Hence, both selective NOP receptor as well as NOP/MOP receptor agonists may hold potential for clinical use as analgesics effective in conditions of acute and chronic pain

Operant Nociception In Nonhuman Primates Kangas BD, Bergman J. Pain. 2014 Sep; 155(9):1821-1828.

The effective management of pain is a longstanding public health concern. Morphine-like opioids have long been front-line analgesics, but produce undesirable side effects that can limit their application. Slow progress in the introduction of novel improved medications for pain management over the last 5 decades has prompted a call for innovative translational research, including new preclinical assays. Most current in vivo procedures (eg, tail flick, hot plate, warm water tail withdrawal) assay the effects of nociceptive stimuli on simple spinal reflexes or unconditioned behavioral reactions. However, clinical treatment goals may include the restoration of previous behavioral activities, which can be limited by medication-related side effects that are not measured in such procedures. The present studies describe an apparatus and procedure to study the disruptive effects of nociceptive stimuli on voluntary behavior in nonhuman primates, and the ability of drugs to restore such behavior through their analgesic actions. Squirrel monkeys were trained to pull a

cylindrical thermode for access to a highly palatable food. Next, sessions were conducted in which the temperature of the thermode was increased stepwise until responding stopped, permitting the determination of stable nociceptive thresholds. Tests revealed that several opioid analgesics, but not d-amphetamine or Δ(9)-THC, produced dose-related increases in threshold that were antagonist sensitive and efficacy dependent, consistent with their effects using traditional measures of antinociception. Unlike traditional reflex-based measures, however, the results also permitted the concurrent evaluation of response disruption, providing an index with which to characterize the behavioral selectivity of antinociceptive drugs.

Effects Of the Neuropeptide S Receptor Antagonist RTI-118 On Abuse-Related Facilitation Of Intracranial Self-Stimulation Produced By Cocaine and Methylenedioxypyrovalerone (MDPV) In Rats Bonano JS, Runyon SP, Hassler C, Glennon RA, Stevens Negus S. Eur J Pharmacol. 2014 Nov 15;743: 98-105.

Neuropeptide S (NPS) is a neurotransmitter that activates the NPS receptor to modulate biological functions including anxiety-like behaviors, feeding, and drug reinforcement. RTI-118 is a novel NPS receptor antagonist that decreased cocaine self-administration in rats at doses that had little or no effect on food-maintained responding. To build on these previous findings, this study examined effects of RTI-118 on cocaine-induced facilitation of intracranial self-stimulation (ICSS) in rats. To provide a context for data interpretation, effects of RTI-118 were compared to effects of the kappa opioid receptor agonist U69,593, because the kappa opioid receptor is another peptide neurotransmitter receptor reported to modulate abuse-related cocaine effects. RTI-118 effects were also examined on ICSS facilitation produced by methylenedioxypyrovalerone (MDPV), a novel designer drug of abuse with some cocaine-like effects. Male Sprague-Dawley rats (n=12) with electrodes targeting the medial forebrain bundle responded under a fixed-ratio 1 schedule for range of brain stimulation frequencies. Under control conditions, brain stimulation maintained a frequency-dependent increase in ICSS rates. Cocaine (1.0-10mg/kg) and MDPV (3.2mg/kg) facilitated ICSS. RTI-118 (3.2-32mg/kg) alone produced little effect on ICSS but dose dependently blocked cocaine-induced ICSS facilitation. U69,593 (0.25-0.5mg/kg) also attenuated cocaine effects, but blockade of cocaine effects was incomplete even at a U69,593 dose that alone depressed ICSS. RTI-118 (32mg/kg) failed to block MDPV-induced ICSS facilitation. These results support further consideration of NPS receptor antagonists as candidate treatments for cocaine abuse and provide evidence for differential effects of a candidate treatment on abuse-related effects of cocaine and MDPV.

Effects Of the Novel, Selective and Low-Efficacy Mu Opioid Receptor Ligand NAQ On Intracranial Self-Stimulation In Rats Altarifi AA, Yuan Y, Zhang Y, Selley DE, Negus SS. Psychopharmacology (Berl). 2014 Sep 3. [Epub ahead of print].

Low-efficacy mu opioid receptor agonists may be useful for some clinical indications, but clinically available low-efficacy mu agonists also have low selectivity for mu vs. kappa opioid receptors. NAQ (17-cyclopropylmethyl-3,14ß-dihydroxy-4,5α-epoxy-6α-[(3'-isoquinolyl)acetamido] morphinan) is a novel opioid receptor ligand with low-efficacy at mu receptors and greater mu-receptor selectivity than existing low-efficacy agonists. This study examined behavioral effects of NAQ in rats using an intracranial self-stimulation (ICSS) procedure that has been used previously to examine other opioids. NAQ effects were examined before, during, and after chronic morphine treatment, and effects of NAQ were compared to effects of nalbuphine and naltrexone. Adult male Sprague-Dawley rats were trained to respond for electrical brain stimulation delivered via electrodes implanted in the medial forebrain bundle. A range of brain stimulation frequencies maintained a wide range of baseline ICSS rates. Effects of NAQ (0.32-10 mg/kg), nalbuphine

(1.0 mg/kg), and naltrexone (0.1 mg/kg) were determined before morphine treatment and during treatment with 3.2 and 18 mg/kg/day morphine. NAQ effects were also redetermined beginning 2 weeks after termination of morphine treatment. NAQ produced weak ICSS facilitation in morphine-naïve rats but more robust ICSS facilitation during and after morphine treatment and also reversed morphine withdrawal-associated depression of ICSS. These effects were similar to effects of nalbuphine. These results agree with the in vitro characterization of NAQ as a low-efficacy mu agonist. Opioid exposure may enhance abuse-related effects of NAQ, but NAQ may also serve as a low-efficacy and relatively safe option for treatment of opioid withdrawal or dependence

First Human Study Of A Chimeric Anti-Methamphetamine Monoclonal Antibody In Healthy Volunteers Stevens MW, Henry RL, Owens SM, Schutz R, Gentry WB. MAbs. 2014 Nov; 6(6): 1649-1656.

This first-in-human study examined the safety and pharmacokinetics of ch-mAb7F9, an anti-methamphetamine monoclonal antibody, in healthy volunteers. Single, escalating doses of ch-mAb7F9 over the range of 0. 2 to 20 mg/kg were administered to 42 subjects who were followed for 147 d. Safety was measured by physical examinations, adverse events, vital signs, electrocardio-grams, and clinical laboratory testing. Serum ch-mAb7F9 concentration and immunogenicity analyses were performed. There were no serious adverse reactions or discontinuations from the study due to adverse events. No trends emerged in the frequency, relatedness, or severity of adverse events with increased dose or between active and placebo treated subjects. Ch-mAb7F9 displayed expected IgG pharmacokinetic parameters, including a half-life of 17-19 d in the 3 highest dose groups and volume of distribution of 5-6 L, suggesting the antibody is confined primarily to the vascular compartment. Four (12. 5%) of the 32 subjects receiving ch-mAb7F9 were confirmed to have developed a human anti-chimeric antibody response by the end of the study; however, this response did not appear to be dose related. Overall, no apparent safety or tolerability concerns were identified; a maximum tolerated dose was not reached in this Phase 1 study. Ch-mAb7F9 therefore appears safe for human administration.

The Effects Of A Humanized Recombinant Anti-Cocaine Monoclonal Antibody On The Disposition Of Cocaethylene In Mice Wetzel HN, Tabet MR, Ball WJ, Norman AB. Int Immunopharmacol. 2014 Nov; 23(2):387-390.

The chimeric human/mouse anti-cocaine monoclonal antibody (mAb) 2E2 and its further humanized variant h2E2 have been reported to sequester a significant portion of cocaine in plasma and decrease cocaine concentrations in the brain in mice and rats. However, many cocaine users co-abuse alcohol, leading to the formation of the centrally active metabolite cocaethylene. This potentially compromises the efficacy of a cocaine-specific immunotherapy. Because h2E2 has high affinity for cocaethylene as well as cocaine, the ability of h2E2 to prevent cocaethylene entry into the brain was investigated. Mice were infused with h2E2 (1.6μmol/kg i.v.) or vehicle and after one hour were injected with cocaethylene fumarate (1.2μmol/kg i.v.). At times from 45s to 60min, brain and plasma were collected and cocaethylene concentrations were measured using GC/MS. In control mice, a two-compartment pharmacokinetic model generated values for cocaethylene distribution and terminal elimination half-lives of 0.5 and 8. 1min respectively. Initial plasma cocaethylene concentrations increased 13-fold from controls in the presence of h2E2. In brain, h2E2 produced a 92% decrease in the area under the time-concentration curve for cocaethylene. The pharmacokinetics of h2E2 was also characterized in detail. A three-compartment model resolved an initial distribution half-life of 4. 4min and a second distribution half-life of 4.2h, and a terminal elimination half-life of 7.8days. The ability of h2E2 to protect the brain from both cocaine and cocaethylene predicts that the clinical efficacy of h2E2 will be retained in cocaine users who co-

abuse alcohol.

Attenuation Of Cocaine-Induced Locomotor Activity In Male and Female Mice By Active Immunization Kosten TA, Shen XY, Kinsey BM, Kosten TR, Orson FM. Am J Addict. 2014 23(6): 604-607.
Immunotherapy for drug addiction is being investigated in several laboratories but most studies are conducted in animals of one sex. Yet, women show heightened immune responses and are more likely to develop autoimmune diseases than men. The purpose of this study was to compare the effects of an active anti-cocaine vaccine, succinyl-norcocaine conjugated to keyhole limpet hemocyanin, for its ability to elicit antibodies and alter cocaine-induced ambulatory activity in male versus female mice. Male and female BALB/c mice were vaccinated (n=44) or served as non-vaccinated controls (n=34). Three weeks after initial vaccination, a booster was given. Ambulatory activity induced by cocaine (20mg/kg) was assessed at 7 weeks and plasma obtained at 8 weeks to assess antibody levels. High antibody titers were produced in mice of both sexes. The vaccine reduced ambulatory activity cocaine-induced but this effect was greater in female compared to male mice. The efficacy of this anti-cocaine vaccine is demonstrated in mice of both sexes but its functional consequences are greater in females than males. Results point to the importance of testing animals of both sexes in studies of immunotherapies for addiction.

Characterization and Optimization Of Heroin Hapten-Bsa Conjugates: Method Development For the Synthesis Of Reproducible Hapten-Based Vaccines Torres OB, Jalah R, Rice KC, Li F, Antoline JF, Iyer MR, Jacobson AE, Boutaghou MN, Alving CR, Matyas GR. Anal Bioanal Chem. 2014 Sep; 406(24): 5927-5937.
A potential new treatment for drug addiction is immunization with vaccines that induce antibodies that can abrogate the addictive effects of the drug of abuse. One of the challenges in the development of a vaccine against drugs of abuse is the availability of an optimum procedure that gives reproducible and high yielding hapten-protein conjugates. In this study, a heroin/morphine surrogate hapten (MorHap) was coupled to bovine serum albumin (BSA) using maleimide-thiol chemistry. MorHap-BSA conjugates with 3, 5, 10, 15, 22, 28, and 34 haptens were obtained using different linker and hapten ratios. Using this optimized procedure, MorHap-BSA conjugates were synthesized with highly reproducible results and in high yields. The number of haptens attached to BSA was compared by 2,4,6-trinitrobenzenesulfonic acid (TNBS) assay, modified Ellman's test and matrix assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). Among the three methods, MALDI-TOF MS discriminated subtle differences in hapten density. The effect of hapten density on enzyme-linked immunosorbent assay (ELISA) performance was evaluated with seven MorHap-BSA conjugates of varying hapten densities, which were used as coating antigens. The highest antibody binding was obtained with MorHap-BSA conjugates containing 3-5 haptens. This is the first report that rigorously analyzes, optimizes and characterizes the conjugation of haptens to proteins that can be used for vaccines against drugs of abuse. The effect of hapten density on the ELISA detection of antibodies against haptens demonstrates the importance of careful characterization of the hapten density by the analytical techniques described.

Pharmacological Effects Of Two Anti-Methamphetamine Monoclonal Antibodies: Supporting Data For Lead Candidate Selection For Clinical Development Laurenzana EM, Stevens MW, Frank JC, Hambuchen MD, Hendrickson HP, White SJ, Williams DK, Owens SM, Gentry WB. Hum Vaccin Immunother. 2014 Jul; 10(9).
This lead candidate selection study compared two anti-(+)-methamphetamine (METH) monoclonal antibodies (mAb) to determine their ability to reduce METH-induced locomotor effects and

redistribute METH and (+)-amphetamine (AMP) in a preclinical overdose model. Both mAbs have high affinity for METH, but mAb4G9 has moderate and mAb7F9 has low affinity for AMP. In the placebo-controlled behavioral experiment, the effects of each mAb on the locomotor response to a single 1 mg/kg intravenous (IV) METH dose were determined in rats. The doses of mAb binding sites were administered such that they equaled 1, 0.56, 0.32, and 0. 1 times the molar equivalent (mol-eq) of METH in the body 30 min after the METH dose. METH disposition was determined in separate animals that similarly received either a 1 or 0.32 mol-eq dose of mAb binding sites 30 min after a 1 mg/kg METH dose. Total METH-induced distance traveled was significantly reduced in rats that received the highest three doses of each mAb compared with saline. The duration of METH effects was also significantly reduced by mAb7F9 at the highest dose. The disposition of METH was altered dose-dependently by both mAbs as shown in reductions of volume of distribution and total clearance, and increases in elimination half-life. These data indicate that both mAbs are effective at reducing METH-induced behavior and favorably altering METH disposition. Both were therefore suitable for further preclinical testing as potential human medications for treating METH use; however, due to results reported here and in later studies, mAb7F9 was selected for clinical development.

Role Of GABA-Active Neurosteroids In the Efficacy Of Metyrapone Against Cocaine Addiction Schmoutz CD, Guerin GF, Goeders NE. Behav Brain Res. 2014 Sep; 271[Epub ahead of print] 269-276.

Previous research has demonstrated a complicated role for stress and HPA axis activation in potentiating various cocaine-related behaviors in preclinical models of drug dependence. However, the investigation of several antiglucocorticoid therapies has yielded equivocal results in reducing cocaine-related behaviors, possibly because of varying mechanisms of actions. Specifically, research suggests that metyrapone (a corticosterone synthesis inhibitor) may reduce cocaine self-administration in rats via a nongenomic, extra-adrenal mechanism without altering plasma corticosterone. In the current experiments, male rats were trained to self-administer cocaine infusions and food pellets in a multiple, alternating schedule of reinforcement. Metyrapone pretreatment dose-dependently decreased cocaine self-administration as demonstrated previously. Pharmacological inhibition of neurosteroid production by finasteride had significant effects on cocaine self-administration, regardless of metyrapone pretreatment. However, metyrapone's effects on cocaine self-administration were significantly attenuated with bicuculline pretreatment, suggesting a role for GABA-active neurosteroids in cocaine-reinforced behaviors. In vitro binding data also confirmed that metyrapone does not selectively bind to GABA-related proteins. The results of these experiments support the hypothesis that metyrapone may increase neurosteroidogenesis to produce effects on cocaine-related behaviors.

The Extra-Adrenal Effects Of Metyrapone and Oxazepam On Ongoing Cocaine Self-Administration Guerin GF, Schmoutz CD, Goeders NE. Brain Res. 2014 Aug; 1575[Epub ahead of print] 45-54.

Investigation of the role of stress in cocaine addiction has yielded an efficacious combination of metyrapone and oxazepam, hypothesized to decrease relapse to cocaine use by reducing stress-induced craving. However, recent data suggest an extra-adrenal role for metyrapone in mediating stress- and addiction-related behaviors. The interactions between the physiological stress response and cocaine self-administration were characterized in rodents utilizing surgical adrenalectomy and pharmacological treatment. Male Wistar rats were trained to self-administer cocaine (0. 25mg/kg/ infusion) and food pellets under a concurrent alternating fixed-ratio schedule of reinforcement. Surgical removal of the adrenal glands resulted in a significant decrease in plasma corticosterone

and a consequent increase in ACTH, as expected. However, adrenalectomy did not significantly affect ongoing cocaine self-administration. Pretreatment with metyrapone, oxazepam and their combinations in intact rats resulted in a significant decrease in cocaine-reinforced responses. These same pharmacological treatments were still effective in reducing cocaine- and food-reinforced responding in adrenalectomized rats. The results of these experiments demonstrate that adrenally-derived steroids are not necessary to maintain cocaine-reinforced responding in cocaine-experienced rats. These results also demonstrate that metyrapone may produce effects outside of the adrenal gland, presumably in the central nervous system, to affect cocaine-related behaviors.

Discovery Of VU0431316: A Negative Allosteric Modulator Of mGlu5 With Activity In A Mouse Model Of Anxiety Bates BS, Rodriguez AL, Felts AS, Morrison RD, Venable DF, Blobaum AL, Byers FW, Lawson KP, Daniels JS, Niswender CM, Jones CK, Conn PJ, Lindsley CW, Emmitte KA. Bioorg Med Chem Lett. 2014 Aug; 24(15): 3307-3314.
Development of SAR in an aryl ether series of mGlu5 NAMs leading to the identification of pyrazine analog VU0431316 is described in this Letter. VU0431316 is a potent and selective non-competitive antagonist of mGlu5 that binds at a known allosteric binding site. VU0431316 demonstrates an attractive DMPK profile, including moderate clearance and good bioavailability in rats. Intraperitoneal (IP) dosing of VU0431316 in a mouse marble burying model of anxiety, an assay known to be sensitive to mGlu5 antagonists and other anxiolytics, produced dose proportional effects.

A Human Recombinant Monoclonal Antibody To Cocaine: Preparation, Characterization and Behavioral Studies Eubanks LM, Ellis BA, Cai X, Schlosburg JE, Janda KD. Bioorg Med Chem Lett. 2014 Oct; 24(19):c4664-4666.
Cocaine abuse remains prevalent worldwide and continues to be a major health concern; nonetheless, there is no effective therapy. Immunopharmacotherapy has emerged as a promising treatment strategy by which anti-cocaine antibodies bind to the drug blunting its effects. Previous passive immunization studies using our human monoclonal antibody, GNCgzk, resulted in protection against cocaine overdose and acute toxicity. To further realize the clinical potential of this antibody, a recombinant IgG form of the antibody has been produced in mammalian cells. This antibody displayed a high binding affinity for cocaine (low nanomolar) in line with the superior attributes of the GNCgzk antibody and reduced cocaine-induced ataxia in a cocaine overdose model.

Rational Design, Preparation, and Characterization Of A Therapeutic Enzyme Mutant With Improved Stability And Function For Cocaine Detoxification Fang L, Chow KM, Hou S, Xue L, Chen X, Rodgers DW, Zheng F, Zhan CG. ACS Chem Biol. 2014 Aug; 9(8): 1764-1772.
Cocaine esterase (CocE) is known as the most efficient natural enzyme for cocaine hydrolysis. The major obstacle to the clinical application of wild-type CocE is the thermoinstability with a half-life of only ~12 min at 37 °C. The previously designed T172R/G173Q mutant (denoted as enzyme E172-173) with an improved in vitro half-life of ~6 h at 37 °C is currently in clinical trial Phase II for cocaine overdose treatment. Through molecular modeling and dynamics simulation, the authors designed and characterized a promising new mutant of E172-173 with extra L196C/I301C mutations (denoted as enzyme E196-301) to produce cross-subunit disulfide bonds that stabilize the dimer structure. The cross-subunit disulfide bonds were confirmed by X-ray diffraction. The designed L196C/I301C mutations have not only considerably extended the in vitro half-life at 37 °C to >100 days, but also significantly improved the catalytic efficiency against cocaine by ~150%. In addition, the thermostable E196-301 can be PEGylated to significantly prolong the residence time

in mice. The PEGylated E196-301 can fully protect mice from a lethal dose of cocaine (180 mg/kg, LD100) for at least 3 days, with an average protection time of ~94h. This is the longest in vivo protection of mice from the lethal dose of cocaine demonstrated within all studies using an exogenous enzyme reported so far. Hence, E196-301 may be developed to become a more valuable therapeutic enzyme for cocaine abuse treatment, and it demonstrates that a general design strategy and protocol to simultaneously improve both the stability and function are feasible for rational protein drug design.

Primary Care-Based Buprenorphine Taper vs Maintenance Therapy for Prescription Opioid Dependence: A Randomized Clinical Trial Fiellin DA, Schottenfeld RS, Cutter CJ, Moore BA, Barry DT, O'Connor PG. JAMA Intern Med. 2014 Dec 1;174(12):1947-1954,
Prescription opioid dependence is increasing and creates a significant public health burden, but primary care physicians lack evidence-based guidelines to decide between tapering doses followed by discontinuation of buprenorphine hydrochloride and naloxone hydrochloride therapy (hereinafter referred to as buprenorphine therapy) or ongoing maintenance therapy. The objective of this study was to determine the efficacy of buprenorphine taper vs ongoing maintenance therapy in primary care-based treatment for prescription opioid dependence. The authors conducted a 14-week randomized clinical trial that enrolled 113 patients with prescription opioid dependence from February 17, 2009, through February 1, 2013, in a single primary care site. Patients were randomized to buprenorphine taper (taper condition) or ongoing buprenorphine maintenance therapy (maintenance condition). The buprenorphine taper was initiated after 6 weeks of stabilization, lasted for 3 weeks, and included medications for opioid withdrawal, after which patients were offered naltrexone treatment. The maintenance group received ongoing buprenorphine therapy. All patients received physician and nurse support and drug counseling. Main outcomes and measures collected were illicit opioid use via results of urinanalysis and patient report, treatment retention, and reinitiation of buprenorphine therapy (taper group only). During the trial, the mean percentage of urine samples negative for opioids was lower for patients in the taper group (35.2% [95% CI, 26.2%-44.2%]) compared with those in the maintenance group (53.2% [95% CI, 44.3%-62.0%]). Patients in the taper group reported more days per week of illicit opioid use than those in the maintenance group once they were no longer receiving buprenorphine (mean use, 1.27 [95% CI, 0.60-1.94] vs 0.47 [95% CI, 0.19-0.74] days). Patients in the taper group had fewer maximum consecutive weeks of opioid abstinence compared with those in the maintenance group (mean abstinence, 2.70 [95% CI, 1.72-3.75] vs 5.20 [95% CI, 4.16-6.20] weeks). Patients in the taper group were less likely to complete the trial (6 of 57 [11%] vs 37 of 56 [66%]; P<.001). Sixteen patients in the taper group reinitiated buprenorphine treatment after the taper owing to relapse. The authors conclude that tapering is less efficacious than ongoing maintenance treatment in patients with prescription opioid dependence who receive buprenorphine therapy in primary care.

Butyrylcholinesterase Levels and Subjective Effects Of Smoked Cocaine In Healthy Cocaine Users Askalsky P, Kalapatapu RK, Foltin RW, Comer SD. Am J Drug Alcohol Abuse. 2014 Oct; [Epub ahead of print]1-5.
Butyrylcholinesterase (BChE) is beginning to attract attention as a possible target for cocaine abuse treatment because of its role in metabolizing cocaine. The purpose of this analysis was to assess whether endogenous BChE levels are associated with the subjective effects of cocaine. Data from 28 participants in five inpatient cocaine self-administration studies were included in the present analysis. Four minutes after each smoked cocaine dose, participants rated their drug-related effects from 0-100 using a computerized self-report Visual Analogue Scale (VAS). The main outcome measures were nine change-in-VAS ratings between a baseline placebo dose and a 25-mg smoked

cocaine dose. After controlling for age, sex, total years of cocaine use, total milligrams of cocaine administered before the 25-mg dose being analyzed, and baseline diastolic blood pressure, endogenous BChE was not significantly associated with any of the nine change-in-VAS ratings. Though BChE appears to be a possible target for cocaine abuse treatment, these data suggest that endogenous levels of BChE may not play a role in modifying the subjective effects of cocaine. Future larger studies of BChE in respect to the subjective effects produced by cocaine are needed to confirm or refute these findings.

Cannabis Use History and Characteristics Of Quit Attempts: A Comparison Study Of Treatment-Seeking and Non-Treatment-Seeking Cannabis Users Pacek LR, Vandrey R. Exp Clin Psychopharmacol. 2014 Dec; 22(6):517-523.

Cannabis is the most commonly used illicit substance worldwide, and cannabis use disorders (CUDs) are correspondingly high. Increased demand for treatment and relatively low rates of positive clinical outcomes has led to a large scientific investment in the development of interventions for the treatment of CUD. Much of this research is conducted with cannabis users who are not seeking treatment at the time of study participation, and it is unknown whether these individuals are representative of those who seek treatment. This study contrasted samples of cannabis users participating in screening interviews for treatment and nontreatment research studies. Several differences between groups emerged: Treatment-seekers were more likely to be female (43% vs. 29%), older (33.4 vs. 29.7 years), and have longer cannabis use histories compared with non-treatment-seekers (p =.007). Treatment-seekers were more likely to report experiencing guilt after using cannabis and to feel that cannabis use has been a problem for them. Additionally, treatment-seekers reported a greater mean number of reasons for making a quit attempt, experiencing a greater number of withdrawal symptoms, and employing more coping strategies during prior quit attempts. Despite the aforementioned differences, the 2 groups were similar on several key characteristics, particularly with regards to current levels of cannabis use and related problems.

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

Agonist replacement may be a viable treatment approach for managing stimulant use disorders. This study sought to determine the effects of d-amphetamine maintenance on methamphetamine self-administration in stimulant using human participants. The authors predicted that d-amphetamine maintenance would reduce methamphetamine self-administration. Eight participants completed the protocol, which tested 2 d-amphetamine maintenance conditions in counterbalanced order (0 and 40 mg/d). Participants completed 4 experimental sessions under each maintenance condition in which they first sampled 1 of 4 doses of intranasal methamphetamine (0, 10, 20, or 30 mg). Participants then had the opportunity to respond on a computerized progressive-ratio task to earn portions of the sampled methamphetamine dose. Subject-rated drug effect and physiological measures were completed at regular intervals prior to and after sampling methamphetamine. Methamphetamine was self-administered as an orderly function of dose regardless of the maintenance condition. Methamphetamine produced prototypical subject-rated effects on 12 items of the drug-effects questionnaires, 8 of which were attenuated by d-amphetamine maintenance (eg, increased ratings were attenuated on items such as Any Effect, Like Drug, and Willing to Take Again on the Drug Effect Questionnaire). Methamphetamine produced significant increases in systolic blood pressure, which were attenuated by d-amphetamine maintenance compared to placebo maintenance. Methamphetamine was well tolerated during d-amphetamine maintenance and no adverse events

occurred. Although d-amphetamine attenuated some subject-rated effects of methamphetamine, the self-administration results are concordant with those of clinical trials showing that d-amphetamine did not reduce methamphetamine use. Unique pharmacological approaches may be needed for treating amphetamine use disorders.

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

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

Fixation Time Is A Sensitive Measure Of Cocaine Cue Attentional Bias Marks KR, Roberts W, Stoops WW, Pike E, Fillmore MT, Rush CR. Addiction. 2014 Sep; 109(9):1501-1508.
Attentional bias has been demonstrated to a variety of substances. Evidence suggests that fixation time is a more direct measure of attentional bias than response time. The aims of this experiment were to demonstrate that fixation time during the visual probe task is a sensitive and stable measure of cocaine cue attentional bias in cocaine-using adults compared to controls. A between-subject, repeated-measures experiment. An out-patient research unit. Fifteen cocaine using and 15 non-cocaine-using adults recruited from the community. Participants completed a visual probe task with eye tracking and a modified Stroop during two experimental sessions. A significant interaction between cue type and group (F=13. 5; P<0. 05) indicated that cocaine users, but not controls, displayed an attentional bias to cocaine-related images as measured by fixation time. There were no changes in the magnitude of attentional bias across sessions (F=3. 4; P>0.05) and attentional bias correlated with self-reported life-time cocaine use (r=0. 64, P<0.05). Response time on the visual probe (F=1. 1; P>0.05) as well as on the modified Stroop (F=0.1; P>0.05) failed to detect an attentional bias. Fixation time on cocaine-related stimuli (propensity to remain focused on the stimulus) is a sensitive and stable measure of cocaine cue attentional bias in cocaine-using adults.

Sex Differences in the Brain's Dopamine Signature of Cigarette Smoking Cosgrove KP, Wang S, Kim Su-Jin, McGovern E, Nabulsi N, Gao H, Labaree D, Tagare HD, Sullivan JM, and Morris ED. J Neurosci 2014; 34(50): 16851–16855.
Cigarette smoking is a major public health danger. Women and men smoke for different reasons and cessation treatments, such as the nicotine patch, are preferentially beneficial to men. The biological substrates of these sex differences are unknown. Earlier PET studies reported conflicting findings but were each hampered by experimental and/or analytical limitations. The authors' new image analysis technique, lp-ntPET (Normandin et al., 2012; Morris et al., 2013; Kim et al., 2014), has been optimized for capturing brief (lasting only minutes) and highly localized dopaminergic events in dynamic PET data. The authors coupled their analysis technique with high-resolution brain scanning and high-frequency motion correction to create the optimal experiment for capturing and characterizing the effects of smoking on the mesolimbic dopamine system in humans. Their main finding is that male smokers smoking in the PET scanner activate dopamine in the right ventral striatum during smoking but female smokers do not. This finding—men activating more ventrally than women—is consistent with the established notion that men smoke for the reinforcing drug effect of cigarettes whereas women smoke for other reasons, such as mood regulation and cue reactivity. lp-ntPET analysis produces a novel multidimensional endpoint: voxel-level temporal patterns of neurotransmitter release ("DA movies") in individual subjects. By examining these endpoints quantitatively, we demonstrate that the timing of dopaminergic responses to cigarette smoking differs between men and women. Men respond consistently and rapidly in the ventral striatum whereas women respond faster in a discrete subregion of the dorsal putamen.

Association Of CHRNA5-A3-B4 SNP Rs2036527 With Smoking Cessation Therapy Response In African-American Smokers Zhu A Z X, Zhou, Q, Cox,L S, David SP, Ahluwalia JS, Benowitz NL, Tyndale RF. Clin Pharmacol Ther. 2014; 96(2): 256-265.
Associations between CHRNA5-A3-B4 variants and smoking behaviors exist; however, the association with smoking abstinence is less understood, particularly that among African Americans. In 1,295 African Americans enrolled in two clinical trials, the authors investigated the association between CHRNA5-A3-B4 and smoking abstinence. The rs2056527(A) allele was associated with lower abstinence with active pharmacotherapy (during treatment: odds ratio (OR) = 0.42, P < 0.001; end of treatment (EOT): OR = 0.55, P = 0.004), or with nicotine gum alone (during treatment: OR =

0.31, P < 0.001; EOT: OR = 0.51, P = 0.02), but not significantly with bupropion, although similar directions and magnitudes were observed (during treatment: OR = 0.54, P = 0.05; EOT: OR = 0.59, P = 0.08). In addition, the rs588765(T) allele was associated with abstinence with gum during treatment (OR = 2.31, P < 0.01). The SNP rs16969968 occurred at a low frequency and was not consistently associated with abstinence. CHRNA5-A3-B4 variants were not associated with tobacco consumption, and adjustments for smoking behaviors did not alter the associations with smoking abstinence. Together, these data suggest that among African Americans, CHRNA5-A3-B4 variants are not associated with baseline smoking but can influence smoking abstinence during active pharmacotherapy.

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Low-dose Nicotine Self-administration Is Reduced In Adult Male Rats Naive To High Doses Of Nicotine: Implications For Nicotine Product Standards Smith T, Schassburger R, Buffalari D, Sved, A, Donny E. Exp Clin Psychopharmacol. 2014; 22(5): 453-459.

Product standards that greatly reduce the content of nicotine within cigarettes may result in improved public health. The study presented here used an animal model to investigate whether individuals who start smoking after implementation of regulation may be affected differently from current smokers who form the basis of most clinical studies. One group of adult male rats (n = 14/group) acquired nicotine self-administration at a high nicotine dose (60 *g/kg/infusion) before experiencing a reduction to one to three low doses of nicotine (3.75, 7.5, or 15 *g/kg/infusion) or vehicle. Their self-administration behavior at the low doses was compared with a group of adult male rats given the opportunity to acquire nicotine self-administration at one of the same low doses or vehicle (n = 7-14/group). Second, the self-administration behavior of the acquisition group of rats was compared with their own self-administration behavior after experience self-administering a high dose of nicotine. A cocktail of non-nicotine cigarette smoke constituents was included in the vehicle for all rats across all phases of the study. Rats with a history of self-administering a high dose of nicotine had a higher rate of self-administration across the low doses than rats with no history. In addition, the number of earned infusions increased after rats experienced self-administration of a higher dose of nicotine. These data show that low-dose nicotine self-administration is higher after a dose reduction than during acquisition. If a nicotine reduction policy were implemented, then this policy may be especially effective at reducing acquisition of smoking.

IV Nicotine Self-administration In Rats Using A Consummatory Operant Licking Response: Sensitivity To Serotonergic, Glutaminergic and Histaminergic Drugs Cousins V, Rose J, Levin E. Prog Neuropsychopharmacol Biol Psychiatry. 2014; 54: 200-205.

Tobacco smoking is characterized by repeated self-administration of nicotine by placing the cigarette in the mouth. The repeated hand-to-mouth self-administration is essentially a consummatory act. The authors recently developed a paradigm in which rats lick one of two spouts to trigger intravenous (IV) delivery of nicotine, which combines a consummatory act with rapid delivery of nicotine to model the act of tobacco smoking. The authors have found that rats will lick hundreds of times per nicotine infusion. In the current study, using the operant licking nicotine self-administration model with young adult Sprague-Dawley rats (0.03mg/kg/infusion of nicotine), the authors tested the effect of antagonists of H1 histamine receptors pyrilamine, serotonin (5HT) type 2 receptors ketanserin and N-methyl-d-aspartate (NMDA) glutamate receptors with d-cycloserine as well as an agonist of 5HT2c receptors lorcaserin, in dose ranges that they have found in previous studies to significantly reduce IV nicotine self-administration with the operant lever press operand. The H1 antagonist pyrilamine significantly reduced operant licking for nicotine self-administration. Pyrilamine caused significant reductions in the operant licking paradigm at lower doses (10 and 20mg/kg) than those we previously observed to affect responding in the operant lever press

paradigm. In contrast, the 5HT2A and C antagonist ketanserin did not show an effect of reducing nicotine self-administration in the same dose range the authors had found in a previous study to significantly reduce operant lever press nicotine self-administration. The 5HT2C agonist lorcaserin significantly decreased nicotine self-administration in the licking paradigm at the same dose threshold as with lever press responding. The NMDA glutamate partial agonist d-cycloserine did not produce any change in nicotine self-administration with the licking operand, in contrast to its effect on the classic lever-pressing task. The rat model incorporating consummatory aspects of tobacco addiction can provide distinct and potentially more relevant information concerning possible new avenues of treatment to combat tobacco addiction.

Known and Novel Sources Of Variability In the Nicotine Metabolite Ratio In A Large Sample Of Treatment-seeking Smokers Chenoweth M, Novalen M, Hawk Jr L, Schnoll R, George T, Cinciripini P, Lerman C, Tyndale R. Cancer Epidemiol Biomarkers Prev. 2014; 23(9): 1773-1782.
The ratio of 3'hydroxycotinine to cotinine, or nicotine metabolite ratio (NMR), is strongly associated with CYP2A6 genotype, CYP2A6-mediated nicotine and cotinine metabolism, and nicotine clearance. Higher NMR (faster nicotine clearance) is associated retrospectively with heavier smoking and lower cessation rates. NMR as a predictive biomarker of cessation outcomes is being investigated (NCT01314001). In addition to strong CYP2A6 genetic influences on NMR, demographic and hormonal factors alter NMR. Here, the authors analyzed, for the first time together, these sources of variation on NMR in smokers screened for this clinical trial (N = 1,672). Participants (mean age = 45.9) were 65.1% Caucasian, 34.9% African American, and 54.8% male. Mean NMR (SD) was higher in Caucasians versus African Americans [0.41 (0.20) vs. 0.33 (0.21); $P < 0.001$], and in females versus males [0.41 (0.22) vs. 0.37 (0.20); $P < 0.001$]. Among females, birth control pill use (N = 17) and hormone replacement therapy (N = 14) were associated with 19.5% ($P = 0.09$) and 29.3% ($P = 0.06$) higher mean NMR, respectively, albeit nonsignificantly. BMI was negatively associated with NMR (Rho = -0.14; $P < 0.001$), whereas alcohol use (Rho = 0.11; $P < 0.001$) and cigarette consumption (Rho = 0.12; $P < 0.001$) were positively associated with NMR. NMR was 16% lower in mentholated cigarette users ($P < 0.001$). When analyzed together in a linear regression model, these predictors (each ≤2%) accounted for <8% of total NMR variation. Although these factors significantly affected NMR, they contributed little (together <8%; each ≤2%) to total NMR variation. Thus, when using NMR, for example, to prospectively guide smoking cessation therapy, these sources of variation are unlikely to cause NMR misclassification.

Nicotine Pharmacokinetics In Rats Is Altered As A Function Of Age, Impacting The Interpretation Of Animal Model Data Craig E, Zhao B, Cui J, Novalen M, Miksys S, Tyndale R. Drug Metab Dispos. 2014; 42(9): 1447-1455.
Several behavioral studies report that adolescent rats display a preference for nicotine compared with adults. However, age-related pharmacokinetic differences may confound the interpretation of these findings. Thus, differences in pharmacokinetic analyses of nicotine were investigated. Nicotine was administered via acute s.c. (1.0 mg base/kg) or i.v. (0.2 mg base/kg) injection to early adolescent (EA; postnatal day 25) and adult (AD; postnatal day 71) male Wistar rats. Nicotine and its primary metabolite, cotinine, and additional metabolites nornicotine, nicotine-1'-N-oxide, trans-3'-hydroxycotinine, and norcotinine were sampled from 10 minutes to 8 hours (plasma) and 2 to 8 hours (brain) post nicotine and analyzed by liquid chromatography-tandem mass spectrometry. Following s.c. nicotine, the EA cohort had lower levels of plasma nicotine, cotinine, and nicotine-1'-N-oxide at multiple time points, resulting in a lower area under the plasma concentration-time curve (AUC) for nicotine ($P < 0.001$), cotinine ($P < 0.01$), and nicotine-1'-N-oxide ($P < 0.001$). Brain levels were also lower for these compounds. In contrast, the EA cohort had higher plasma and

brain AUCs ($P < 0.001$) for the minor metabolite nornicotine. Brain-to-plasma ratios varied for nicotine and its metabolites, and by age. Following i.v. nicotine administration, similar age-related differences were observed, and this route allowed detection of a 1.6-fold-larger volume of distribution and 2-fold higher plasma clearance in the EA cohort compared with the AD cohort. Thus, unlike in humans, there are substantial age differences in nicotine pharmacokinetics such that for a given nicotine dose, adolescent rats will have lower plasma and brain nicotine compared with adults, suggesting that this should be considered when interpreting animal model data.

UGT1A and UGT2B Genetic Variation Alters Nicotine and Nitrosamine Glucuronidation In European and African American Smokers Wassenaar C, Conti D, Das S, Chen P, Cook E, Ratain M, Mark J, Benowitz NL, Tyndale RF. Cancer Epidemiol Biomarkers Prev. 2014.
Identifying sources of variation in the nicotine and nitrosamine metabolic inactivation pathways is important to understanding the relationship between smoking and cancer risk. Numerous UGT1A and UGT2B enzymes are implicated in nicotine and nitrosamine metabolism in vitro; however, little is known about their roles in vivo. Within UGT1A1, UGT1A4, UGT1A9, UGT2B7, UGT2B10, and UGT2B17, 47 variants were genotyped, including UGT2B10*2 and UGT2B17*2. The association between variation in these UGTs and glucuronidation activity within European and African American current smokers (n=128), quantified as urinary ratios of the glucuronide over unconjugated compound for nicotine, cotinine, trans-3'-hydroxycotinine, and NNAL, was investigated in regression models assuming a dominant effect of variant alleles. Correcting for multiple testing, three UGT2B10 variants were associated with cotinine glucuronidation, rs2331559 and rs11726322 in European Americans and rs835309 in African Americans (P.0002). Additional variants predominantly in UGT2B10 were nominally associated with nicotine (P=.008-.04) and cotinine (P=<.001-.02) glucuronidation in both ethnicities in addition to UGT2B10*2 in European Americans (P=.01, P<.001). UGT2B17*2 (P=.03) in European Americans and UGT2B7 variants (P=.02-.04) in African Americans were nominally associated with 3HC glucuronidation. UGT1A (P=.007-.01), UGT2B10 (P=.02) and UGT2B7 (P=.02-03) variants in African Americans were nominally associated with NNAL glucuronidation. Findings from this initial in vivo study support a role for multiple UGTs in the glucuronidation of tobacco-related compounds in vivo, in particular UGT2B10 and cotinine glucuronidation. Findings also provide insight into ethnic differences in glucuronidation activity, which could be contributing to ethnic disparities in the risk for smoking-related cancers.

Effects Of Tobacco Smoke Constituents, Anabasine and Anatabine, On Memory and Attention In Female Rats Levin E, Hao I, Burke D. Cauley M, Hall B, Rezvani A. J Psychopharmacol. 2014; 28(10): 915-922.
Nicotine has been well characterized to improve memory and attention. Nicotine is the primary, but not only neuroactive compound in tobacco. Other tobacco constituents such as anabasine and anatabine also have agonist actions on nicotinic receptors. The current study investigated the effects of anabasine and anatabine on memory and attention. Adult female Sprague-Dawley rats were trained on a win-shift spatial working and reference memory task in the 16-arm radial maze or a visual signal detection operant task to test attention. Acute dose-effect functions of anabasine and anatabine over two orders of magnitude were evaluated for both tasks. In the radial-arm maze memory test, anabasine but not anatabine significantly reduced the memory impairment caused by the NMDA antagonist dizocilpine (MK-801). In the signal detection attentional task, anatabine but not anabasine significantly attenuated the attentional impairment caused by dizocilpine. These studies show that non-nicotine nicotinic agonists in tobacco, similar to nicotine, can significantly improve memory and attentional function. Both anabasine and anatabine produced cognitive

improvement, but their effectiveness differed with regard to memory and attention. Follow-up studies with anabasine and anatabine are called for to determine their efficacy as therapeutics for memory and attentional dysfunction.

Lorcaserin, A Selective 5-HT(2C) Receptor Agonist, Decreases Alcohol Intake In Female Alcohol Preferring Rats Rezvani A, Cauley M, Levin E. Pharmacol Biochem Behav. 2014; 125: 8-14.

Serotonergic systems in the brain have been found to be important in the addiction to alcohol. The purpose of this study was to evaluate the efficacy of a novel 5-HT2c receptor agonist, lorcaserin for reducing alcohol consumption in alcohol-preferring (P) rats. Adult female rats were allowed to drink water or alcohol (12%, v/v) using a standard two-bottle choice procedure. Once stable baselines were established, the acute (0, 0.3125, 0.625 and 1.25 mg/kg, s.c.), and chronic (0, 0.625 mg/kg, sc for 10 days) effects of lorcaserin on alcohol intake and preference were assessed at different time points. In a separate experiment, the effects of lorcaserin on locomotor activity were determined. These results show that both 0.625 and 1.25 mg/kg lorcaserin significantly reduced alcohol intake at 2, 4 and 6 h. after the drug administration. The chronic administration of 0.625 mg/kg lorcaserin significantly reduced alcohol intake up to 6h every day after the injection and there was no sign of diminished efficacy of the drug during 10-day treatment. To determine the effects of lorcaserin on sucrose intake, rats were put on a two-bottle choice of water vs a solution of 7% sucrose. The high dose of lorcaserin (1.25 mg/kg, s.c.) reduced sucrose intake only for up to 2 h. When tested for locomotor activity, lorcaserin injected 20 min before testing significantly reduced locomotor activity at all doses. However, when it was injected 5.5h before the start of the 1-h session, neither dose had a significant effect on locomotor activity. These results show the efficacy of lorcaserin in reducing alcohol intake without a significant effect on water intake and locomotion suggesting the involvement of 5-HT2c receptors in alcohol seeking behavior. Further research is warranted to determine the possible efficacy of lorcaserin or similar drugs as treatments for the treatment of alcoholism.

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

Chronic Administration of Δ9-Tetrahydrocannabinol Induces intestinal Anti-inflammatory MicroRNA Expression During Acute SIV Infection of Rhesus Macaques Chandra LC, Kumar V, Torben W, Vande Stouwe C, Winsauer P, Amedee A, Molina PE, Mohana M. J. Virol. published online ahead of print 5 November 2014.

Recreational and medical use of cannabis among HIV-infected individuals has increased in 30 recent years. In SIV-infected macaques, chronic administration of Δ9-tetrahydrocannabinol (Δ9-THC), inhibited viral replication, intestinal inflammation and slowed disease progression. Persistent gastrointestinal disease/inflammation has been proposed to facilitate microbial translocation, systemic immune activation and promote disease progression. Cannabinoids including Δ9-THC attenuated intestinal inflammation in mouse colitis models and SIV-infected rhesus macaques. To determine if the anti-inflammatory effects of Δ9-THC involved differential microRNA (miRNA) modulation, the authors profiled miRNA expression at 14, 30 and 60 days postinfection (DPI) in the intestine of uninfected macaques receiving Δ9-THC (n=3) and SIV-nfected macaques administered either vehicle (VEH/SIV; n=4) or THC (THC/SIV; n=4). Chronic Δ9-THC administration to uninfected macaques significantly and positively modulated intestinal miRNA expression by increasing the total number of differentially expressed miRNAs from 14 to 60DPI. At 60DPI, ~28% of miRNAs showed decreased expression in VEH/SIV compared to none in the THC/SIV group. Furthermore, compared to the VEH/SIV group, THC selectively upregulated the expression of miR-10a, miR-24, miR-99b, miR-145, miR-149 and miR-187 previously been shown to target proinflammatory molecules. NOX4, a potent reactive oxygen species generato was confirmed as a direct miR-99b target. A significant increase in NOX4+ crypt epithelial cells was detected in VEH/SIV compared to the THC/SIV group. The authors speculate that miR-99b mediated NOX4 downregulation may protect the intestinal epithelium from oxidative stress induced damage. These results support a role for differential miRNA induction in THC-mediated suppression of intestinal inflammation. Whether similar miRNA modulation occurs in other tissues requires further investigation.

Association Of Opioid Agonist Therapy With Lower Incidence Of Hepatitis C Virus Infection In Young Adult Injection Drug Users Tsui JI, Evans JL, Lum PJ, Hahn JA, Page K. JAMA Intern Med. 2014 Dec 1;174(12):1974-1981.

Injection drug use is the primary mode of transmission for hepatitis C virus (HCV) infection. Prior studies suggest opioid agonist therapy may reduce the incidence of HCV infection among injection drug users; however, little is known about the effects of this therapy in younger users. The objective of this study was to evaluate whether opioid agonist therapy was associated with a lower incidence of HCV infection in a cohort of young adult injection drug users. This was an observational cohort study conducted from January 3, 2000, through August 21, 2013, with quarterly interviews and blood sampling. The authors recruited young adult (younger than 30 years) injection drug users who were negative for anti-HCV antibody and/or HCV RNA. Exposures recorded were substance use treatment within the past 3 months, including non-opioid agonist forms of treatment, opioid agonist (methadone hydrochloride or buprenorphine hydrochloride) detoxification or maintenance therapy, or no treatment. Main outcomes and measures were incident HCV infection documented with a new positive result for HCV RNA and/or HCV antibodies. Cumulative incidence rates (95% CI) of HCV infection were calculated assuming a Poisson distribution. Cox proportional hazards regression models were fit adjusting for age, sex, race, years of injection drug use, homelessness, and incarceration. Baseline characteristics of the sample (n=552) included median age of 23

(interquartile range, 20-26) years; 31.9% female; 73.1% white; 39.7% who did not graduate from high school; and 69.2% who were homeless. During the observation period of 680 person-years, 171 incident cases of HCV infection occurred (incidence rate, 25.1 [95% CI, 21.6-29.2] per 100 person-years). The rate ratio was significantly lower for participants who reported recent maintenance opioid agonist therapy (0.31 [95% CI, 0.14-0.65]; P=.001) but not for those who reported recent non-opioid agonist forms of treatment (0.63 [95% CI, 0.37-1.08]; P=.09) or opioid agonist detoxification (1.45 [95% CI, 0.80-2.69]; P=.23). After adjustment for other covariates, maintenance opioid agonist therapy was associated with lower relative hazards for acquiring HCV infection over time (adjusted hazard ratio, 0.39 [95% CI, 0.18-0.87]; P=.02). In this cohort of young adult injection drug users, recent maintenance opioid agonist therapy was associated with a lower incidence of HCV infection. Maintenance treatment with methadone or buprenorphine for opioid use disorders may be an important strategy to prevent the spread of HCV infection among young injection drug users.

A Correlate Of HIV-1 Control Consisting Of Both Innate And Adaptive Immune Parameters Best Predicts Viral Load By Multivariable Analysis In HIV-1 Infected Viremic Controllers And Chronically-Infected Non-Controllers Tomescu C, Liu Q, Ross BN, Yin X, Lynn K, Mounzer KC, Kostman JR, Montaner LJ. PLoS One. 2014;9(7):e103209.
HIV-1 infected viremic controllers maintain durable viral suppression below 2000 copies viral RNA/ml without anti-retroviral therapy (ART), and the immunological factor(s) associated with host control in presence of low but detectable viral replication are of considerable interest. Here, the authors utilized a multivariable analysis to identify which innate and adaptive immune parameters best correlated with viral control utilizing a cohort of viremic controllers (median 704 viral RNA/ml) and non-controllers (median 21,932 viral RNA/ml) that were matched for similar CD4+ T cell counts in the absence of ART. They observed that HIV-1 Gag-specific CD8+ T cell responses were preferentially targeted over Pol-specific responses in viremic controllers (p=0.0137), while Pol-specific responses were positively associated with viral load (rho=0. 7753, p=0. 0001, n=23). Viremic controllers exhibited significantly higher NK and plasmacytoid dendritic cells (pDC) frequency as well as retained expression of the NK CD16 receptor and strong target cell-induced NK cell IFN-gamma production compared to non-controllers (p<0. 05). Despite differences in innate and adaptive immune function however, both viremic controllers (p<0. 05) and non-controller subjects (p<0. 001) exhibited significantly increased CD8+ T cell activation and spontaneous NK cell degranulation compared to uninfected donors. Overall, the authors identified that a combination of innate (pDC frequency) and adaptive (Pol-specific CD8+ T cell responses) immune parameters best predicted viral load (R2=0.5864, p=0.0021, n=17) by a multivariable analysis. Together, this data indicates that preferential Gag-specific over Pol-specific CD8+ T cell responses along with a retention of functional innate subsets best predict host control over viral replication in HIV-1 infected viremic controllers compared to chronically-infected non-controllers.

P2X4 Receptor Regulates Alcohol-Induced Responses In Microglia Gofman L, Cenna JM, Potula R. J Neuroimmune Pharmacol. 2014 Dec; 9(5):668-678.
Mounting evidence indicates that alcohol-induced neuropathology may result from multicellular responses in which microglia cells play a prominent role. Purinergic receptor signaling plays a key role in regulating microglial function and, more importantly, mediates alcohol-induced effects. The authors' findings demonstrate that alcohol increases expression of P2X4 receptor (P2X4R), which alters the function of microglia, including calcium mobilization, migration and phagocytosis. Their results show a significant up-regulation of P2X4 gene expression as analyzed by real-time qPCR (***p<0. 002) and protein expression as analyzed by flow cytometry (**p<0. 004) in embryonic

stem cell-derived microglial cells (ESdM) after 48 hours of alcohol treatment, as compared to untreated controls. Calcium mobilization in ethanol treated ESdM cells was found to be P2X4R dependent using 5-BDBD, a P2X4R selective antagonist. Alcohol decreased migration of microglia towards fractalkine (CX3CL1) by 75 % following 48 h of treatment compared to control (***p<0.001). CX3CL1-dependent migration was confirmed to be P2X4 receptor-dependent using the antagonist 5-BDBD, which reversed the effects as compared to alcohol alone (***p<0. 001). Similarly, 48 h of alcohol treatment significantly decreased phagocytosis of microglia by 15 % compared to control (*p<0.05). 5-BDBD pre-treatment prior to alcohol treatment significantly increased microglial phagocytosis (***p<0.001). Blocking P2X4R signaling with 5-BDBD decreased the level of calcium mobilization compared to ethanol treatment alone. These findings demonstrate that P2X4 receptor may play a role in modulating microglial function in the context of alcohol abuse.

Chronic Cocaine Use And Its Association With Myocardial Steatosis Evaluated By 1H Magnetic Resonance Spectroscopy In African Americans Lai S, Gerstenblith G, Li J, Zhu H, Bluemke DA, Liu CY, Zimmerman SL, Chen S, Lai H, Treisman G. J Addict Med. 2014 Oct; [Epub ahead of print].

Cardiac steatosis is a manifestation of ectopic fat deposition and is associated with obesity. The impact of chronic cocaine use on obesity measures and on the relationship between obesity measures and cardiac steatosis is not well-characterized. The objectives of this study were to compare obesity measures in chronic cocaine users and nonusers, and to explore which factors, in addition to obesity measures, are associated with myocardial triglyceride in African Americans, using noninvasive magnetic resonance spectroscopy. Between June 2004 and January 2014, 180 healthy African American adults without HIV infection, hypertension, and diabetes were enrolled in an observational proton magnetic resonance spectroscopy and imaging study investigating factors associated with cardiac steatosis. Among these 180 participants, 80 were chronic cocaine users and 100 were nonusers. The median age was 42 (interquartile range, 34-47) years. Obesity measures trended higher in cocaine users than in nonusers. The median myocardial triglyceride was 0. 6% (interquartile range, 0. 4%-1. 1%). Among the factors investigated, years of cocaine use, leptin, and visceral fat were independently associated with myocardial triglyceride. Body mass index and visceral fat, which were significantly associated with myocardial triglyceride in noncocaine users, were not associated with myocardial triglyceride content in cocaine users. This study shows (1) cocaine users may have more fat than nonusers and (2) myocardial triglyceride is independently associated with duration of cocaine use, leptin, and visceral fat in all subjects, whereas leptin and high-density lipoprotein cholesterol, but not visceral fat or body mass index, in cocaine users, suggesting that chronic cocaine use may modify the relationships between obesity measures and myocardial triglyceride.

Reference Values Of Myocardial Structure, Function, and Tissue Composition By Cardiac Magnetic Resonance In Healthy African-Americans At 3T and Their Relations To Serologic And Cardiovascular Risk Factors Liu CY, Bluemke DA, Gerstenblith G, Zimmerman SL, Li J, Zhu H, Lai S, Lai H. Am J Cardiol. 2014 Sep; 114(5):789-795.

Cardiac magnetic resonance (CMR) is a standard of reference for cardiac structure and function. Recent advances in T1 mapping and spectroscopy also provide assessment of myocardial tissue composition. However, the reference ranges of left ventricular parameters have rarely been assessed in an African-American (AA) population without known cardiac disease. To estimate the reference values of myocardial structure, function, and tissue composition by CMR and to explore their relationships to serologic factors and cardiovascular risk factors in asymptomatic AAs with low

Framingham risk, between November 2010 and June 2012, 92 healthy AAs aged ≥21 years, from Baltimore, MD, were enrolled in an observational study. CMR examination was performed on a 3T scanner. Proton magnetic resonance spectroscopy was performed to noninvasively quantify myocardial triglyceride content. Native T1 values were obtained from modified Look-Locker inversion recovery sequence. The median age was 37 (interquartile range IQR 27 to 44) years (41% men). The median native T1 time of the myocardium was 1,228 ms (IQR 1,200 to 1,263) with no gender difference. The median myocardial fat content was 0. 6% (IQR 0. 7% to 4. 6%). Native T1 time was not influenced by age, sex, and body mass index. Among the factors investigated, myocardial fat and elevated C-reactive protein (>2. 0 mg/dL) were independently associated with T1 relaxation time. Native T1 time was also independently associated with left ventricular end-diastolic volume indexed to body surface area. In conclusion, this study of asymptomatic AAs provides reference ranges for cardiovascular structure, function, and tissue composition. Alterations in myocardial fat are associated with native T1 time, a CMR measure of interstitial fibrosis.

Differences In Hepatitis C Virus Prevalence and Clearance By Mode Of Acquisition Among Men Who Have Sex With Men Seaberg EC, Witt MD, Jacobson LP, Detels R, Rinaldo CR, Young S, Phair JP, Thio CL. J Viral Hepat. 2014 Oct; 21(10):696-705.
The authors examined the characteristics associated with hepatitis C virus (HCV) antibody (anti-HCV) prevalence and HCV clearance between injection drug using (IDU) and non-IDU men who have sex with men (MSM). Stored serum and plasma samples were tested for anti-HCV and HCV RNA to determine the HCV status of 6925 MSM at enrolment into the Multicentre AIDS Cohort Study (MACS). Prevalence and clearance ratios were calculated to determine the characteristics associated with HCV prevalence and clearance. Multivariable analyses were performed using Poisson regression methods with robust variance estimation. Anti-HCV prevalence was significantly higher among IDU than among non-IDU MSM (42. 9% vs 4. 0%), while clearance was significantly lower among IDU MSM (11. 5% vs 34. 5% among non-IDU MSM). HIV infection, Black race, and older age were independently associated with higher prevalence in both groups, while smoking, transfusion history, and syphilis were significantly associated with prevalence only among non-IDU MSM. The rs12979860-C/C genotype was the only characteristic independently associated with HCV clearance in both groups, but the effects of both rs12979860-C/C genotype [clearance ratio (CR) = 4. 16 IDUs vs 1. 71 non-IDUs; P = 0. 03] and HBsAg positivity (CR = 5.06 IDUs vs 1.62 non-IDUs; P= 0.03) were significantly larger among IDU MSM. HIV infection was independently associated with lower HCV clearance only among non-IDU MSM (CR = 0.59, 95% CI=0.40-0.87). IDU MSM have higher anti-HCV prevalence and lower HCV clearance than non-IDU MSM. Differences in the factors associated with HCV clearance suggest that the mechanisms driving the response to HCV may differ according to the mode of acquisition.

Genome-Wide Association Study Of Hepatitis C Virus- and Cryoglobulin-Related Vasculitis Zignego AL, Wojcik GL, Cacoub P, Visentini M, Casato M, Mangia A, Latanich R, Charles ED, Gragnani L, Terrier B, Piazzola V, Dustin LB, Khakoo SI, Busch MP, Lauer GM, Kim AY, Alric L, Thomas DL, Duggal P. Genes Immun. 2014 Oct; 15(7):500-505.
The host genetic basis of mixed cryoglobulin vasculitis is not well understood and has not been studied in large cohorts. A genome-wide association study was conducted among 356 hepatitis C virus (HCV) RNA-positive individuals with cryoglobulin-related vasculitis and 447 ethnically matched, HCV RNA-positive controls. All cases had both serum cryoglobulins and a vasculitis syndrome. A total of 899 641 markers from the Illumina HumanOmni1-Quad chip were analyzed using logistic regression adjusted for sex, as well as genetically determined ancestry. Replication of select single-nucleotide polymorphisms (SNPs) was conducted using 91 cases and 180 controls,

adjusting for sex and country of origin. The most significant associations were identified on chromosome 6 near the NOTCH4 and MHC class II genes. A genome-wide significant association was detected on chromosome 6 at SNP rs9461776 (odds ratio=2.16, P=1.16E-07) between HLA-DRB1 and DQA1: this association was further replicated in additional independent samples (meta-analysis P=7.1 × 10(-9)). A genome-wide significant association with cryoglobulin-related vasculitis was identified with SNPs near NOTCH4 and MHC Class II genes. The two regions are correlated and it is difficult to disentangle which gene is responsible for the association with mixed cryoglobulinemia vasculitis in this extended major histocompatibility complex region.

Antiretroviral Therapy, Interferon Sensitivity, and Virologic Setpoint In Human Immunodeficiency Virus/Hepatitis C Virus Coinfected Patients Balagopal A, Kandathil AJ, Higgins YH, Wood J, Richer J, Quinn J, Eldred L, Li Z, Ray SC, Sulkowski MS, Thomas DL. Hepatology. 2014 Aug; 60(2): 477-486.
Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) cause substantial mortality, especially in persons chronically infected with both viruses. HIV infection raises plasma HCV RNA levels and diminishes the response to exogenous alpha interferon (IFN). The degree to which antiretroviral therapy (ART) control of infection overcomes these HIV effects is unknown. Participants with HIV-HCV coinfection were enrolled in a trial to measure HCV viral kinetics after IFN administration (ΔHCVIFN) twice: initially before (pre-ART) and then after (post-ART) HIV RNA suppression. Liver tissue was obtained 2-4 hours before each IFN injection to measure interferon stimulated genes (ISGs). Following ART, the ΔHCVIFN at 72 hours (ΔHCVIFN,72) increased in 15/19 (78. 9%) participants by a median (interquartile range [IQR]) of 0.11 log10 IU/mL (0.00-0.40; P<0.05). Increases in ΔHCVIFN,72 post-ART were associated with decreased hepatic expression of several ISGs (r=-0.68; P=0.001); a 2-fold reduction in a four-gene ISG signature predicted an increase in ΔHCVIFN,72 of 0.78 log10 IU/mL (95% confidence interval [CI] 0.36,1.20). Pre- and post-ART ΔHCVIFN,72 were closely associated (r=0.87; P<0.001). HCV virologic setpoint also changed after ART (ΔHCVART): transient median increases of 0.28 log10 IU/mL were followed by eventual median decreases from baseline of 0.21 log10 IU/mL (P=0.002). A bivariate model of HIV RNA control (P<0. 05) and increased expression of a nine-gene ISG signature (P<0. 001) predicted the eventual decreased ΔHCVART. ART is associated with lower post-IFN HCV RNA levels and that change is linked to reduced hepatic ISG expression. These data support recommendations to provide ART prior to IFN-based treatment of HCV and may provide insights into the pathogenesis of HIV-HCV coinfection.

Poverty Matters: Contextualizing The Syndemic Condition Of Psychological Factors and Newly Diagnosed HIV Infection In The United States Oldenburg CE, Perez-Brumer AG, Reisner SL. AIDS. 2014 Nov; 28(18):2763-2769.
'Syndemic factors', defined as co-occurring psychological conditions including major depressive disorder, substance and alcohol use, and intimate partner violence, have been shown to increase HIV incidence among MSM in the United States. However, this relationship has not been well characterized in the general population, particularly in the context of poverty. Prospective cohort study including a nationally-representative sample of 34,427 men and women in the National Epidemiologic Survey on Alcohol and Related Conditions wave 1 (2001-2002) and wave 2 (2004-2005). Weighted multivariable logistic regression models were used to assess the association between syndemic factors and newly diagnosed HIV infection, and to assess how living below the poverty line (based on 2001 US Poverty Guidelines) modified this relationship. The proportion of participants reporting new HIV diagnosis in the past year was 0. 22%, increasing from 0. 19% among individuals with no syndemic factor to 5.1% among those with four syndemic factors.

Adjusting for potentially confounding factors, each additional syndemic factor was associated with a 47% increase in odds of HIV infection [adjusted odds ratio (aOR) 1.47, 95% confidence interval (CI) 1.30-1.65]. The effect of syndemic factors was stronger among individuals living below federal poverty guidelines (aOR 1.96, 95% CI 1.57-2.44) compared to those living above poverty guidelines (aOR 1.21, 95% CI 1.07-1.36). Among the US general population, the association between co-occurring syndemic factors and incident HIV infection was stronger in the setting of poverty. Mental health interventions, particularly in socioeconomically disadvantaged areas, should be considered to reduce transmission of HIV.

Childhood Friendships and Psychological Difficulties In Young Adulthood: An 18-Year Follow-Up Study Sakyi KS, Surkan PJ, Fombonne E, Chollet A, Melchior M. Eur Child Adolesc Psychiatry. 2014 Oct; [Epub ahead of print]. Childhood friendships have been shown to impact mental health over the short term; however, it is unclear whether these effects are sustained into young adulthood. The authors studied the prospective association between childhood friendships and psychological difficulties in young adulthood. Data come from 1,103 French 22-35 year olds participating in the TEMPO study. Childhood friendships were ascertained in 1991 when participants were 4-16 years old. Psychological difficulties were measured in 2009 using the Adult Self-Report. Logistic regression models controlled for participants' age, sex, childhood psychological difficulties and parental characteristics. Young adults who had no childhood friends had higher odds of psychological difficulties than those with at least one friend: (adjusted ORs 2. 45; 95 % CI 1. 32-4. 66, p = 0.01 for high internalizing symptoms; 1. 81; 95 % CI 0. 94-3. 54, p = 0. 08 for high externalizing symptoms). Social relations early in life may have consequences for adult psychological well-being.

Investigating the Contribution Of Cyp2J2 To Ritonavir Metabolism In Vitro and In Vivo Kaspera R, Kirby BJ, Sahele T, Collier AC, Kharasch ED, Unadkat JD, Totah RA. Biochem Pharmacol. 2014 Sep; 91(1):109-118.
Ritonavir, an HIV protease inhibitor, is successfully used for the prevention and treatment of HIV infections. Ritonavir pharmacokinetics are complicated by inhibition, induction and pharmacogenetics of cytochrome P450 (CYP) enzymes mediating its clearance. This investigation revealed that CYP2J2, along with CYP3A4/5 and CYP2D6, efficiently metabolizes ritonavir, and to a CYP2J2-specific (minor) metabolite. Chemical inhibition of ritonavir metabolism, clearance, KI/kinact and abundance of CYP2J2 in liver microsomes were evaluated and then applied to an in vitro-in vivo static scaling model to estimate the contribution of each isozyme, as a function of CYP abundance, activity, and genotype. Disposition of the CYP2J2-specific metabolite was also evaluated in vivo. In plasma, metabolite abundance was well above previously reported levels with circulating concentrations measured at 2 μM for the main hydroxylisopropyl metabolite. Ritonavir and metabolite plasma profiles were simulated using Simcyp(®). A modest (2-6%) contribution of CYP2J2 to ritonavir clearance is predicted which increases to more than 20% in subjects carrying CYP2D6 poor metabolizer polymorphisms and CYP3A4 irreversible inhibition. These results indicate that minor drug metabolizing enzymes could become quantitatively important in RTV clearance if main metabolic pathways are impeded.

A Comparison Of Seminal Hepatitis C Virus (HCV) RNA Levels During Recent And Chronic HCV Infection In HIV-Infected And HIV-Uninfected Individuals Bradshaw D, Lamoury F, Catlett B, Applegate TL, Mcallister J, Dore GJ, Matthews GV, Danta M. J Infect Dis. 2014 Oct; [Epub ahead of print].

The authors aimed to characterize seminal hepatitis C virus (HCV) RNA dynamics in human immunodeficiency virus (HIV)-positive men with acute HCV infection given its potential role in sexual transmission of HCV. Men with acute HCV infection (duration, ≤12 months) or chronic HCV infection (duration, >12 months) were prospectively recruited. Paired semen and blood samples were assayed for HCV RNA levels. Results were analyzed using $\chi(2)$, Fisher exact, Mann-Whitney U, and Kruskal-Wallis tests. Eighteen men (27.3%) had acute HCV and HIV coinfection, 22 (33.3%) had chronic HCV infection and HIV coinfection, and 26 (39.4%) had chronic HCV monoinfection. HCV RNA was detected in semen specimens from 29 of 66 men (43.9%). The median HCV RNA level in blood was 4. 0 log IU/mL higher than that in semen. HCV RNA levels were correlated in semen and blood ($r(2) = 0.142$). Neither HIV positivity nor acute HCV infection was associated with an increased frequency of seminal HCV RNA detection. Among men with acute HCV and HIV coinfection, the median HCV RNA level in blood specimens from those with seminal HCV RNA was higher than that in blood specimens from those without seminal HCV RNA ($P = .001$). Seminal HCV RNA was detected in ≥1 sample for 26 of 35 men (74.3%) attending follow up. HCV RNA was detected in semen during both acute and chronic HCV infection. This was unaffected by HIV positivity or the phase of HCV infection. Elevated seminal HCV RNA levels could contribute to sexual transmission of HCV, but other factors, including high-risk behaviors, may be the main drivers for HCV transmission in HIV-infected individuals.

Naturally Occurring Dominant Drug Resistance Mutations Occur Infrequently In The Setting Of Recently Acquired Hepatitis C Applegate TL, Gaudieri S, Plauzolles A, Chopra A, Grebely J, Lucas M, Hellard M, Luciani F, Dore GJ, Matthews GV. Antivir Ther. 2014 Aug; [Epub ahead of print].

Directly Acting Antivirals (DAAs) are predicted to transform hepatitis C (HCV) therapy, yet little is known about the prevalence of naturally occurring resistance mutations in recently acquired HCV. This study aimed to determine the prevalence and frequency of drug resistance mutations in the viral quasispecies among HIV positive and negative individuals with recent HCV. The NS3 protease, NS5A and NS5B polymerase genes were amplified from fifty genotype 1a participants of the Australian Trial in Acute Hepatitis C. Amino acid variations at sites known to be associated with possible drug resistance were analysed by ultra-deep pyrosequencing. Twelve percent of individuals harboured dominant resistance mutations, while 36% demonstrated non dominant resistant variants below that detectable by bulk sequencing (ie < 20%) but above a threshold of 1%. Resistance variants (< 1%) were observed at most sites associated with DAA resistance from all classes, with the exception of sofosbuvir. Dominant resistant mutations were uncommonly observed in the setting of recent HCV. However, low level mutations to all DAA classes were observed by deep sequencing at the majority of sites, and in most individuals. The significance of these variants and impact on future treatment options remains to be determined.

Dynamics Of HCV RNA Levels During Acute Hepatitis C Virus Infection Hajarizadeh B, Grebely J, Applegate T, Matthews GV, Amin J, Petoumenos K, Hellard M, Rawlinson W, Lloyd A, Kaldor J, Dore GJ. J Med Virol. 2014 Oct; 86(10):1722-1729.

Understanding viral dynamics during acute hepatitis C virus (HCV) infection can provide important insights into immunopathogenesis and guide early treatment. The aim of this study was to investigate the dynamics of HCV RNA and alanine transaminase (ALT) levels during recent HCV

infection in the Australian Trial in Acute Hepatitis C (ATAHC). ATAHC was a prospective study of the natural history of recently acquired HCV infection. Longitudinal HCV RNA and ALT levels were compared among individuals with persistent infection and spontaneous clearance. Among those with HCV persistence (n=104) and HCV clearance (n=30), median HCV RNA (5. 2 vs. 4. 1logIU/ml, respectively) and ALT levels (779 vs. 1,765IU/L, respectively) were high during month two following infection, and then declined during months three and four in both groups. Among those with HCV persistence, median HCV RNA was 2.9logIU/ml during months four, increased to 5. 5logIU/ml during month five, and remained subsequently relatively stable. Among those with HCV clearance, median HCV RNA was undetectable by month five. Median HCV RNA levels were comparable between individuals with HCV persistence and HCV clearance during month three following infection (3. 2 vs. 3. 5logIU/ml, respectively; P=0. 935), but markedly different during month five (5.5 vs. 1.0logIU/ml, respectively; P<0. 001). In conclusion, dynamics of HCV RNA levels in those with HCV clearance and HCV persistence diverged between months three and five following infection, with the latter time-point being potentially useful for commencing early treatment.

Assessing the Feasibility Of Hepatitis C Virus Vaccine Trials: Results From The Hepatitis C Incidence and Transmission Study-Community (HITS-C) Vaccine Preparedness Study White B, Madden A, Prins M, Hellard M, Wand H, Dore GJ, Page K, Maher L. Vaccine. 2014 Sep; 32(42):5460-5467.

Efficacy trials of preventive hepatitis C virus (HCV) vaccine candidates raise challenging scientific and ethical issues. Based on data from the first 3 years of a community-based prospective observational study - the Hepatitis C Incidence and Transmission Study-community (HITS-c) - this paper examines the feasibility of conducting trials of candidate HCV vaccines with people who inject drugs (PWID) in Sydney, Australia. Of the 166 PWID confirmed HCV antibody negative and eligible for enrolment, 156 (94%) completed baseline procedures. Retention was high, with 89% of participants retained at 48 weeks and 76% of participants completing at least 75% of study visits within 2 weeks of schedule. The rate of primary HCV infection was 7. 9/100 py (95% CI 4.9, 12.7). Of the 17 incident cases, 16 completed at least one follow-up assessment and 12 (75%) had evidence of chronic viraemia with progression to chronic HCV infection estimated to be 6/100 py. Power calculations suggest a chronic HCV infection rate of at least 12/100 py (primary HCV infection rate 16/100 py) will be required for stand-alone trials of highly efficacious candidates designed to prevent chronic infection. However, elevated primary HCV infection was observed among participants not receiving opioid substitution therapy who reported heroin as the main drug injected (26.9/100 py, A95% CI 14.5, 50.0) and those who reported unstable housing (23.5/100 py, 95% CI 7.6, 72.8), daily or more frequent injecting (22.7/100 py, 95% CI 12.2, 42.2) and receptive syringe sharing (23.6/100 py, 95% CI 9. 8, 56.7) in the 6 months prior to baseline. These data suggest that it is possible to recruit and retain at-risk PWID who adhere to study protocols and that modification of eligibility criteria may identify populations with sufficiently high HCV incidence. Results support the feasibility of large multi-centre HCV vaccine trials, including in the Australian setting.

Concordance Of Risk Behavior Reporting Within HCV Serodiscordant Injecting Partnerships Of Young Injection Drug Users In San Francisco, CA Evans JL, Morris MD, Yu M, Page K, Hahn JA. Drug Alcohol Depend. 2014 Sep; 142[Epub ahead of print] 239-244.

Young injection drug users (IDU, under age 30) often inject with other IDU, creating an environment for risk of blood-borne disease transmission through sharing of needles and drug preparation equipment. Epidemiologic studies rely on self reported injection behavior data for

measures of transmission risk, therefore we sought to quantify the degree of concordance of reported injecting risk behaviors between injecting dyads. From May, 2006 through 2013 we enrolled 72 injecting dyads in San Francisco, California, who were hepatitis C virus (HCV) RNA discordant. Each partnership was followed prospectively for up to six months. Monthly interviews from each partner were date-matched and responses to relationship characteristics and risk behavior questions were compared. Concordance of reporting was estimated with the concordance correlation coefficient for longitudinal data (CCC) and the prevalence adjusted bias adjusted kappa (PABAK). Participants had a median age of 26 (IQR: 23, 28) years and median years injecting of 7. 0 (IQR: 3. 0, 10. 6). Thirty-eight percent of the injecting dyads were also sexual partners. Concordance levels were highest for partnership characteristics, such as length of acquaintance, number of days cohabitating, and sexual intercourse in the past month (CCC=0. 95; 0. 82, and 0. 90, respectively). Shared injection risk behaviors such as injecting with the HCV+ partner's previously used syringe and using contaminated injection preparation equipment had slight to fair agreement (CCC=0. 22; 0. 23; PABAK=0. 43, 0. 36, respectively). Concordance levels ranged from low to high. Potential sources of measurement error for low agreement items include recall and social-desirability biases and question interpretation.

Comparison Of Phosphatidylethanol Results To Self-Reported Alcohol Consumption Among Young Injection Drug Users Jain J, Evans JL, Briceño A, Page K, Hahn JA. Alcohol Alcohol. 9(5):520-524.

The objective iof this studywas to test the value of phosphatidylethanol (PEth) as a biomarker for alcohol consumption among injecting drug users (IDUs). As part of a longitudinal study of young IDUs, dried blood spots and self-reported alcohol by structured interview were collected at baseline. The authors compared self-reported alcohol use to detectable PEth (≥8ng/ml) in the blood spots as well as the relationships between quantitative PEth results and quantity measures of alcohol consumption. There were strong associations between PEth and self-reported categorical measures of alcohol consumption (all $P < 0.01$). There was high specificity for reporting abstaining from alcohol; 94% of those who reported not consuming alcohol in the prior month tested negative for PEth. PEth was well correlated with measures of alcohol use (e. g. with reported number of days drinking in the prior month: Spearman $r = 0.70$ ($P < 0.001$)). The positive correlation of PEth with reported alcohol consumption suggests that PEth may be a useful marker in settings where alcohol consumption is difficult to assess, or to corroborate or invalidate self-reported measures of alcohol consumption.

A Study On Particles And Some Microbial Markers In Waterpipe Tobacco Smoke Markowicz P, Löndahl J, Wierzbicka A, Suleiman R, Shihadeh A, Larsson L. Sci Total Environ. 2014 Nov; 499[Epub ahead of print]107-113.

Waterpipe smoking is becoming increasingly popular worldwide. Research has shown that cigarette smoke, in addition to hundreds of carcinogenic and otherwise toxic compounds, may also contain compounds of microbiological origin. In the present study the authors analyzed waterpipe smoke for some microbial compounds. Both of the two markers studied, viz 3-hydroxy fatty acids of bacterial lipopolysaccharide (LPS) and ergosterol of fungal biomass, were found in waterpipe tobacco, in amounts similar as previously found in cigarette tobacco, and in smoke. Waterpipe mainstream smoke contained on average 1800 pmol LPS and 84. 4 ng ergosterol produced per session. An average concentration of 2. 8 pmol/m(3) of LPS was found in second hand smoke during a 1-2-h waterpipe smoking session while ergosterol was not detected; corresponding concentrations from smoking five cigarettes were 22. 2 pmol/m(3) of LPS and 87. 5 ng/m(3) of ergosterol. This is the first time that waterpipe smoking has been shown to create a bioaerosol. In

the present study the authors also found that waterpipe smoking generated several polycyclic aromatic hydrocarbons, carbon monoxide, and high fraction of small (<200 nm) particles that may have adverse effects on human health upon inhalation.

Immunopathogenesis Of HIV Infection In Cocaine Users: Role Of Arachidonic Acid

Samikkannu T, Rao KV, Ding H, Agudelo M, Raymond AD, Yoo C, Nair MP. PLoS One. 2014; 9(8):e106348.

Arachidonic acid (AA) is known to be increased in HIV infected patients and illicit drug users are linked with severity of viral replication, disease progression, and impaired immune functions. Studies have shown that cocaine accelerates HIV infection and disease progression mediated by immune cells. Dendritic cells (DC) are the first line of antigen presentation and defense against immune dysfunction. However, the role of cocaine use in HIV associated acceleration of AA secretion and its metabolites on immature dendritic cells (IDC) has not been elucidated yet. The aim of this study is to elucidate the mechanism of AA metabolites cyclooxygenase-2 (COX-2), prostaglandin E2 synthetase (PGE2), thromboxane A2 receptor (TBXA2R), cyclopentenone prostaglandins (CyPG), such as 15-deoxy-Δ12,14-PGJ2 (15d-PGJ2), 14-3-3 ζ/δ and 5-lipoxygenase (5-LOX) mediated induction of IDC immune dysfunctions in cocaine using HIV positive patients. The plasma levels of AA, PGE2, 15d-PGJ2, 14-3-3 ζ/δ and IDC intracellular COX-2 and 5-LOX expression were assessed in cocaine users, HIV positive patients, HIV positive cocaine users and normal subjects. Results showed that plasma concentration levels of AA, PGE2 and COX-2, TBXA2R and 5-LOX in IDCs of HIV positive cocaine users were significantly higher whereas 15d-PGJ2 and 14-3-3 ζ/δ were significantly reduced compared to either HIV positive subjects or cocaine users alone. This report demonstrates that AA metabolites are capable of mediating the accelerative effects of cocaine on HIV infection and disease progression.

Intimate Injection Partnerships Are At Elevated Risk Of High-Risk Injecting: A Multi-Level Longitudinal Study Of HCV-Serodiscordant Injection Partnerships In San Francisco, CA

Morris MD, Evans J, Montgomery M, Yu M, Briceno A, Page K, Hahn JA. PLoS One. 2014; 9(10):e109282.

It is increasingly recognized that the risk for HIV and hepatitis C (HCV) transmission among people who inject drugs (PWID), such as syringe sharing, occurs in the context of relationships between (at least) two people. Evidence suggests that the risk associated with injection behavior varies with injection partner types. The authors utilized longitudinal dyad-level data from a study of young PWID from San Francisco (2006 to 2013) to investigate the relationship-level factors influencing high-risk injecting within HCV-serodiscordant injection partners (i.e., individuals who injected together ≥5 times in the prior month). Utilizing data from 70 HCV-serodiscordant injection partnerships, the authors used generalized linear models to examine relationship-level predictors (i.e., partnership composition, partnership closeness, and partnership dynamics) of: (1) receptive syringe sharing (RSS); and (2) receptive cooker use (RCU), as reported by the HCV-negative injection partner. As reported by the "at-risk" HCV-negative injection partner, receptive syringe sharing (RSS) and receptive cooker use (RCU) were 19% and 33% at enrollment, and 11% and 12% over all visits (total follow-up time 55 person-years) resulting in 13 new HCV-infections (incidence rate: 23. 8/100 person-years). Person-level factors, injection partnership composition, and partnership dynamics were not significantly associated with either RSS or RCU. Instead, intimate injection partnerships (those who lived together and were also in a sexual relationship) were independently associated with a 5-times greater risk of both RSS and a 7-times greater risk of RCU when compared to injecting only partnerships. These findings suggest a positive, and amplified effect of relationship factors on injecting drug risk behaviors among young PWID injection

partnerships. The majority of interventions to reduce injection drug use related harms focus on individual-based education to increase drug use knowledge. These findings support the need to expand harm reduction strategies to relationship-based messaging and interventions.

Automated Radiochemical Synthesis And Biodistribution Of [^{11}C]L-A-Acetylmethadol ([^{11}C]LAAM) Sai KK, Fan J, Tu Z, Zerkel P, Mach RH, Kharasch ED. Appl Radiat Isot. 2014 Sep; 91[Epub ahead of print]135-140.
Long-acting opioid agonists methadone and l-α-acetylmethadol (LAAM) prevent withdrawal in opioid-dependent persons. Attempts to synthesize [(11)C]-methadone for PET evaluation of brain disposition were unsuccessful. Owing, however, to structural and pharmacologic similarities, the authors aimed to develop [(11)C]LAAM as a PET ligand to probe the brain exposure of long-lasting opioids in humans. This manuscript describes [(11)C]LAAM synthesis and its biodistribution in mice. The radiochemical synthetic strategy afforded high radiochemical yield, purity and specific activity, thereby making the synthesis adaptable to automated modules.

A Comparison Of Methamphetamine Users To A Matched Nhanes Cohort: Propensity Score Analyses For Oral Health Care and Dental Service Need Murphy DA, Harrell L, Fintzy R, Belin TR, Gutierrez A, Vitero SJ, Shetty V. J Behav Health Serv Res. 2014 Nov; [Epub ahead of print].
Dental problems are among the most frequently reported health issues of drug users. This study describes, among the largest population of methamphetamine (MA) users to date (N=459, including both HIV-negative and HIV-positive participants) oral hygiene practice, dental care access, and dental quality of life. A matched control group from the Third National Health and Nutrition Examination Survey was utilized. Findings conclusively establish that MA users have severe oral health deficits compared to the general population: they are 3.5 times more likely to experience painful toothaches, 6.6 times to experience difficulty eating, and 8.6 times to be self-conscious due to dental appearance. HIV-positive users were more likely to have regular dental visits than HIV-negative users. Severity of use (both high-frequency use as well as injection as the method) was associated with poorer oral health care. Despite the magnitude of the need, few MA users receive the needed care.

The Clinical Characteristics and Pathological Patterns Of Postinfectious Glomerulonephritis In HIV-Infected Patients Murakami CA, Attia D, Carter-Monroe N, Lucas GM, Estrella MM, Fine DM, Atta MG. PLoS One. 2014 ; 9(10):e108398.
Postinfectious glomerulonephritis (PIGN), a form of immune complex GN, is not well-defined in HIV-infected patients. This study characterizes PIGN in this patients' population and determine the impact of histopathological patterns on renal outcome and mortality. HIV-infected patients with PIGN from September 1998 to July 2013 were identified. Archived slides were reviewed by a blinded renal pathologist, classified into acute, persistent and healed PIGN. Groups were compared using Wilcoxon rank-sum and Fisher's exact test. Survival analyses were performed to determine association of histopathological pattern with renal outcome and mortality. Seventy-two HIV-infected predominantly African American males were identified with PIGN. Median (interquartile range) age and creatinine at the time of renal biopsy was 48 years (41, 53) and 2.5 mg/dl (1.5, 4.9) respectively. Only 2 (3%) had acute PIGN, 42 (58%) had persistent PIGN and 28 (39%) had healed PIGN. Three patients (4%) had IgA-dominant PIGN. Only 46% of the patients had confirmed positive cultures with Staphylococcus the most common infectious agent. During a median follow up of 17 months, the pathological pattern had no impact on renal outcome (P = 0.95). Overall mortality was high occurring in 14 patients (19%); patients with healed PIGN had significantly increased mortality (P = 0.05). In HIV-infected patients, Staphylococcus is the most common cause

of PIGN. Renal outcome was not influenced by the histopathological pattern but those with healed PIGN had greater mortality which was potentially due to a confounder not accounted for in the study.

Characterization Of A Monoclonal Antibody To A Novel Glycan-Dependent Epitope In the V1/V2 Domain Of The HIV-1 Envelope Protein, Gp120 Doran RC, Morales JF, To B, Morin TJ, Theolis R, O'Rourke SM, Yu B, Mesa KA, Berman PW. Mol Immunol. 2014 Nov; 62(1): 219-226.
Recent studies have described several broadly neutralizing monoclonal antibodies (bN-mAbs) that recognize glycan-dependent epitopes (GDEs) in the HIV-1 envelope protein, gp120. These were recovered from HIV-1 infected subjects, and several (e.g., PG9, PG16, CH01, CH03) target glycans in the first and second variable (V1/V2) domain of gp120. The V1/V2 domain is thought to play an important role in conformational masking, and antibodies to the V1/V2 domain were recently identified as the only immune response that correlated with protection in the RV144 HIV-1 vaccine trial. While the importance of antibodies to polymeric glycans is well established for vaccines targeting bacterial diseases, the importance of antibodies to glycans in vaccines targeting HIV has only recently been recognized. Antibodies to GDEs may be particularly significant in HIV vaccines based on gp120, where 50% of the molecular mass of the envelope protein is contributed by N-linked carbohydrate. However, few studies have reported antibodies to GDEs in humans or animals immunized with candidate HIV-1 vaccines. In this report, The authors describe the isolation of a mouse mAb, 4B6, after immunization with the extracellular domain of the HIV-1 envelope protein, gp140. Epitope mapping using glycopeptide fragments and in vitro mutagenesis showed that binding of this antibody depends on N-linked glycosylation at asparagine N130 (HXB2 numbering) in the gp120 V1/V2 domain. These results demonstrate that, in addition to natural HIV-1 infection, immunization with recombinant proteins can elicit antibodies to the GDEs in the V1/V2 domain of gp120. Although little is known regarding conditions that favor antibody responses to GDEs, these studies demonstrate that these antibodies can arise from a short-term immunization regimen. These results suggest that antibodies to GDEs are more common than previously suspected, and that further analysis of antibody responses to the HIV-1 envelope protein will lead to the discovery of additional antibodies to GDEs.

HIV-1 Envelope Proteins and V1/V2 Domain Scaffolds With Mannose-5 To Improve the Magnitude and Quality Of Protective Antibody Responses To HIV-1 Morales JF, Morin TJ, Yu B, Tatsuno GP, O'Rourke SM, Theolis R, Mesa KA, Berman PW. J Biol Chem. 2014 Jul; 289(30): 20526-20542.
Two lines of investigation have highlighted the importance of antibodies to the V1/V2 domain of gp120 in providing protection from HIV-1 infection. First, the recent RV144 HIV-1 vaccine trial documented a correlation between non-neutralizing antibodies to the V2 domain and protection. Second, multiple broadly neutralizing monoclonal antibodies to the V1/V2 domain (e. g. PG9) have been isolated from rare infected individuals, termed elite neutralizers. Interestingly, the binding of both types of antibodies appears to depend on the same cluster of amino acids (positions 167–171) adjacent to the junction of the B and C strands of the four-stranded V1/V2 domain β-sheet structure. However, the broadly neutralizing mAb, PG9, additionally depends on mannose-5 glycans at positions 156 and 160 for binding. Because the gp120 vaccine immunogens used in previous HIV-1 vaccine trials were enriched for complex sialic acid-containing glycans, and lacked the high mannose structures required for the binding of PG9-like mAbs, we wondered if these immunogens could be improved by limiting glycosylation to mannose-5 glycans. Here, the authors describe the PG9 binding activity of monomeric gp120s from multiple strains of HIV-1 produced with mannose-5 glycans. They also describe the properties of glycopeptide scaffolds from the V1/V2 domain also

expressed with mannose-5 glycans. The V1/V2 scaffold from the A244 isolate was able to bind the PG9, CH01, and CH03 mAbs with high affinity provided that the proper glycans were present. The authors further show that immunization with A244 V1/V2 fragments alone, or in a prime/boost regimen with gp120, enhanced the antibody response to sequences in the V1/V2 domain associated with protection in the RV144 trial.

Obesity Is Significantly Associated With Cardiovascular Disease Risk Factors In 2- To 9-Year-Olds Messiah SE, Vidot DC, Gurnurkar S, Alhezayen R, Natale RA, Arheart KL. J Clin Hypertens (Greenwich). 2014 Oct; [Epub ahead of print].
The objective of this analysis was to estimate the prevalence of cardiovascular disease risk factors in ethnically diverse young children. A retrospective medical chart review identified overweight/ obese 2- to 9-year-old children (N=147) from a local pediatric clinic who were matched (for age, sex, and ethnicity) with normal weight patients from the 2005-2010 National Health and Nutrition Examination Survey (N=294). Comparisons of mean systolic blood pressure and diastolic blood pressure, total, and high-density lipoprotein (HDL) cholesterol were conducted. Results showed that compared with the population-based normal-weight sample, the local overweight/obese sample was significantly more likely to have diastolic prehypertension (15% vs 75%, P<. 0001), systolic prehypertension (10% vs 43%, P<. 0001), and the lowest quintile of HDL cholesterol (19% vs 34%, P=. 003). At this young age, excess weight is significantly associated with cardiovascular disease risk factors. These results suggest that overweight/obese children in this age group should be monitored closely to prevent potential chronic disease risk.

Costs Of Telaprevir-Based Triple Therapy For Hepatitis C: $189,000 Per Sustained Virological Response Bichoupan K, Martel-Laferriere V, Sachs D, Ng M, Schonfeld EA, Pappas A, Crismale J, Stivala A, Khaitova V, Gardenier D, Linderman M, Perumalswami PV, Schiano TD, Odin JA, Liu L, Moskowitz AJ, Dieterich DT, Branch AD. Hepatology. 2014 Oct; 60(4):1187-1195.
In registration trials, triple therapy with telaprevir (TVR), pegylated interferon (Peg-IFN), and ribavirin (RBV) achieved sustained virological response (SVR) rates between 64% and 75%, but the clinical effectiveness and economic burdens of this treatment in real-world practice remain to be determined. Records of 147 patients who initiated TVR-based triple therapy at the Mount Sinai Medical Center (May-December 2011) were reviewed. Direct medical costs for pretreatment, on-treatment, and posttreatment care were calculated using data from Medicare reimbursement databases, RED Book, and the Healthcare Cost and Utilization Project database. Costs are presented in 2012 U. S. dollars. SVR (undetectable hepatitis C virus [HCV] RNA 24 weeks after the end of treatment) was determined on an intention-to-treat basis. Cost per SVR was calculated by dividing the median cost by the SVR rate. Median age of the 147 patients was 56 years (interquartile range [IQR]=51-61), 68% were male, 19% were black, 11% had human immunodeficiency virus/HCV coinfection, 36% had advanced fibrosis/cirrhosis (FIB-4 scores ≥3.25), and 44% achieved an SVR. The total cost of care was $11.56 million. Median cost of care was $83,721 per patient (IQR=$66,652-$98,102). The median cost per SVR was $189,338 (IQR=$150,735-$221,860). Total costs were TVR (61%), IFN (24%), RBV (4%), adverse event management (8%), professional fees (2%), and laboratory tests (1%). TVR and Peg-IFN accounted for 85% of costs. Pharmaceutical prices and the low (44%) SVR rate, in this real-world study, were major contributors to the high cost per SVR.

High Mobility Group Box-1 (Hmgb1) Participates In The Pathogenesis Of Alcoholic Liver Disease (ALD) Ge X, Antoine DJ, Lu Y, Arriazu E, Leung TM, Klepper AL, Branch AD, Fiel MI, Nieto N. J Biol Chem. 2014 Ahug; 289(33):22672-22691.

Growing clinical and experimental evidence suggests that sterile inflammation contributes to alcoholic liver disease (ALD). High mobility group box-1 (HMGB1) is highly induced during liver injury; however, a link between this alarmin and ALD has not been established. Thus, the aim of this work was to determine whether HMGB1 contributes to the pathogenesis of ALD. Liver biopsies from patients with ALD showed a robust increase in HMGB1 expression and translocation, which correlated with disease stage, compared with healthy explants. Similar findings were observed in chronic ethanol-fed wild-type (WT) mice. Using primary cell culture, the authors validated the ability of hepatocytes from ethanol-fed mice to secrete a large amount of HMGB1. Secretion was time- and dose-dependent and responsive to prooxidants and antioxidants. Selective ablation of Hmgb1 in hepatocytes protected mice from alcohol-induced liver injury due to increased carnitine palmitoyltransferase-1, phosphorylated 5'AMP-activated protein kinase-α, and phosphorylated peroxisome proliferator-activated receptor-α expression along with elevated LDL plus VLDL export. Native and post-translationally modified HMGB1 were detected in humans and mice with ALD. In liver and serum from control mice and in serum from healthy volunteers, the lysine residues within the peptides containing nuclear localization signals (NLSs) 1 and 2 were non-acetylated, and all cysteine residues were reduced. However, in livers from ethanol-fed mice, in addition to all thiol/non-acetylated isoforms of HMGB1, the authors observed acetylated NLS1 and NLS2, a unique phosphorylation site in serine 35, and an increase in oxidation of HMGB1 to the disulfide isoform. In serum from ethanol-fed mice and from patients with ALD, there was disulfide-bonded hyperacetylated HMGB1, disulfide-bonded non-acetylated HMGB1, and HMGB1 phosphorylated in serine 35. Hepatocytes appeared to be a major source of these HMGB1 isoforms. Thus, hepatocyte HMGB1 participates in the pathogenesis of ALD and undergoes post-translational modifications (PTMs) that could condition its toxic effects.

SERVICES RESEARCH

Buprenorphine Treatment for Hospitalized, Opioid-dependent Patients: A Randomized Clinical Trial Liebschutz JM, Crooks D, Herman D, Anderson B, Tsui J, Meshesha LZ, Dossabhoy S, Stein M. JAMA Intern Med. 2014; 174(8): 1369-1376.
Buprenorphine opioid agonist treatment (OAT) has established efficacy for treating opioid dependency among persons seeking addiction treatment. However, effectiveness for out-of-treatment, hospitalized patients is not known. To determine whether buprenorphine administration during medical hospitalization and linkage to office-based buprenorphine OAT after discharge increase entry into office-based OAT, increase sustained engagement in OAT, and decrease illicit opioid use at 6 months after hospitalization. From August 1, 2009, through October 31, 2012, a total of 663 hospitalized, opioid-dependent patients in a general medical hospital were identified. Of these, 369 did not meet eligibility criteria. A total of 145 eligible patients consented to participation in the randomized clinical trial. Of these, 139 completed the baseline interview and were assigned to the detoxification (n=67) or linkage (n=72) group. Five-day buprenorphine detoxification protocol or buprenorphine induction, intra-hospital dose stabilization, and post-discharge transition to maintenance buprenorphine OAT affiliated with the hospital's primary care clinic (linkage).Entry and sustained engagement with buprenorphine OAT at 1, 3, and 6 months (medical record verified) and prior 30-day use of illicit opioids (self-report).During follow-up, linkage participants were more likely to enter buprenorphine OAT than those in the detoxification group (52 [72.2%] vs 8 [11.9%], P<.001). At 6 months, 12 linkage participants (16.7%) and 2 detoxification participants (3.0%) were receiving buprenorphine OAT (P=.007). Compared with those in the detoxification group, participants randomized to the linkage group reported less illicit opioid use in the 30 days before the 6-month interview (incidence rate ratio, 0.60; 95% CI, 0.46-0.73; P<.01) in an intent-to-treat analysis. Compared with an inpatient detoxification protocol, initiation of and linkage to buprenorphine treatment is an effective means for engaging medically hospitalized patients who are not seeking addiction treatment and reduces illicit opioid use 6 months after hospitalization. However, maintaining engagement in treatment remains a challenge.clinicaltrials.gov Identifier: NCT00987961.

Cost-effectiveness of Rapid HCV Testing and Simultaneous Rapid HCV and HIV Testing in Substance Abuse Treatment Programs Schackman BR, Leff JA, Barter DM, DiLorenzo MA, Feaster DJ, Metsch LR, Freedberg KA, Linas BP. Addiction. 2014.
The objective of this study was to evaluate the cost-effectiveness of rapid hepatitis C virus (HCV) and simultaneous HCV/HIV antibody testing in substance abuse treatment programs. The authors used a decision analytic model to compare the cost-effectiveness of no HCV testing referral or offer, off-site HCV testing referral, on-site rapid HCV testing offer, and on-site rapid HCV and HIV testing offer. Base case inputs included 11% undetected chronic HCV, 0.4% undetected HIV, 35% HCV co-infection among HIV-infected, 53% linked to HCV care after testing antibody positive, and 67% linked to HIV care. Disease outcomes were estimated from established computer simulation models of HCV (HEP-CE) and HIV (CEPAC). Data on test acceptance and costs were from a national randomized trial of HIV testing strategies conducted at 12 substance abuse treatment programs in the USA. Lifetime costs (2011 US dollars) and quality-adjusted life years (QALYs) discounted at 3% annually; incremental cost-effectiveness ratios (ICERs). On-site rapid HCV testing had an ICER of $18,300/QALY compared with no testing, and was more efficient than (dominated) off-site HCV testing referral. On-site rapid HCV and HIV testing had an ICER of $64,500/QALY compared with on-site rapid HCV testing alone. In one and two-way sensitivity analyses, the ICER of on-site rapid HCV and HIV testing remained <$100,000/QALY, except when

undetected HIV prevalence was <0.1% or when we assumed frequent HIV testing elsewhere. The ICER remained <$100,000/QALY in approximately 90% of probabilistic sensitivity analyses. On-site rapid hepatitis C virus and HIV testing in substance abuse treatment programs is cost-effective at a <$100,000/ quality-adjusted life years threshold.

Brief Intervention for Problem Drug Use In Safety-net Primary Care Settings: A Randomized Clinical Trial Roy-Byrne P, Bumgardner K, Krupski A, Dunn C, Ries R, Donovan D, West II, Maynard C, Atkins DC, Graves MC, Joesch JM, Zarkin GA. JAMA. 2014; 312(5): 492-501.
Although brief intervention is effective for reducing problem alcohol use, few data exist on its effectiveness for reducing problem drug use, a common issue in disadvantaged populations seeking care in safety-net medical settings (hospitals and community health clinics serving low-income patients with limited or no insurance). The objective of this study was to determine whether brief intervention improves drug use outcomes compared with enhanced care as usual. A randomized clinical trial with blinded assessments at baseline and at 3, 6, 9, and 12 months conducted in 7 safety-net primary care clinics in Washington State. Of 1621 eligible patients reporting any problem drug use in the past 90 days, 868 consented and were randomized between April 2009 and September 2012. Follow-up participation was more than 87% at all points. Participants received a single brief intervention using motivational interviewing, a handout and list of substance abuse resources, and an attempted 10-minute telephone booster within 2 weeks (n=435) or enhanced care as usual, which included a handout and list of substance abuse resources (n=433).The primary outcomes were self-reported days of problem drug use in the past 30 days and Addiction Severity Index-Lite (ASI) Drug Use composite score. Secondary outcomes were admission to substance abuse treatment; ASI composite scores for medical, psychiatric, social, and legal domains; emergency department and inpatient hospital admissions, arrests, mortality, and human immunodeficiency virus risk behavior. Mean days used of the most common problem drug at baseline were 14.40 (SD, 11.29) (brief intervention) and 13.25 (SD, 10.69) (enhanced care as usual); at 3 months post-intervention, means were 11.87 (SD, 12.13) (brief intervention) and 9.84 (SD, 10.64) (enhanced care as usual) and not significantly different (difference in differences, *= 0.89 [95% CI, -0.49 to 2.26]). Mean ASI Drug Use composite score at baseline was 0.11 (SD, 0.10) (brief intervention) and 0.11 (SD, 0.10) (enhanced care as usual) and at 3 months was 0.10 (SD, 0.09) (brief intervention) and 0.09 (SD, 0.09) (enhanced care as usual) and not significantly different (difference in differences, *= 0.008 [95% CI, -0.006 to 0.021]). During the 12 months following intervention, no significant treatment differences were found for either variable. No significant differences were found for secondary outcomes. A one-time brief intervention with attempted telephone booster had no effect on drug use in patients seen in safety-net primary care settings. This finding suggests a need for caution in promoting widespread adoption of this intervention for drug use in primary care.clinicaltrials.gov Identifier: NCT00877331.

Screening and Brief Intervention for Drug Use in Primary Care: The ASPIRE Randomized Clinical Trial Saitz R, Palfai TPA, Cheng DM, Alford DP, Bernstein JA, Lloyd-Travaglini CA, Meli SM, Chaisson CE, Samet JH. JAMA. 2014; 312(5): 502-513.
The United States has invested substantially in screening and brief intervention for illicit drug use and prescription drug misuse, based in part on evidence of efficacy for unhealthy alcohol use. However, it is not a recommended universal preventive service in primary care because of lack of evidence of efficacy. To test the efficacy of 2 brief counseling interventions for unhealthy drug use (any illicit drug use or prescription drug misuse)-a brief negotiated interview (BNI) and an adaptation of motivational interviewing (MOTIV)-compared with no brief intervention. This 3-group randomized trial took place at an urban hospital-based primary care internal medicine

practice; 528 adult primary care patients with drug use (Alcohol, Smoking, and Substance Involvement Screening Test [ASSIST] substance-specific scores of 4) were identified by screening between June 2009 and January 2012 in Boston, Massachusetts. Two interventions were tested: the BNI is a 10- to 15-minute structured interview conducted by health educators; the MOTIV is a 30- to 45-minute intervention based on motivational interviewing with a 20- to 30-minute booster conducted by master's-level counselors. All study participants received a written list of substance use disorder treatment and mutual help resources. Primary outcome was number of days of use in the past 30 days of the self-identified main drug as determined by a validated calendar method at 6 months. Secondary outcomes included other self-reported measures of drug use, drug use according to hair testing, ASSIST scores (severity), drug use consequences, unsafe sex, mutual help meeting attendance, and health care utilization. At baseline, 63% of participants reported their main drug was marijuana, 19% cocaine, and 17% opioids. At 6 months, 98% completed follow-up. Mean adjusted number of days using the main drug at 6 months was 12 for no brief intervention vs 11 for the BNI group (incidence rate ratio [IRR], 0.97; 95% CI, 0.77-1.22) and 12 for the MOTIV group (IRR, 1.05; 95% CI, 0.84-1.32; P=.81 for both comparisons vs no brief intervention). There were also no significant effects of BNI or MOTIV on any other outcome or in analyses stratified by main drug or drug use severity. Brief intervention did not have efficacy for decreasing unhealthy drug use in primary care patients identified by screening. These results do not support widespread implementation of illicit drug use and prescription drug misuse screening and brief intervention.clinicaltrials.gov Identifier: NCT00876941.

A Pilot Study to Examine the Feasibility and Potential Effectiveness of Using Smartphones to Provide Recovery Support for Adolescents Dennis ML, Scott CK, Funk RR, Nicholson L. Subst Abus. 2014.

Smartphone applications can potentially provide recovery monitoring and support in real-time, real-life contexts. Study aims included determining feasibility of: a) Adolescents completing ecological momentary assessments (EMA) and utilizing phone-based ecological momentary interventions (EMI); and b) Using EMA and EMI data to predict substance use in the subsequent week. Twenty-nine adolescents were recruited at discharge from residential treatment, regardless of their discharge status or length of stay. During the 6-week pilot, youth were prompted to complete an EMA at 6 random times per day and were provided access to a suite of recovery support EMI. Youth completed 87% of the 5,580 EMAs. Based on use in the next 7 days, EMA observations were classified into 3 risk groups: "Current Use" in the past 30 minutes (3% of observations), "Unrecognized Risk" (42%), or "Recognized Risk" (55%). All youth had observations in 2 or more risk groups and 38%, in all three. Youth accessed an EMI on-average 162 times each week. Participants were: 31% female, 48% African American, 21% Caucasian, 7% Hispanic, 24% Mixed/Other, average age 16.6 years. During the 90 days prior to entering treatment, youth reported using alcohol (38%), marijuana (41%), and other drugs (7%). When compared to the "Recognized Risk" group's use in the following week (31%), both the "Unrecognized Risk" (50%, OR = 2.08) and "Current Use" (96%, OR = 50.30) groups reported significantly higher rates of use in the next week. When an EMI was accessed 2 or more times within the hour following an EMA, the rate of using during the next week was significantly lower than when EMIs were not accessed (32% vs. 43%, OR = 0.62). Conclusions: Results demonstrate the feasibility of using smartphones for recovery monitoring and support with adolescents, with potential to reduce use.

The Impact of Prior Authorization on Buprenorphine Dose, Relapse Rates, and Cost for Massachusetts Medicaid Beneficiaries with Opioid Dependence Clark RE, Baxter JD, Barton BA, Aweh G, O'Connell E, Fisher WH. HSR: Health Services Research 49:6 (December 2014): 1964-1979.
The objective of this study was to assess the impact of a 2008 dose-based prior authorization policy for Massachusetts Medicaid beneficiaries using buprenorphine + naloxone for opioid addiction treatment. Doses higher than 16 mg required progressively more frequent authorizations. Data sources were Mediciaid claims for 2007 and 2008 linked with Department of Public Health (DPH) service records. The authors conducted time series for all buprenorphine users and a longitudinal cohort analysis of 2,049 individuals who began buprenorphine treatment in 2007. Outcome measures included use of relapse-related services, health care expenditures per person, and buprenorphine expenditures. Data Collection/Extraction The authors used ICD-9 codes and National Drug Codes to identify individuals with opioid dependence who filled prescriptions for buprenorphine. Medicaid and DPH data were linked with individual identifiers. Individuals using doses >24 mg decreased from 16.5 to 4.1 percent. Relapses increased temporarily for some users but returned to previous levels within 3 months. Buprenorphine expenditures decreased but total expenditures did not change significantly. Prior authorization policies strategically targeted by dose level appear to successfully reduce use of higher than recommended buprenorphine doses. Savings from these policies are modest and may be accompanied by brief increases in relapse rates. Lower doses may decrease diversion of buprenorphine.

Combination HIV Prevention Interventions: The Potential of Integrated Behavioral and Biomedical Approaches Brown JL, Sales JM, DiClemente RJ. Curr HIV/AIDS Rep. 2014.
Combination HIV prevention interventions that integrate efficacious behavioral and biomedical strategies offer the potential to reduce new HIV infections. The authors overview the efficacy data for three biomedical HIV prevention approaches, namely microbicides, pre-exposure prophylaxis (PrEP), and HIV vaccination; review factors associated with differential acceptability and uptake of these methods; and suggest strategies to optimize the effectiveness and dissemination of combination HIV prevention approaches. A narrative review was conducted highlighting key efficacy data for microbicides, PrEP, and an HIV vaccination and summarizing acceptability data for each of the three biomedical HIV prevention approaches. Recommendations for the integration and dissemination of combined behavioral and biomedical HIV prevention approaches are provided. To date, microbicides and an HIV vaccination have demonstrated limited efficacy for the prevention of HIV. However, PrEP has demonstrated efficacy in reducing HIV incident infections. A diverse array of factors influences both hypothetical willingness and actual usage of each biomedical prevention method. Strategies to effectively integrate and evaluate combination HIV prevention interventions are urgently needed.

The PROMIS Smoking Initiative: Initial Validity Evidence for Six New Smoking Item Banks Edelen MO, Stucky BD, Hansen M, Tucker JS, Shadel WG, Cai L. Nicotine Tob Res. 2014; 16 Suppl 3: S250-260.
The Patient-Reported Outcomes Measurement Information System (PROMIS) Smoking Initiative has developed 6 item banks for assessing smoking behaviors and bio-psychosocial correlates of smoking among daily and nondaily adult cigarette smokers. This paper presents descriptive information and preliminary validity evidence for the item banks (Nicotine Dependence, Coping Expectancies, Emotional and Sensory Expectancies, Health Expectancies, Psychosocial Expectancies, and Social Motivations). Using data from a large sample of daily (N = 4,201) and nondaily (N = 1,183) smokers, the authors generated mean daily and nondaily smoking bank scores

according to select demographic groups. They also examined correlations among the 6 banks and examined the associations of bank scores with smoking behavior items (e.g., quantity of smoking, interest in quitting) and select health-related quality of life measures (i.e., physical functioning, anxiety, alcohol consumption). Correlations among the 6 banks are moderate (daily mean r = .48, range = .04-.80; nondaily mean r = .47, range = .12-.75). The pattern of associations between bank scores and other measures provides validity evidence for the bank domains (e.g., nicotine dependence is most strongly associated with smoking quantity and time to first cigarette of the day; health and psychosocial expectancies are most related to quitting regency and interest; coping expectancies are strongly associated with anxiety). These analyses provide useful descriptive information about the 6 smoking item banks as well as preliminary evidence for their validity. Independent sample data are currently being collected to replicate these findings, to establish test-retest reliability, and to develop crosswalks to existing smoking measures (e.g., nicotine dependence to Fagerstrom Test for Nicotine Dependence). Future research will also evaluate the bank scores' sensitivity to change.

Sustained, New, Never, and Discontinued Tobacco Cessation Services Adopters Eby LT, Laschober TC, Muilenburg JL. J Subst Abuse Treat. 2014.
This study examined longitudinal adoption patterns of tobacco cessation (TC) counseling and TC pharmacotherapy in substance use disorder treatment programs and baseline predictors (program characteristics and program culture) of these patterns 12-months later. Telephone survey data were collected in 2010 from 685 randomly sampled program administrators working in geographically representative treatment programs across the U.S. Regarding TC counseling, about 41% of programs never adopt, 33% sustain, and 27% change adoption patterns. Concerning TC pharmacotherapy, about 62% of programs never adopt, 19% sustain, and 18% change adoption patterns. The three most consistent predictors of counseling adoption patterns are TC reimbursement, TC financial resource availability, and smoking culture. For TC pharmacotherapy adoption patterns, the most consistent predictors include profit status, TC reimbursement, and level of care, TC financial resource availability, and smoking culture. Findings provide insights into program characteristics and program culture as both potential barriers and facilitators of longitudinal TCS adoption.

Bias Associated with Using the Estimated Propensity Score as a Regression Covariate
Hade EM, Lu B. Stat Med. 2014; 33(1): 74-87.
The use of propensity score methods to adjust for selection bias in observational studies has become increasingly popular in public health and medical research. A substantial portion of studies using propensity score adjustment treat the propensity score as a conventional regression predictor. Through a Monte Carlo simulation study, the authors investigated the bias associated with treatment effect estimation when the propensity score is used as a covariate in nonlinear regression models, such as logistic regression and Cox proportional hazards models. They show that the bias exists even in a linear regression model when the estimated propensity score is used and derive the explicit form of the bias. They also conduct an extensive simulation study to compare the performance of such covariate adjustment with propensity score stratification, propensity score matching, inverse probability of treatment weighted method, and nonparametric functional estimation using splines. The simulation scenarios are designed to reflect real data analysis practice. Instead of specifying a known parametric propensity score model, the authors generate the data by considering various degrees of overlap of the covariate distributions between treated and control groups. Propensity score matching excels when the treated group is contained within a larger control pool, while the model-based adjustment may have an edge when treated and control groups

do not have too much overlap. Overall, adjusting for the propensity score through stratification or matching followed by regression or using splines, appears to be a good practical strategy.

Communication Technology Use and mHealth Acceptance among HIV-infected Men Who Have Sex With Men in Peru: Implications For HIV Prevention and Treatment
Krishnan A, Ferro EG, Weikum D, Vagenas P, Lama JR, Sanchez J, Altice FL. AIDS Care. 2014; 1-10.
The HIV epidemic in Peru is concentrated among men who have sex with men (MSM). Given that MSM have been documented as early adopters of emerging technology, the authors examined communication technology access and utilization, and mobile health (mHealth) acceptance among Peruvian MSM and transgender women (TGW) in order to gauge opportunities for mHealth-enabled HIV interventions. A convenience sample of 359 HIV-infected MSM and TGW recruited from three sites in Lima, Peru completed standardized assessments of alcohol use disorders (AUDs), risky sexual behavior, and antiretroviral therapy (ART) adherence along with self-constructed measures of communication technology access and utilization, and mHealth acceptance. Most participants (86%) had daily access to any cell phone, including smartphones (30%). The most frequent communication activities were receiving and making calls, and receiving and sending text messages using cell phones. On a 5-point Likert scale, participants expressed interest in using mHealth for medication reminders (M = 3.21, SD = 1.32) and engaging in anonymous online interactions with health professionals to discuss HIV-related issues (M = 3.56, SD = 1.33). Importantly, no significant differences were found in communication technology use and mHealth acceptance among participants with AUDs, depression, and suboptimal ART adherence, all of which are associated with poor HIV treatment outcomes. Findings show support for implementing mHealth-based intervention strategies using cell phones to assess and reduce HIV-risk behaviors among HIV-infected MSM and TGW.

Perceived Neighborhood Safety, Recovery Capital, and Successful Outcomes among Mothers 10 Years after Substance Abuse Treatment Evans E, Li L, Buoncristiani S, Hser, Y-I. Subst Use Misuse. 2014; 49(11): 1491-1503.
This study examines perceived neighborhood characteristics associated with successful outcome among mothers 10 years after being treated for substance use disorders. Data were obtained from 713 mothers first studied at admission to drug treatment in California in 2000-2002 and followed up in 2009-2011. At follow-up, 53.6% of mothers had a successful outcome (i.e., no use of illicit drugs and not involved with the criminal justice system). Perceived neighborhood safety almost doubled the odds of success. Perceived neighborhood safety interacted with social involvement, decreasing the odds of success among mothers who reported more versus less neighborhood social involvement. Perceived neighborhood climate is associated with long-term outcomes among mothers with substance use disorders independent of individual-level characteristics, underscoring the need for further efforts to understand its interaction with recovery capital in ways that promote and impede health.

Alcohol Use Disorders Negatively Influence Antiretroviral Medication Adherence among Men Who Have Sex With Men in Peru Ferro EG, Weikum D, Vagenas P, Copenhaver MM, Gonzales P, Peinado J, Cabello R, Lama JR, Sanchez J, Altice FL. AIDS Care. 2014; 1-12.
As international guidelines increase access to antiretroviral therapy (ART) globally, ART adherence becomes increasingly important to achieve HIV treatment as prevention (TasP) goals. In the concentrated HIV epidemic among men who have sex with men (MSM) and transgendered women (TGW) in Lima, Peru, the independent correlates of ART non-adherence were examined to inform

treatment intervention priorities. Cross sectional survey of HIV-infected MSM and TGW who are engaged in clinical care in Lima, Peru. From June to August 2012, 302 HIV-infected Peruvian MSM/TGW from three clinical care sites were recruited using convenience sampling to participate in a cross-sectional computer-assisted adherence survey. Several standardized screening measures associated with ART non-adherence were examined in order to determine the independent correlates of optimal (≥90%) and perfect (100%) adherence, which were assessed using logistic regression. Of the 302 participants recruited, 263 (87.1%) were prescribed ART. Among those prescribed ART, 229 (87.1%) reported optimal and 146 (55.5%) reported perfect adherence. The prevalence of alcohol use disorders (AUD; 43.2%), alcohol dependence (5.3%), recent drug use (6.0%), and depression (44.5%) was high, and most participants had some evidence of neurocognitive impairment. Meeting criteria for having an AUD and depression were collinear ($p < 0.001$). On multivariate analysis, having an AUD was inversely related and the only independent correlate of optimal (AOR = 0.427; 95% CI = 0.187-0.976) and perfect (AOR = 0.552; 95% CI = 0.327-0.930) ART adherence. AUDs are highly prevalent among Peruvian HIV-infected MSM and contribute significantly to ART non-adherence. These findings support the need for screening and treating underlying AUDs. In order to meet HIV TasP goals, evidence-based strategies targeting AUDs are likely to directly improve ART adherence and indirectly improve overall individual health, HIV treatment engagement, and reduce transmission to sexual partners among this vulnerable and disproportionally affected population.

Examining the Associations of Racism, Sexism, and Stressful Life Events on Psychological Distress among African-American Women Stevens-Watkins D, Perry B, Pullen E, Jewell J, Oser CB. Cultur Divers Ethnic Minor Psychol. 2014; 20(4): 561-569.
African-American women may be susceptible to stressful events and adverse health outcomes as a result of their distinct social location at the intersection of gender and race. Here, racism and sexism are examined concurrently using survey data from 204 African-American women residing in a southeastern U.S. urban city. Associations among racism, sexism, and stressful events across social roles and contexts (i.e., social network loss, motherhood and childbirth, employment and finances, personal illness and injury, and victimization) are investigated. Then, the relationships among these stressors on psychological distress are compared, and a moderation model is explored. Findings suggest that racism and sexism are a significant source of stress in the lives of African-American women and are correlated with one another and with other stressful events. Implications for future research and clinical considerations are discussed.

A 'missing Not At Random' (MNAR) and 'missing At Random' (MAR) Growth Model Comparison With a Buprenorphine/naloxone Clinical Trial McPherson S, Barbosa-Leiker C, Mamey MR, McDonell M, Enders CK, Roll J. Addiction. 2014.
The aim of this study was to compare three missing data strategies: (i) the latent growth model that assumes the data are missing at random (MAR) model; (ii) the Diggle-Kenward missing not at random (MNAR) model, where dropout is a function of previous/concurrent urinalysis (UA) submissions; and (iii) the Wu-Carroll MNAR model where dropout is a function of the growth factors. Secondary data analysis of a National Drug Abuse Treatment Clinical Trials Network trial that examined a 7-day versus 28-day taper (i.e. stepwise decrease in buprenorphine/naloxone) on the likelihood of submitting an opioid-positive UA during treatment.11 out-patient treatment settings in 10 US cities. A total of 516 opioid-dependent participants. Opioid UAs provided across the 4-week treatment period. The MAR model showed a significant effect ($B=-0.45$, $P<0.05$) of trial arm on the opioid-positive UA slope (i.e. 28-day taper participants were less likely to submit a positive UA over time) with a small effect size ($d=0.20$). The MNAR Diggle-Kenward model

demonstrated a significant (B=-0.64, P<0.01) effect of trial arm on the slope with a large effect size (d=0.82). The MNAR Wu-Carroll model showed a significant (B=-0.41, P<0.05) effect of trial arm on the UA slope that was relatively small (d=0.31). This performance comparison of three missing data strategies (latent growth model, Diggle-Kenward selection model, Wu-Carrol selection model) on sample data indicates a need for increased use of sensitivity analyses in clinical trial research. Given the potential sensitivity of the trial arm effect to missing data assumptions, it is critical for researchers to consider whether the assumptions associated with each model are defensible.

HIV Risk Behaviors in The U.S. Transgender Population: Prevalence and Predictors in a Large Internet Sample Feldman J, Romine RS, Bockting WO. J Homosex. 2014; 61(11): 1558-1588.
To study the influence of gender on HIV risk, a sample of the U.S. transgender population (N = 1,229) was recruited via the Internet. HIV risk and prevalence were lower than reported in prior studies of localized, urban samples but higher than the overall U.S. population. Findings suggest that gender nonconformity alone does not itself result in markedly higher HIV risk. Sex with non-transgender men emerged as the strongest independent predictor of unsafe sex for both male-to-female (MtF) and female-to-male (FtM) participants. These sexual relationships constitute a process that may either affirm or problematize gender identity and sexual orientation, with different emphases for MtFs and FtMs, respectively.

Treatment Outcomes for Prescription Drug Misusers: The Negative Effect of Geographic Discordance Oser CB, Harp KLH. J Subst Abuse Treat. 2014.
This is the first known study to examine geographic discordance (traveling from one's home residence to a county with a different socio-cultural context to receive substance abuse treatment) as a predictor of clinical and social functioning treatment outcomes (i.e., relapse, self-help attendance, anxiety, and incarceration) among a sample of prescription drug misusers. Treatment entry and 12-month follow-up client-level survey data were collected from 187 clients who misused prescription drugs, and center-level survey data were collected from the supervisors at treatment centers attended by the clients. Multivariate models reveal that geographic discordance significantly increased the odds that prescription drug misusers would report relapse to prescription opioid misuse, anxiety, and any incarceration at follow-up. Moreover, geographically discordant clients were significantly less likely to have attended a self-help group, net of the effect of other individual- and center-level factors. Implications for clinical practice and substance abuse treatment policy are provided.

Understanding Counselors' Implementation of Tobacco Cessation Services with Patients Eby LT, Laschober TC, Muilenburg JL. J Subst Abuse Treat. 2014; 47(5): 314-320.
This study aimed to understand substance use disorder counselors' implementation of evidence-based tobacco cessation services (TCS) with their patients who smoke. Drawing from an established adoption of innovations framework, we investigated the association between counselors' perceptions of the availability of TCS (both pharmacotherapies and behavioral treatments) in their treatment program and the implementation of TCS (both pharmacotherapies and behavioral treatments) with their patients who smoke and whether this association is moderated by the strength of an organization's climate for implementation and the fit of the innovation with users' values. Data were collected in 2010 from 682 counselors working in 239 treatment programs across the U.S. that offer evidence-based TCS. Mixed-effect models showed that perceived availability of TCS was related with greater TCS implementation. This relationship was moderated by several indicators of climate for implementation but not by the fit of the innovation with users' values.

HIV Testing and Engagement in Care among Highly Vulnerable Female Sex Workers: Implications for Treatment as Prevention Models Surratt HL, O'Grady CL, Kurtz SP, Buttram ME, Levi-Minzi MA. J Health Care Poor Underserved. 2014; 25(3): 1360-1378.
Although emerging Treatment as Prevention models can be effective in reducing HIV incidence among high-risk populations, many HIV infected individuals remain undiagnosed or fail to engage in HIV care. This study examined the factors associated with HIV testing and care among a population of substance using female sex workers. Recent HIV testing was associated with higher education level, having a regular health care provider or clinic, recent crack use, and higher sexual risk behaviors; HIV treatment utilization was associated with higher levels of social support, having a regular health care provider or clinic, housing stability and insurance coverage. Qualitative data revealed HIV-related stigma, denial, social isolation, and substance use as barriers to HIV testing and treatment; social support and accessibility of services were key enablers .Improving HIV testing and linkage to treatment among female sex workers will require structural initiatives to reduce stigma and increase service seeking support.

Latent Tuberculosis Infection Screening in Foreign-born Populations: A Successful Mobile Clinic Outreach Model Morano JP, Zelenev A, Walton MR, Bruce RD, Altice FL. Am J Public Health. 2014; 104(8): 1508-1515.
The authors evaluated the efficacy of a mobile medical clinic (MMC) screening program for detecting latent tuberculosis infection (LTBI) and active tuberculosis. A LTBI screening program in a MMC in New Haven, Connecticut, used medical surveys to examine risk factors and tuberculin skin test (TST) screening eligibility. They assessed clinically relevant correlates of total (prevalent; n = 4650) and newly diagnosed (incident; n = 4159) LTBI from 2003 to 2011. Among 8322 individuals, 4159 (55.6%) met TST screening eligibility criteria, of which 1325 (31.9%) had TST assessed. Similar to LTBI prevalence (16.8%; 779 of 4650), newly diagnosed LTBI (25.6%; 339 of 1325) was independently correlated with being foreign-born (adjusted odds ratio [AOR] = 8.49; 95% confidence interval [CI] = 5.54, 13.02), Hispanic (AOR = 3.12; 95% CI = 1.88, 5.20), Black (AOR = 2.16; 95% CI = 1.31, 3.55), employed (AOR = 1.61; 95% CI = 1.14, 2.28), and of increased age (AOR = 1.04; 95% CI = 1.02, 1.05). Unstable housing (AOR = 4.95; 95% CI = 3.43, 7.14) and marijuana use (AOR =1.57; 95% CI=1.05, 2.37) were significantly correlated with incident LTBI, and being male, heroin use, interpersonal violence, employment, not having health insurance, and not completing high school were significantly correlated with prevalent LTBI. Screening for TST in MMCs successfully identifies high-risk foreign-born, Hispanic, working, and uninsured populations and innovatively identifies LTBI in urban settings.

Sexual Risk Behaviors among Adolescents in Port-au-Prince, Haiti Carver JW, Devieux JG, Gaston SC, Altice FL, Niccolai LM. AIDS Behav. 2014; 18(8): 1595-1603.
Engagement in sexual activity among Haitian youth is increasing. The present cross-sectional study examined the independent correlates of sexual risk behaviors among 200 (108 male/92 female) 13-18 year-old adolescents in Port-au-Prince, Haiti using face-to-face interviews. The majority (60.0 %) had engaged in sexual intercourse. Multivariate modeling found males to be 3.52 times more likely to have had sex, 5.42 times more likely to report sexual debut before age 14, 9.75 times more likely to have >1 sexual partner, and 3.33 times more likely to not have used a condom during last sex. Adolescents living with parents, grandparents, aunts or uncles were less likely to report having unprotected sex compared with those without adult family members in the home (AOR range 0.26-0.51). The high prevalence of risky sex among males and the protective influence of stable family cohesiveness have important implications for HIV prevention efforts.

Predictors of Quit Attempts and Successful Quit Attempts among Individuals with Alcohol Use Disorders in a Nationally Representative Sample Chiappetta V, Garcia-Rodriguez O, Jin CJ, Secades-Villa R, Blanco C. Drug Alcohol Depend. 2014; 141: 138-144.
This study sought to identify predictors of attempting to quit and of successfully quitting alcohol abuse or dependence in the general population. Data were drawn from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Approximately 10% of individuals with alcohol abuse and 18% of those with dependence attempted to quit over the three year follow-up period. Of those who tried, 38% of individuals with abuse and 30% of those with dependence successfully quit. Among individuals with alcohol abuse or dependence, being single, younger than 40 years old, having low income, a co-occurring psychiatric disorder and greater number of dependence symptoms increased the likelihood of attempting to quit. Among individuals with alcohol abuse, male gender and low educational attainment further increased the odds of quit attempts. However, greater severity of alcohol use disorder, having a co-occurring drug use disorder and greater number of psychiatric disorders decreased the odds of success among individuals with alcohol abuse, while female gender, being married and older than 40 years old increased the odds of success. Among individuals with alcohol dependence, having nicotine dependence, greater number of psychiatric disorders and personality disorders decreased the odds of success. Predictors of attempts to quit are different and sometimes opposite from those leading to successful quitting probably indicating that some factors that increase motivation may decrease ability to quit. These findings may help in the development of more targeted and effective interventions for alcohol use disorders.

Positive Posttraumatic Stress Disorder Screens among First-time Medical Cannabis Patients: Prevalence and Association with Other Substance Use Bohnert KM, Perron BE, Ashrafioun L, Kleinberg F, Jannausch M, Ilgen MA. Addict Behav. 2014; 39(10): 1414-1417.
Twenty-one states and the District of Columbia have passed legislation allowing for the use of medical cannabis for those individuals with qualifying medical conditions, which include posttraumatic stress disorder (PTSD) for a growing number of states. Little information is available regarding PTSD among medical cannabis patients. This study seeks to provide initial data on this topic by examining the prevalence and correlates of positive PTSD screens among a sample of patients seeking medical cannabis certification for the first time (n=186). Twenty-three percent (42/186; 95% confidence interval [CI] =17%-29%) of the patients in the study sample screened positive for PTSD. Moreover, the group that screened positive for PTSD had higher percentages of lifetime prescription opioid, cocaine, prescription sedative, and street opioid use, as well as a higher percentage of recent prescription sedative use, than the group that screened negative for PTSD. These findings highlight the relatively common use of other substances among medical cannabis patients with significant PTSD symptoms, even when compared with other patients seeking medical cannabis for the first time. As a growing number of states include PTSD among the list of qualifying medical conditions for medical cannabis, additional research is needed to better characterize the longitudinal relationship between medical cannabis use and PTSD symptoms.

A Randomized Controlled Trial of Prison-initiated Buprenorphine: Prison Outcomes and Community Treatment Entry Gordon MS, Kinlock TW, Schwartz RP, Fitzgerald TT, O'Grady KE, Vocci F. J. Drug Alcohol Depend. 2014; 142: 33-40.
Buprenorphine is a promising treatment for heroin addiction. However, little is known regarding its provision to pre-release prisoners with heroin dependence histories who were not opioid-tolerant, the relative effectiveness of the post-release setting in which it is provided, and gender differences in treatment outcome in this population. This is the first randomized clinical trial of prison-initiated

buprenorphine provided to male and female inmates in the US who were previously heroin-dependent prior to incarceration. A total of 211 participants with 3-9 months remaining in prison were randomized to one of four conditions formed by crossing In-Prison Treatment Condition (received buprenorphine vs. counseling only) and Post-release Service Setting (at an opioid treatment center vs. a community health center). Outcome measures were: entered prison treatment; completed prison treatment; and entered community treatment 10 days post-release. There was a significant main effect (p=.006) for entering prison treatment favoring the In-Prison buprenorphine Treatment Condition (99.0% vs. 80.4%). Regarding completing prison treatment, the only significant effect was Gender, with women significantly (p<.001) more likely to complete than men (85.7% vs. 52.7%). There was a significant main effect (p=.012) for community treatment entry, favoring the In-Prison buprenorphine Treatment Condition (47.5% vs. 33.7%).Buprenorphine appears feasible and acceptable to prisoners who were not opioid-tolerant and can facilitate community treatment entry. However, concerns remain with in-prison treatment termination due to attempted diversion of medication.

Illicit Buprenorphine Use, Interest in and Access to Buprenorphine Treatment among Syringe Exchange Participants Fox AD, Chamberlain A, Sohler NL, Frost T, Cunningham CO. J Subst Abuse Treat. 2014.
Poor access to buprenorphine maintenance treatment (BMT) may contribute to illicit buprenorphine use. This study investigated illicit buprenorphine use and barriers to BMT among syringe exchange participants. Computer-based interviews conducted at a New York City harm reduction agency determined: prior buprenorphine use; barriers to BMT; and interest in BMT. Of 102 opioid users, 57 had used illicit buprenorphine and 32 had used prescribed buprenorphine. When illicit buprenorphine users were compared to non-users: barriers to BMT ("did not know where to get treatment") were more common (64 vs. 36%, p<0.01); mean levels of interest in BMT were greater (3.37ýý1.29 vs. 2.80ýý1.34, p=0.03); and more participants reported themselves likely to initiate treatment (82 vs. 50%, p<0.01). Illicit buprenorphine users were interested in BMT but did not know where to go for treatment. Addressing barriers to BMT could reduce illicit buprenorphine use.

Within-prison Drug Injection among HIV-infected Ukrainian Prisoners: Prevalence and Correlates of an Extremely High-risk Behavior Izenberg JM, Bachireddy C, Wickersham JA, Soule M, Kiriazova T, Dvoriak S, Altice FL. Int J Drug Policy. 2014; 25(5): 845-852.
In Ukraine, HIV-infection, injection drug use, and incarceration are syndemic; however, few services are available to incarcerated people who inject drugs (PWIDs). While data are limited internationally, within-prison drug injection (WP-DI) appears widespread and may pose significant challenges in countries like Ukraine, where PWIDs contribute heavily to HIV incidence. To date, WP-DI has not been specifically examined among HIV-infected prisoners, the only persons that can transmit HIV. A convenience sample of 97 HIV-infected adults recently released from prison within 1-12 months was recruited in two major Ukrainian cities. Post-release surveys inquired about WP-DI and injection equipment sharing, as well as current and prior drug use and injection, mental health, and access to within-prison treatment for HIV and other comorbidities. Logistic regression identified independent correlates of WP-DI.Complete data for WP-DI were available for 95 (97.9%) respondents. Overall, 54 (56.8%) reported WP-DI, among whom 40 (74.1%) shared injecting equipment with a mean of 4.4 (range 0-30) other injectors per needle/syringe. Independent correlates of WP-DI were recruitment in Kyiv (AOR 7.46, p=0.003), male gender (AOR 22.07, p=0.006), and active pre-incarceration opioid use (AOR 8.66, p=0.005).Among these recently released HIV-infected prisoners, WP-DI and injection equipment sharing were frequent and involved many injecting partners per needle/syringe. The overwhelming majority of respondents

reporting WP-DI used opioids both before and after incarceration, suggesting that implementation of evidence-based harm reduction practices, such as opioid substitution therapy and/or needle/syringe exchange programs within prison, is crucial to addressing continuing HIV transmission among PWIDs within prison settings. The positive correlation between Kyiv site and WP-DI suggests that additional structural interventions may be useful.

Scaling Up The Evaluation of Psychotherapy: Evaluating Motivational Interviewing Fidelity Via Statistical Text Classification Atkins DC, Steyvers M, Imel ZE, Smyth P. Implement Sci. 2014; 9: 49.

Behavioral interventions such as psychotherapy are leading, evidence-based practices for a variety of problems (e.g., substance abuse), but the evaluation of provider fidelity to behavioral interventions is limited by the need for human judgment. The current study evaluated the accuracy of statistical text classification in replicating human-based judgments of provider fidelity in one specific psychotherapy--motivational interviewing (MI). Participants (n=148) came from five previously conducted randomized trials and were either primary care patients at a safety-net hospital or university students. To be eligible for the original studies, participants met criteria for either problematic drug or alcohol use. All participants received a type of brief motivational interview, an evidence-based intervention for alcohol and substance use disorders. The Motivational Interviewing Skills Code is a standard measure of MI provider fidelity based on human ratings that was used to evaluate all therapy sessions. A text classification approach called a labeled topic model was used to learn associations between human-based fidelity ratings and MI session transcripts. It was then used to generate codes for new sessions. The primary comparison was the accuracy of model-based codes with human-based codes. Receiver operating characteristic (ROC) analyses of model-based codes showed reasonably strong sensitivity and specificity with those from human raters (range of area under ROC curve (AUC) scores: 0.62 - 0.81; average AUC: 0.72). Agreement with human raters was evaluated based on talk turns as well as code tallies for an entire session. Generated codes had higher reliability with human codes for session tallies and also varied strongly by individual code. To scale up the evaluation of behavioral interventions, technological solutions will be required. The current study demonstrated preliminary, encouraging findings regarding the utility of statistical text classification in bridging this methodological gap.

Substance Use Recovery Outcomes among A Cohort of Youth Participating In a Mobile-based Texting Aftercare Pilot Program Gonzales R, Ang A, Murphy DA, Glik DC, Anglin MD. J Subst Abuse Treat. 2014; 47(1): 20-26.

Project ESQYIR (Educating & Supporting Inquisitive Youth in Recovery) is a pilot study examining the feasibility of a 12-week mobile-based aftercare intervention for youth (ages 12 to 24) transitioning out of community-based substance abuse treatment programs. From January 2012 through July 2013, a total of 80 youth were recruited from outpatient and residential treatment programs, geographically dispersed throughout Los Angeles County, California. Results revealed that youth who participated in the texting mobile pilot intervention were significantly less likely to relapse to their primary compared to the aftercare as usual control condition (OR=0.52, p=0.002) over time (from baseline throughout the 12-week aftercare pilot program to a 90-day follow-up). Participants in the texting aftercare pilot program also reported significantly less substance use problem severity (*=-0.46, p=0.03) and were more likely to participate in extracurricular recovery behaviors (*=1.63, p=0.03) compared to participants in the standard aftercare group. Collectively, findings from this pilot aftercare study suggest that mobile texting could provide a feasible way to engage youth in recovery after substance abuse treatment to aid with reducing relapse and promoting lifestyle behavior change.

Feasibility of a Computerized Intervention for Offenders with Substance Use Disorders: A Research Note Chaple M, Sacks S, McKendrick K, Marsch LA, Belenko S, Leukefeld C, Prendergast M, French M. J Exp Criminol. 2014; 10: 105-127.
Despite evidence that treatment is effective in reducing recidivism among inmates with substance use problems, scarce resources mean that few of those in need of treatment actually receive it. Computerized substance abuse interventions could be used to expand access to treatment in prisons without placing an undue burden on resources. The major aim of the study was to compare treatment conditions in terms of their service utilization, skills acquisition, and treatment satisfaction. The study recruited men and women with substance use disorders from 10 prisons in 4 states. In an open label clinical trial, 494 subjects were randomly assigned either to the Experimental condition, a computerized drug treatment intervention, the Therapeutic Education System (TES; n= 249), or to the Control condition, Standard Care (n= 245). Chi-square tests compared groups on categorical variables and independent samples t tests were used for interval level continuous variables. Initial evidence demonstrated: (1) comparable group rates of session attendance and high rates of TES module completion for experimental subjects; (2) comparable group gains in the development of coping skills; and (3) a more favorable view of TES than of Standard Care. Collectively, these results show that a computerized intervention, such as TES, can be implemented successfully in prison. Given the barriers to the delivery of substance abuse treatment typically encountered in correctional settings, computerized interventions have the potential to fill a significant treatment gap and are particularly well suited to inmates with mild to moderate substance use disorders that often are not treated.

Difference in Method of Administration Did Not Significantly Impact Item Response: An IRT-based Analysis from the Patient-Reported Outcomes Measurement Information System (PROMIS) Initiative Bjorner JB, Rose M, Gandek B, Stone AA, Junghaenel DU, Ware Jr, JE. Qual Life Res. 2014; 23(1): 217-227.
The aim of this study was to test the impact of method of administration (MOA) on the measurement characteristics of items developed in the Patient-Reported Outcomes Measurement Information System (PROMIS). Two non-overlapping parallel 8-item forms from each of three PROMIS domains (physical function, fatigue, and depression) were completed by 923 adults (age 18-89) with chronic obstructive pulmonary disease, depression, or rheumatoid arthritis. In a randomized cross-over design, subjects answered one form by interactive voice response (IVR) technology, paper questionnaire (PQ), personal digital assistant (PDA), or personal computer (PC) on the Internet, and a second form by PC, in the same administration. Structural invariance, equivalence of item responses, and measurement precision were evaluated using confirmatory factor analysis and item response theory methods. Multigroup confirmatory factor analysis supported equivalence of factor structure across MOA. Analyses by item response theory found no differences in item location parameters and strongly supported the equivalence of scores across MOA. The authors found no statistically or clinically significant differences in score levels in IVR, PQ, or PDA administration as compared to PC. Availability of large item response theory-calibrated PROMIS item banks allowed for innovations in study design and analysis.

Improved Virologic Suppression with HIV Subspecialty Care In a Large Prison System Using Telemedicine: An Observational Study with Historical Controls Young JD, Patel M, Badowski M, Mackesy-Amiti ME, Vaughn P, Shicker L, Puisis M, Ouellet L. J. Clin Infect Dis. 2014.
Correctional populations have an elevated human immunodeficiency virus (HIV) prevalence, yet many individuals lack access to subspecialty care. This study showed that HIV-infected inmates had significantly greater virologic suppression and higher CD4 T-lymphocyte counts when managed by

a multidisciplinary team of subspecialists conducting clinics via telemedicine. In other studies, these outcomes have been associated with reductions on HIV-related morbidity and mortality, as well as HIV transmission.

Randomized Trial Outcomes of a TTM-tailored Condom Use and Smoking Intervention in Urban Adolescent Females Redding CA, Prochaska JO, Armstrong K, Rossi JS, Hoeppner BB, Sun X, Kobayashi H, Yin H-Q, Coviello D, Evers K, Velicer WF. Health Educ Res. 2014.
Smoking and sexual risk behaviors in urban adolescent females are prevalent and problematic. Family planning clinics reach those who are at most risk. This randomized effectiveness trial evaluated a trans theoretical model (TTM)-tailored intervention to increase condom use and decrease smoking. At baseline, a total of 828 14- to 17-year-old females were recruited and randomized within four urban family planning clinics. Participants received TTM or standard care (SC) computerized feedback and stage-targeted or SC counseling at baseline, 3, 6 and 9 months. Blinded follow-up telephone surveys were conducted at 12 and 18 months. Analyses revealed significantly more consistent condom use in the TTM compared with the SC group at 6 and 12, but not at 18 months. In baseline consistent condom users (40%), significantly less relapse was found in the TTM compared with the SC group at 6 and 12, but not at 18 months. No significant effects for smoking prevention or cessation were found, although cessation rates matched those found previously. This TTM-tailored intervention demonstrated effectiveness for increasing consistent condom use at 6 and 12 months, but not at 18 months, in urban adolescent females. This intervention, if replicated, could be disseminated to promote consistent condom use and additional health behaviors in youth at risk.

Interaction of Motivation and Psychiatric Symptoms on Substance Abuse Outcomes in Sober Living Houses Polcin DL, Korcha RA, Bond JC. Subst Use Misuse. 2014.
Studies show residents of sober living recovery houses (SLHs) make improvements in a variety of areas including alcohol and drug use, arrests, and employment. Longitudinal measures of motivation (assessed as costs and benefits of continuing sobriety) have been shown to be associated with alcohol and drug outcomes in SLHs. However, how motivation interacts with other potentially important factors, such as psychiatric severity, is unclear. The present study aimed to assess how perceived costs and benefits of sobriety among residents of SLHs differed by psychiatric severity. The study also aimed to assess how costs and benefits interacted with psychiatric severity to influence outcome. Two hundred forty-five residents of SLHs were assessed at baseline and 6, 12, and 18 months. High psychiatric severity was associated with higher severity of alcohol and drug problems and higher perceived costs of sobriety at all data collection time points. Perceived costs and benefits of sobriety were strong predictors of alcohol and drug problems for participants with low psychiatric severity. Perceived costs, but not perceived benefits, predicted outcomes for residents with high psychiatric severity. High psychiatric severity is a serious impediment for some residents in SLHs. These individuals perceive sobriety as difficult and that perception is associated with worse outcome. Finding ways to decrease perceived costs and challenges to sustained sobriety among these individuals is essential as is collaboration with local mental health services. SLHs should consider whether additional onsite services or modifications of SLH operations might help this population.

Comparison of Health Care Needs of Child Family Members of Adults With Alcohol or Drug Dependence Versus Adults with Asthma or Diabetes Ray GT, Mertens JR, Weisner C. J Dev Behav Pediatr. 2014; 35(4): 282-291.
The aim of this study was to compare the health problems, preventive care utilization, and medical costs of child family members (CFMs) of adults diagnosed with alcohol or drug dependence (AODD) to CFMs of adults diagnosed with diabetes or asthma. Child family members of adults diagnosed with AODD between 2002 and 2005 and CFMs of matched adults diagnosed with diabetes or asthma were followed up to 7 years after diagnosis of the index adult. Logistic regression was used to determine whether the CFMs of AODD adults were more likely to be diagnosed with medical conditions, or get preventive care, than the CFMs of adults with asthma or diabetes. Children's health services use was compared using multivariate models. In Year 5 after index date, CFMs of adults with AODD were more likely to be diagnosed with depression and AODD than CFMs of adults with asthma or diabetes and were less likely to be diagnosed with asthma, otitis media, and pneumonia than CFMs of adults with asthma. CFMs of AODD adults were less likely than CFMs of adult asthmatic patients to have annual well-child visits. CFMs of AODD adults had similar mean annual total health care costs to CFMs of adults with asthma but higher total costs ($159/yr higher, confidence interval, $56-$253) than CFMs of adult diabetic patients. CFMs of adults with AODD had higher emergency department, higher outpatient alcohol and drug program, higher outpatient psychiatry, and lower primary care costs than CFMs of either adult asthmatic patients or diabetic patients. Children in families with an alcohol- or drug-dependent adult have unique patterns of health conditions, and differences in the types of health services used, compared to children in families with an adult asthmatic or diabetic family member. However, overall cost and utilization for health care services is similar or only somewhat higher. This is the first study of its kind, and the results have implications for the reduction of parental alcohol or drug dependence stigma by health care providers, clearly an important issue in this era of health reform.

Factors Associated With One Year Retention To Methadone Maintenance Treatment Program Among Patients With Heroin Dependence In China Jiang H, Han Y, Du J, Wu F, Zhang R, Zhang H, Wang J, Zhou Z, Hser Y-I, Zhao M. Subst Abuse Treat Prev Policy. 2014; 9: 11.
The aim of this study was to evaluate the risk factors associated with dropout from Methadone Maintenance Treatment (MMT) clinics within a 1 year follow-up cohort study in China. A data analysis is to explore the adherence of MMT during one year from three hundred and twenty patients with heroin dependence at five clinics (3 in Shanghai, 2 in Kunming) in China. All participants were from the part of China-United States cooperation project entitled "Research about improving the compliance and efficacy of methadone maintenance treatment in China". Our data analysis includes the patients' attendance in the 6 months clinical study and the data in another 6 months afterward. The data of patients at baseline were collected with the Addiction Severity Index (ASI) which is a semi-structured questionnaire covering socio-demographic characteristics and drug use history. The one year attendance after recruitment at the clinics and daily dose were abstracted from the MMT clinic register system. The Cox proportional hazards model were used to explore the risk factor of dropout, defined as seven consecutive days without methadone. By the end of 1 year of treatment 86 patients still remained in MMT without dropout (87% in Shanghai and 13% patients in Kunming). Over the entire 1-year period the median days of remaining in the program were 84 days (in Shanghai and Kunming were 317 days and 22 days).The factors associated with retention included age (HR=0.98, 95%C.I.:0.96-0.99, P=0.0062) and ASI alcohol scores (HR=5.72, 95%C.I.:1.49-21.92, P=0.0109) at baseline. One year retention of newly recruited patients with

heroin dependence was related to age and ASI alcohol scores at baseline. The adherence is poorer for the patients who are young and having more serious alcohol problems.

Co-occurring Risk Factors for Arrest among Persons with Opioid Abuse and Dependence: Implications for Developing Interventions to Limit Criminal Justice Involvement Fisher WH, Clark R, Baxter J, Barton B, O'Connell E, Aweh G. J Subst Abuse Treat. 2014; 47(3): 197-201.
Persons who abuse or are dependent on opioids are at elevated risk for arrest. Co-occurring behavioral health problems may exacerbate that risk, although the extent of any such increase has not been described. This study examines such risk factors among 40,238 individuals with a diagnosis of opioid abuse or dependence who were enrolled in the Massachusetts Medicaid program in 2010. Medicaid data were merged with statewide arrest data to assess the effects of co-existing mental illness, substance abuse, and previous arrests on arrest during 2010. Persons with serious mental illnesses (psychotic and bipolar disorders) and those with two or more pre-2010 arrests had significantly increased greater odds of arrest. The authors believe this to be the first study examining effects of co-occurring risk factors on arrest in a large population with opioid dependency/abuse. These findings identify predictors of arrest that could be used to design interventions targeting specific co-occurring risk factors.

Do Improvements in Substance Use and Mental Health Symptoms During Treatment Translate to Long-term Outcomes in the Opposite Domain? Ramchand R, Griffin BA, Slaughter ME, Almirall D, McCaffrey DF. J Subst Abuse Treat. 2014; 47(5): 339-346.
Providers who treat adolescents with co-occurring substance use and mental health issues may prioritize treatment of one set of symptoms believing that improvements in one domain will result in improvements of the other. However, limited empirical data for adolescents provide evidence of such "spillover effects." Using data from 2900 youth in an outpatient treatment, the authors examined whether during-treatment changes in substance use or mental health symptoms predicted 12-month outcomes in the analogous and opposite domains. There was very little evidence of spillover effects, only that youth with no internal distress at 0 and 3 months reported lower levels of substance use problems at 12-months relative to youth with internal distress that stayed the same from 0 to 3 months. These findings suggest that providers treat both sets of substance use and mental health symptoms in an integrated manner given that these symptoms commonly co-occur among youth with either set.

Validation of the Depression Item Bank from the Patient-Reported Outcomes Measurement Information System (PROMIS) in a Three-month Observational Study Pilkonis PA, Yu L, Dodds NE, Johnston KL, Maihoefer CC, Lawrence SM. J Psychiatr Res. 2014; 56: 112-119.
The Patient-Reported Outcomes Measurement Information System (PROMIS) is an NIH Roadmap initiative devoted to developing better measurement tools for assessing constructs relevant to the clinical investigation and treatment of all diseases-constructs such as pain, fatigue, emotional distress, sleep, physical functioning, and social participation. Following creation of item banks for these constructs, our priority has been to validate them, most often in short-term observational studies. The authors report here on a three-month prospective observational study with depressed outpatients in the early stages of a new treatment episode (with assessments at intake, one-month follow-up, and three-month follow-up). The protocol was designed to compare the psychometric properties of the PROMIS depression item bank (administered as a computerized adaptive test, CAT) with two legacy self-report instruments: the Center for Epidemiological Studies Depression scale (CESD; Radloff, 1977) and the Patient Health Questionnaire (PHQ-9; Spitzer et al., 1999). PROMIS depression demonstrated strong convergent validity with the CESD and the PHQ-9 (with

correlations in a range from .72 to .84 across all time points), as well as responsiveness to change when characterizing symptom severity in a clinical outpatient sample. Identification of patients as "recovered" varied across the measures, with the PHQ-9 being the most conservative. The use of calibrations based on models from item response theory (IRT) provides advantages for PROMIS depression both psychometrically (creating the possibility of adaptive testing, providing a broader effective range of measurement, and generating greater precision) and practically (these psychometric advantages can be achieved with fewer items-a median of 4 items administered by CAT-resulting in less patient burden).

Predictors of High Level of Hostility among Homeless Men on Parole Nyamathi A, Salem B, Farabee D, Hall E, Zhang S, Khalilifard F, Faucette M, Leake B. J Offender Rehabil. 2014; 53(2): 95-115.
High levels of hostility present a formidable challenge among homeless ex-offenders. This cross-sectional study assessed correlates of high levels of hostility using baseline data collected on recently-released male parolees (N=472; age 18-60) participating in a randomized trial focused on prevention of illicit drug use and recidivism. Predictors of high levels of hostility included greater depressive symptomatology, lower self-esteem, having a mother who was treated for alcohol/drugs, belonging to a gang, more tangible support, having used methamphetamine and having a history of cognitive difficulties. These findings highlight the need to understand predictors of hostility among recently released homeless men and how these predictors may relate to recidivism. Research implications are discussed as these findings will shape future nurse-led harm reduction and community-based interventions.

Development of the PROMIS Positive Emotional and Sensory Expectancies of Smoking Item Banks Tucker JS, Shadel WG, Edelen MO, Stucky BD, Li Z, Hansen M, Cai Li. Nicotine Tob Res. 2014; 16 Suppl 3: S212-222.
The positive emotional and sensory expectancies of cigarette smoking include improved cognitive abilities, positive affective states, and pleasurable sensorimotor sensations. This paper describes development of Positive Emotional and Sensory Expectancies of Smoking item banks that will serve to standardize the assessment of this construct among daily and nondaily cigarette smokers. Data came from daily (N = 4,201) and nondaily (N =1,183) smokers who completed an online survey. To identify a uni-dimensional set of items, the authors conducted item factor analyses, item response theory analyses, and differential item functioning analyses. Additionally, they evaluated the performance of fixed-item short forms (SFs) and computer adaptive tests (CATs) to efficiently assess the construct. Eighteen items were included in the item banks (15 common across daily and nondaily smokers, 1 unique to daily, 2 unique to nondaily). The item banks are strongly uni-dimensional, highly reliable (reliability = 0.95 for both), and perform similarly across gender, age, and race/ethnicity groups. A SF common to daily and nondaily smokers consists of 6 items (reliability = 0.86). Results from simulated CATs indicated that, on average, less than 8 items are needed to assess the construct with adequate precision using the item banks. These analyses identified a new set of items that can assess the positive emotional and sensory expectancies of smoking in a reliable and standardized manner. Considerable efficiency in assessing this construct can be achieved by using the item bank SF, employing computer adaptive tests, or selecting subsets of items tailored to specific research or clinical purposes.

Development of the PROMIS Nicotine Dependence Item Banks Shadel WG, Edelen MO, Tucker JS, Stucky BD, Hansen M, Cai Li. Nicotine Tob Res. 2014; 16 Suppl 3: S190-201.
Nicotine dependence is a core construct important for understanding cigarette smoking and smoking cessation behavior. This article describes analyses conducted to develop and evaluate item banks for assessing nicotine dependence among daily and nondaily smokers. Using data from a sample of daily (N = 4,201) and nondaily (N =1,183) smokers, the authors conducted a series of item factor analyses, item response theory analyses, and differential item functioning analyses (according to gender, age, and race/ethnicity) to arrive at a uni-dimensional set of nicotine dependence items for daily and nondaily smokers. The authors also evaluated performance of short forms (SFs) and computer adaptive tests (CATs) to efficiently assess dependence. A total of 32 items were included in the Nicotine Dependence item banks; 22 items are common across daily and nondaily smokers, 5 are unique to daily smokers, and 5 are unique to nondaily smokers. For both daily and nondaily smokers, the Nicotine Dependence item banks are strongly uni-dimensional, highly reliable (reliability = 0.97 and 0.97, respectively), and perform similarly across gender, age, and race/ethnicity groups. SFs common to daily and nondaily smokers consist of 8 and 4 items (reliability = 0.91 and 0.81, respectively). Results from simulated CATs showed that dependence can be assessed with very good precision for most respondents using fewer than 6 items adaptively selected from the item banks. Nicotine dependence on cigarettes can be assessed on the basis of these item banks via one of the SFs, by using CATs, or through a tailored set of items selected for a specific research purpose.

Development of the PROMIS Social Motivations for Smoking Item Banks Tucker JS, Shadel WG, Edelen MOrlando, Stucky BD, Kuhfeld M, Hansen M, Cai Li. Nicotine Tob Res. 2014; 16 Suppl 3: S241-249.
Smoking behavior is influenced by social motivations such as the expected social benefits of smoking and the social cues that induce craving. This paper describes development of the PROMIS Social Motivations for Smoking item banks, which will serve to standardize assessment of these social motivations among daily and nondaily smokers. Daily (N = 4,201) and nondaily (N =1,183) smokers completed an online survey. Item factor analyses, item response theory analyses, and differential item functioning analyses were conducted to identify a uni-dimensional set of items for each group. Short forms (SFs) and computer adaptive tests (CATs) were evaluated as tools for more efficiently assessing this construct. A total of 15 items were included in the item banks (9 items common to daily and nondaily smokers, 3 unique to daily, 3 unique to nondaily). Scores based on full item banks are highly reliable (reliability = 0.90-0.91). Additionally, the item banks are strongly uni-dimensional and perform similarly across gender, age, and race/ethnicity groups. A fixed SF for use with both daily and nondaily smokers consists of 4 items (reliability = 0.80). Results from simulated CATs showed that, on average, fewer than 5 items are needed to assess this construct with adequate precision using the item banks. A new set of items has been identified for assessing the social motivations for smoking in a reliable, standardized manner for daily and nondaily smokers. In addition to using the full item banks, efficient assessment can be achieved by using SFs, employing CATs, or selecting items tailored to specific research or clinical purposes.

The PROMIS Smoking Assessment Toolkit--background and Introduction To Supplement. Edelen, Maria Orlando. Nicotine Tob Res. 2014; 16 Suppl 3(): S170-4.
The PROMIS Smoking Initiative has developed an assessment toolkit for measuring 6 domains of interest to cigarette smoking research: nicotine dependence, coping expectancies, emotional and sensory expectancies, health expectancies, psychosocial expectancies, and social motivations for smoking. The papers in this supplement describe the methods used to develop these item banks,

their psychometric properties, and the preliminary evidence for their validity. This commentary is meant to provide background information for the material in this supplement .After discussing the use of item response theory in behavioral measurement, I will briefly review the initial developmental steps for the smoking assessment toolkit. Finally, I will describe the contents of this supplement and provide some closing remarks. Psychometric evidence strongly supports the utility of the toolkit of item banks, short forms (SFs), and computer adaptive tests (CATs). The item banks for daily smokers produce scores with reliability estimates above 0.90 for a wide range of each cigarette smoking domain continuum, and SF and CAT administrations also achieve high reliability (generally greater than 0.85) using very few items (4-7 items for most banks). Performance of the banks for nondaily smokers is similar. Preliminary evidence supports the concurrent and the discriminant validity of the bank domains. The new smoking assessment toolkit has attractive measurement features that are likely to benefit smoking research as researchers begin to utilize this resource. Information about the toolkit and access to the assessments is available at the project Web site (http://www.rand.org/health/projects/promis-smoking-initiative.html) and can also be accessed via the PROMIS Assessment Center (www.assessmentcenter.net).

Development of The PROMIS Negative Psychosocial Expectancies of Smoking Item Banks
Stucky BD, Edelen MO, Tucker JS, Shadel WG, Cerully J, Kuhfeld M, Hansen M, Cai Li. Nicotine Tob Res. 2014; 16 Suppl 3: S232-240.
Negative psychosocial expectancies of smoking include aspects of social disapproval and disappointment in oneself. This paper describes analyses conducted to develop and evaluate item banks for assessing psychosocial expectancies among daily and nondaily smokers. Using data from a sample of daily (N = 4,201) and nondaily (N =1,183) smokers, the authors conducted a series of item factor analyses, item response theory analyses, and differential item functioning analyses (according to gender, age, and race/ethnicity) to arrive at a uni-dimensional set of psychosocial expectancies items for daily and nondaily smokers. They also evaluated performance of short forms (SFs) and computer adaptive tests (CATs) to efficiently assess psychosocial expectancies. A total of 21 items were included in the Psychosocial Expectancies item banks: 14 items are common across daily and nondaily smokers, 6 are unique to daily, and 1 is unique to nondaily. For both daily and nondaily smokers, the Psychosocial Expectancies item banks are strongly uni-dimensional, highly reliable (reliability = 0.95 and 0.93, respectively), and perform similarly across gender, age, and race/ethnicity groups. A SF common to daily and nondaily smokers consists of 6 items (reliability = 0.85). Results from simulated CATs showed that, on average, fewer than 8 items are needed to assess psychosocial expectancies with adequate precision when using the item banks. Psychosocial expectancies of smoking can be assessed on the basis of these item banks via the SF, by using CAT, or through a tailored set of items selected for a specific research purpose.

Investigating Social Support and Network Relationships in Substance Use Disorder Recovery
Stevens E, Jason LA, Ram D, Light J. Subst Abus. 2014.
Social support and characteristics of one's social network have been shown to be beneficial for abstinence and substance use disorder recovery. The current study explores how specific sources of social support relate to general feelings of social support and abstinence-specific self-efficacy. Data was collected from 31 of 33 individuals residing in five recovery houses. Participants were asked to complete social support and social network measures, along with measures assessing abstinence from substance use, abstinence self-efficacy, and involvement in 12-step groups. A significant positive relationship was found between general social support and abstinence-specific self-efficacy. General social support was also significantly associated with the specific social support measures of sense of community and AA affiliation. Social network size predicted abstinence-

related factors such as AA affiliation and perceived stress. These results provide insight regarding individual feelings of social support and abstinence-specific self-efficacy by showing that one's social network-level characteristics are related to one's perceptions of social support. The authors also found preliminary evidence that individual Oxford Houses influence one's feelings of social support.

The Effects of Participation Level on Recidivism: A Study Of Drug Treatment Courts Using Propensity Score Matching Gifford EJ, Eldred LM, McCutchan SA, Sloan FA. Subst Abuse Treat Prev Policy. 2014; 9: 40.
Empirical evidence has suggested that drug treatment courts (DTCs) reduce re-arrest rates. However, DTC program completion rates are low and little is known about the effectiveness of lower levels of program participation. The authors examined how DTC program referral, enrollment without completion, and completion, affected re-arrest rates during a two-year follow-up. They used statewide North Carolina data from criminal courts merged with DTC data. Propensity score matching was used to select comparison groups based on demographic characteristics, criminal histories, and drug of choice (when available). Average treatment effects on the treated were computed. DTC participation levels included referral without enrollment, (n = 2,174), enrollment without completion (n = 954), and completion (n = 747). Recidivism measured as re-arrest on a substance-related charge, on a violent offense charge not involving an allegation of substance abuse, and on any charge (excluding infractions) was examined by felony and misdemeanor status during a two-year follow-up period. Re-arrest rates were high, 53-76 percent. In general, re-arrest rates were similar for individuals who were referred but who did not enroll and a matched comparison group consisting of individuals who were not referred. In contrast, enrollees who did not complete had lower re-arrest rates than a matched group of individuals who were referred but did not enroll, for arrests on any charge, on any felony charge, and on substance-related charges (felonies and misdemeanors). Finally, relative to persons who enrolled but did not complete, those who completed had lower re-arrest rates on any charge, any felony charge, any misdemeanor charge, any substance-related charge, any substance-related misdemeanor or felony charge, and any violent felony charge. Enrolling in a DTC, even without completing, reduced re-arrest rates. Given the generally low DTC completion rate, this finding implies that only examining effects of completion underestimates the benefits of DTC programs.

Health Outcomes and Retention in Care Following Release from Prison For Patients of an Urban Post-incarceration Transitions Clinic Fox AD, Anderson MR, Bartlett G, Valverde J, Starrels JL, Cunningham CO. J Health Care Poor Underserved. 2014; 25(3): 1139-1152.
Chronic health conditions are overrepresented among prisoners who often face barriers to medical care following release. Transitions clinics seek to provide timely access to medical care following release. This retrospective cohort study investigated care delivery and health outcomes for recently released prisoners receiving care at the Bronx Transitions Clinic. Among 135 recently released prisoners, median time from release to initial medical visit was 10 days (IQ Range: 5-31). Six-month retention in care was high for HIV-infection (86%), but lower for opioid dependence (33%), hypertension (45%) and diabetes (43%). At six months, 54% of HIV-patients had a suppressed viral load, but fewer buprenorphine-treated patients reduced opioid use (19%), and fewer hypertensive and diabetic patients reached respective blood pressure (35%) and hemoglobin A1c (14%) goals. Access to medical care is necessary but not sufficient to control chronic health conditions. Additional interventions are necessary for formerly incarcerated people to achieve optimal health outcomes.

Development of the PROMIS Coping Expectancies of Smoking Item Banks Shadel WG, Edelen MO, Tucker JS, Stucky BD, Hansen M, Cai Li. Nicotine Tob Res. 2014; 16 Suppl 3: S202-211.
Smoking is a coping strategy for many smokers who then have difficulty finding new ways to cope with negative affect when they quit. This paper describes analyses conducted to develop and evaluate item banks for assessing the coping expectancies of smoking for daily and nondaily smokers. Using data from a large sample of daily (N = 4,201) and nondaily (N = 1,183) smokers, we conducted a series of item factor analyses, item response theory analyses, and differential item functioning (DIF) analyses (according to gender, age, and ethnicity) to arrive at a uni-dimensional set of items for daily and nondaily smokers. The authors also evaluated performance of short forms (SFs) and computer adaptive tests (CATs) for assessing coping expectancies of smoking. For both daily and nondaily smokers, the uni-dimensional Coping Expectancies item banks (21 items) are relatively DIF free and are highly reliable (0.96 and 0.97, respectively). A common 4-item SF for daily and nondaily smokers also showed good reliability (0.85). Adaptive tests required an average of 4.3 and 3.7 items for simulated daily and nondaily respondents, respectively, and achieved reliabilities of 0.91 for both when the maximum test length was 10 items. This research provides a new set of items that can be used to reliably assess coping expectancies of smoking, through a SF, CAT, or a tailored set selected for a specific research purpose.

Advancing Methods for Reliably Assessing Motivational Interviewing Fidelity Using the Motivational Interviewing Skills Code Lord SP, Can D, Yi M, Marin R, Dunn CW, Imel ZE, Georgiou P, Narayanan S, Steyvers M, Atkins DC. J Subst Abuse Treat. 2014.
The current paper presents novel methods for collecting MISC data and accurately assessing reliability of behavior codes at the level of the utterance. The MISC 2.1 was used to rate MI interviews from five randomized trials targeting alcohol and drug use. Sessions were coded at the utterance-level. Utterance-based coding reliability was estimated using three methods and compared to traditional reliability estimates of session tallies. Session-level reliability was generally higher compared to reliability using utterance-based codes, suggesting that typical methods for MISC reliability may be biased. These novel methods in MI fidelity data collection and reliability assessment provided rich data for therapist feedback and further analyses. Beyond implications for fidelity coding, utterance-level coding schemes may elucidate important elements in the counselor-client interaction that could inform theories of change and the practice of MI.

Development of the PROMIS Health Expectancies of Smoking Item Banks Edelen MO, Tucker JS, Shadel WG, Stucky BD, Cerully J, Li Z, Hansen M, Cai L. Nicotine Tob Res. 2014; 16 Suppl 3: S223-231.
Smokers' health-related outcome expectancies are associated with a number of important constructs in smoking research, yet there are no measures currently available that focus exclusively on this domain. This paper describes the development and evaluation of item banks for assessing the health expectancies of smoking. Using data from a sample of daily (N = 4,201) and nondaily (N = 1,183) smokers, we conducted a series of item factor analyses, item response theory analyses, and differential item functioning analyses (according to gender, age, and race/ethnicity) to arrive at a uni-dimensional set of health expectancies items for daily and nondaily smokers. The authors also evaluated the performance of short forms (SFs) and computer adaptive tests (CATs) to efficiently assess health expectancies. A total of 24 items were included in the Health Expectancies item banks; 13 items are common across daily and nondaily smokers, 6 are unique to daily, and 5 are unique to nondaily. For both daily and nondaily smokers, the Health Expectancies item banks are uni-dimensional, reliable (reliability = 0.95 and 0.96, respectively), and perform similarly across gender, age, and race/ethnicity groups. A SF common to daily and nondaily smokers consists of 6

items (reliability = 0.87). Results from simulated CATs showed that health expectancies can be assessed with good precision with an average of 5-6 items adaptively selected from the item banks. Health expectancies of smoking can be assessed on the basis of these item banks via SFs, CATs, or through a tailored set of items selected for a specific research purpose.

Childhood Maltreatment and the Course of Bipolar Disorders among Adults: Epidemiologic Evidence of Dose-response Effects Sala R, Goldstein BI, Wang S, Blanco C. J Affect Disord. 2014; 165: 74-80.
Childhood maltreatment (CM) is highly prevalent among individuals with bipolar disorders (BP); however few studies have examined its potential role in the course and outcome of individuals with BP. The authors aim to examine the dose response relationship between the number of types of CM and the course of individuals with BP. As part of the National Epidemiologic Survey on Alcohol and Related Conditions, 1600 adults who met lifetime DSM-IV criteria for BP-I (n=1172) and BP-II (n=428) were included. Individuals were evaluated using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DMS-IV Version and data was analyzed lifetime and from Waves 1 and 2, approximately 3 years apart. Around half of individuals with BP had a history of at least one type of CM. Overall, there was a clear dose-response relationship between number of CM and severity of BP across several domains, including clinical characteristics, probability of treatment, lifetime prevalence of psychiatric comorbidity, incidence of anxiety disorders, substance use disorder, and nicotine dependence, and level of psychosocial functioning. The interviews were conducted by lay professional interviewers rather than clinicians, use of retrospective report to determine CM in individuals with BP, and not all respondents from Wave 1 were able to be interviewed in Wave 2.The number of types of CM confers developmental differences in the course of BP with a worse course and outcome of BP. Early identification and treatment of CM are warranted to improve the course and outcome of individuals with BP.

Sexual Partner Notification of HIV Infection among a National United States-Based Sample of HIV-Infected Men Edelman EJ, Gordon KS, Hogben M, Crystal S, Bryant K, Justice AC, Fiellin DA; VACS Project Team. AIDS Behav. 2014; 18(10): 1898-1903.
Limited data exist on whether sexual partner notification practices among HIV-infected men, particularly those who have sex with men (MSM), vary by HIV viral load. The authors examined factors associated with complete (all partners) versus incomplete partner notification in 760 HIV-infected individuals across the United States, 49 % of whom were MSM. Thirty-four percent reported incomplete partner notification. Incomplete partner notification was more likely among black men, MSM, and those reporting casual partners and non-condom use. Partner notification practices did not vary by HIV viral load except among those with casual partners in whom a detectable viral load was associated with incomplete partner notification. Increased sexual partner notification among HIV-infected men, especially MSM, is needed.

Alternate Tobacco Product and Drug Use among Adolescents Who Use Electronic Cigarettes, Cigarettes Only, and Never Smokers Camenga DR, Kong G, Cavallo DA, Liss A, Hyland A, Delmerico J, Cummings KM, Krishnan-Sarin S. J Adolesc Health. 2014; 55(4): 588-591.
The aim of this study was to determine whether use of alternative tobacco products (i.e., cigars, blunts, hookah, smokeless tobacco), alcohol, and marijuana differs among adolescents who currently use (1) electronic cigarettes (e-cigarettes); (2) cigarettes only; and (3) never smokers. Analysis of a self-reported survey from four high schools in 2010-2011 (n = 3,102) with a subsample (n = 1,556) surveyed on alcohol and marijuana. Analyses were conducted with multinomial logistic regression models accounting for clustering by schools. The sample contained

2.4% (n = 76) e-cigarette users, 12.4% (n = 386) cigarette smokers, and 85.1% (n = 3,197) never smokers. E-cigarette users were more likely than cigarette-only smokers to report blunt (adjusted odds ratio, 1.81; 95% confidence interval, 1.21-2.71) and hookah use (adjusted odds ratio, 3.12; 95% confidence interval, 1.90-5.13), but not cigar, smokeless tobacco, alcohol, or marijuana use. E-cigarette users are more likely than cigarette smokers to use hookah and blunts.

Strategies for Hepatitis C Testing and Linkage to Care for Vulnerable Populations: Point-of-care and Standard HCV Testing in a Mobile Medical Clinic Morano JP, Zelenev A, Lombard A, Marcus R, Gibson BA, Altice FL. J Community Health. 2014; 39(5): 922-934.
Despite new Hepatitis C virus (HCV) therapeutic advances, challenges remain for HCV testing and linking patients to care. A point-of-care (POC) HCV antibody testing strategy was compared to traditional serological testing to determine patient preferences for type of testing and linkage to treatment in an innovative mobile medical clinic (MMC). From 2012 to 2013, all 1,345 MMC clients in New Haven, CT underwent a routine health assessment, including for HCV. Based on patient preferences, clients could select between standard phlebotomy or POC HCV testing, with results available in approximately 1 week versus 20 min, respectively. Outcomes included: (1) accepting HCV testing; (2) preference for rapid POC HCV testing; and (3) linkage to HCV care. All clients with reactive test results were referred to a HCV specialty clinic. Among the 438 (32.6 %) clients accepting HCV testing, HCV prevalence was 6.2 % (N = 27), and 209 (47.7 %) preferred POC testing. Significant correlates of accepting HCV testing was lower for the "baby boomer" generation (AOR 0.67; 95 % CI 0.46-0.97) and white race (AOR 0.55; 95 % CI 0.36-0.78) and higher for having had a prior STI diagnosis (AOR 5.03; 95 % CI 1.76-14.26), prior injection drug use (AOR 2.21; 95 % CI 1.12-4.46), and being US-born (AOR 1.76; 95 % CI 1.25-2.46). Those diagnosed with HCV and preferring POC testing (N = 16) were significantly more likely than those choosing standard testing (N = 11) to be linked to HCV care within 30 days (93.8 vs. 18.2 %; $p < 0.0001$). HCV testing is feasible in MMCs. While patients equally preferred POC and standard HCV testing strategies, HCV-infected patients choosing POC testing were significantly more likely to be linked to HCV treatment. Important differences in risk and background were associated with type of HCV testing strategy selected. HCV testing strategies should be balanced based on costs, convenience, and ability to link to HCV treatment.

Can Hepatitis C Be Eradicated In the United States? Edlin BR, Winkelstein ER. Antiviral Res. 2014; 110: 79-93.
The advent of highly effective antiviral regimens will make the eradication of hepatitis C in high-income countries such as the United States technically feasible. But eradicating hepatitis C will require escalating our response to the epidemic in key domains, including surveillance and epidemiology, prevention, screening, care and treatment, policy, research, and advocacy. Surveillance must be nimble enough to quickly assess the magnitude of new transmission patterns as they emerge. Basic prevention strategies - community-based outreach and education, testing and counseling, and access to sterile injection equipment and opioid substitution therapies - must be scaled up and adapted to target groups in which new epidemics are emerging. All adults should be screened for hepatitis C, but special efforts must focus on groups with increased prevalence through community outreach and rapid testing. Government, industry, and payers must work together to assure full access to health services and antiviral drugs for everyone who is infected. Access to the new regimens must not be compromised by excessively high prices or arbitrary payer restrictions. Partnerships must be forged between hepatitis providers and programs that serve people who inject illicit drugs. Healthcare providers and systems, especially primary care practitioners, need education and training in treating hepatitis C and caring for substance-using populations. Services must be

provided to the disadvantaged and stigmatized members of society who bear a disproportionate burden of the epidemic. Environments must be created where people who use drugs can receive prevention and treatment services without shame or stigma. Action is needed to end the policy of mass incarceration of people who use drugs, reduce the stigma associated with substance use, support the human rights of people who use drugs, expand social safety net services for the poor and the homeless, remove the legal barriers to hepatitis C prevention, and build public health infrastructure to reach, engage, and serve marginalized populations. Governments must take action to bring about these changes. Public health agencies must work with penal institutions to provide prevention and treatment services, including antiviral therapy, to those in need in jails and prisons or on probation or parole. Research is needed to guide efforts in each of these domains. Strong and sustained political advocacy will be needed to build and sustain support for these measures. Leadership must be provided by physicians, scientists, and the public health community in partnership with community advocates and people living with or at risk for hepatitis C. Eliminating hepatitis C from the United States is possible, but will require a sustained national commitment to reach, test, treat, cure, and prevent every case. With strong political leadership, societal commitment, and community support, hepatitis C can be eradicated in the United States. If this is to happen in our lifetimes, the time for action is now. This article forms part of a symposium in Antiviral Research on "Hepatitis C: next steps toward global eradication."

Postpartum Changes in Methadone Maintenance Dose Pace CA, Kaminetzky LB, Winter M, Cheng DM, Saia K, Samet JH, Walley AY. J Subst Abuse Treat. 2014; 47(3): 229-232.
The optimal approach to postpartum dosing among women treated with methadone maintenance is unclear. The authors examined doses among 101 methadone-maintained pregnant women 2, 6 and 12 weeks postpartum, and compared the incidence of having doses held for over sedation during pregnancy and postpartum. The average dose at delivery was 83.3mg, and the mean change from delivery to 12 weeks postpartum was -3.7 mg (95% CI -6.3, -1.1). The incidence of over sedation events per 10,000 days was 2.8 among pregnant women and 5.6 for postpartum women (incidence rate ratio [IRR] 2.04, 95% CI 0.66, 6.28). After adjusting for benzodiazepine prescriptions, the IRR of an over sedation event among postpartum women compared to pregnant women was 1.74 (95% CI 0.56, 5.30). In conclusion, postpartum dose changes were small in a methadone clinic using clinical assessments to determine dose. Although the incidence of over sedation events remained low postpartum, the clinically important but not statistically significant increase in events among postpartum women and those prescribed benzodiazepines requires further research. While there are not yet adequate data to support pre-specified postpartum dose reductions, the findings suggest that more frequent clinical assessments continuing as late as 12 weeks postpartum may be warranted.

Drug Interactions and Antiretroviral Drug Monitoring Foy M, Sperati CJ, Lucas GM, Estrella MM. Curr HIV/AIDS Rep. 2014; 11(3): 212-222.
Owing to the improved longevity afforded by combination antiretroviral therapy (cART), HIV-infected individuals are developing several non-AIDS-related comorbid conditions. Consequently, medical management of the HIV-infected population is increasingly complex, with a growing list of potential drug-drug interactions (DDIs). This article reviews some of the most relevant and emerging potential interactions between antiretroviral medications and other agents. The most common DDIs are those involving protease inhibitors or non-nucleoside reverse transcriptase inhibitors, which alter the cytochrome P450 enzyme system and/or drug transporters such as p-glycoprotein. Of note are the new agents for the treatment of chronic hepatitis C virus infection. These new classes of drugs and others drugs that are increasingly used in this patient population represent a significant challenge with regard to achieving the goals of effective HIV suppression

and minimization of drug-related toxicities. Awareness of DDIs and a multidisciplinary approach are imperative in reaching these goals.

African American Women's Preventative Care Usage: The Role of Social Support and Racial Experiences and Attitudes Pullen E, Perry B, Oser C. Sociol Health Illn. 2014; 36(7): 1037-1053.
Research suggests that African Americans are less likely to utilize preventative care services than Americans of European descent, and that these patterns may contribute to racial health disparities in the United States. Despite the persistence of inequalities in preventative care utilization, culturally relevant factors influencing the use of these gateway health services have been understudied among marginalized groups. Using a stratified sample of 205 low-income African American women, this research examines the predictors of receiving a physical exam, with a particular emphasis on how differing levels of social support from friend and family networks and experiences of racial discrimination and cultural mistrust shape utilization. The findings underscore the importance of traditional predictors of utilization, including insurance status and having a usual physician. However, they also indicate that supportive ties to friendship networks are associated with higher predicted rates of having an annual physical exam, while social support from family and sentiments of cultural mistrust are associated with lower rates of utilization. Broadly, the findings indicate that even as traditional predictors of help-seeking become less relevant, it will be critical to explore how variations in discrimination experiences and social relationships across marginalized groups drive patterns of preventative care utilization.

Beliefs and Attitudes Regarding Drug Treatment: Application of The Theory of Planned Behavior in African-American Cocaine Users Booth BM, Stewart KE, Curran GM, Cheney AM, Borders TF. Addict Behav. 2014; 39(10): 1441-1446.
The Theory of Planned Behavior (TPB) can provide insights into perceived need for cocaine treatment among African American cocaine users. A cross-sectional community sample of 400 (50% rural) not-in-treatment African-American cocaine users was identified through respondent-driven sampling in one urban and two rural counties in Arkansas. Measures included self-reports of attitudes and beliefs about cocaine treatment, perceived need and perceived effectiveness of treatment, and positive and negative cocaine expectancies. Normative beliefs were measured by perceived stigma and consequences of stigma regarding drug use and drug treatment. Perceived control was measured by readiness for treatment, prior drug treatment, and perceived ability to cut down on cocaine use without treatment. Multiple regression analysis found that older age (standardized regression coefficient *=0.15, P<0.001), rural residence (*=-0.09, P=0.025), effectiveness of treatment (*=0.39, P<0.001), negative cocaine expectancies (*=0.138, P=0.003), experiences of rejection (*=0.18, P<0.001), need for secrecy (*=0.12, P=0.002), and readiness for treatment (*=0.15, P<0.001) were independently associated with perceived need for cocaine treatment. TPB is a relevant model for understanding perceived need for treatment among African-American cocaine users. Research has shown perceived need to be a major correlate of treatment participation. Study results should be applicable for designing interventions to encourage treatment participation.

G-protein *3 Subunit Genetic Variation Moderates Five-year Depressive Symptom Trajectories of Primary Care Attendees Bousman CA, Potiriadis M, Everall IP, Gunn JM. J Affect Disord. 2014; 165: 64-68.
Genetic variation in the G-protein *3 subunit (GNB3) has previously been associated with gene splicing that has been further linked to increased signal transduction and major depressive disorder. However, the effect of GNB3 genetic variation on depressive symptom trajectories is currently

unknown. The aim of the present study is to examine whether genetic variation in GNB3 moderates depressive symptom trajectories among 301 primary care attendees enrolled in the Diagnosis, Management and Outcomes of Depression in Primary Care (diamond) prospective cohort study. Depressive symptoms were assessed using three measures: (1) DSM-IV criteria, (2) Primary Care Evaluation of Mental Disorders Patient Health Questionnaire-9 (PHQ-9), and (3) Center for Epidemiologic Studies Depression Scale (CESD). DSM-IV criteria were measured at baseline, 24, 36, 48, and 60 months post-baseline, whereas, PHQ-9 and CESD measurements were taken at baseline, 12, 24, 36, 48, and 60 months post-baseline. Two haplotype-tagging single nucleotide polymorphisms [rs5443 (C825T) and rs5440] spanning the GNB3 gene including ~1Kb upstream and downstream of the gene boundaries were genotyped. Five-year PHQ-9 and CESD depressive symptom trajectories were moderated by rs5440. Carriers of the rs5440 GG genotype had more favorable depressive symptom trajectories compared to AG or AA genotype carriers. The rs5443 polymorphism did not moderate depressive symptom trajectories, regardless of the measure used. Generalizability to depressed populations outside of the primary care setting may be limited. These results provide novel evidence suggesting genetic variation in the 5-prime region of GNB3 moderates depressive symptom trajectories among primary care attendees.

Impact of Trauma Symptomatology on Personal Networks among Substance Using Women
Min MO, Tracy EM, Park H. Drug Alcohol Depend. 2014; 142: 277-282.
Interpersonal trauma poses challenges and complications to the development and maintenance of personal networks of substance using women. Few studies have examined its effects on personal network support availability and quality of relationships, limiting our understanding of the social context in which substance using women with a history of trauma are embedded. Women with substance use disorders (SUD) who received treatment at three county-funded, women-only intensive treatment programs (N=375) were interviewed at intake and at follow ups 1, 6, and 12 months later. A network software program, EgoNet, elicited 25 network members per respondent, social support availability, and the quality of network relationship at each assessment. Trauma symptomatology was assessed with Trauma Symptom Checklist-40 at intake. Findings from longitudinal mixed model analyses indicated that higher levels of trauma symptomatology were associated with both a negative, critical quality and less closeness in network relationships over the 12 month study period. However, trauma symptoms were not related to the number of network members reported as providing emotional, concrete, or sobriety support. Effects of trauma symptoms on the support availability in the network and the quality of network relationships were consistent over the follow-up period. Findings highlight the potential role of trauma symptoms in determining the quality of relationships within personal networks among women with SUD, suggesting the need for routine mapping of network relationships throughout treatment.

Situational Panic Attacks in Social Anxiety Disorder Potter CM, Wong J, Heimberg RG, Blanco C, Liu S-M, Wang S, Schneier FR. J Affect Disord. 2014; 167: 1-7.
Panic attacks (PAs) are common in many psychiatric disorders other than panic disorder, especially social anxiety disorder (SAD). PAs have been associated with increased severity, comorbidity, and impairment in many disorders; therefore, PAs can now be used as a descriptive specified across all DSM-5 disorders. However, the clinical implications of PAs in SAD remain unclear. The aim of the present investigation was to examine demographic and clinical characteristics associated with SAD-related situational panic attacks in a large, representative epidemiological sample of individuals with SAD (N=1138). The authors compared individuals with SAD who did and did not endorse situational PAs in terms of demographic factors, fear/avoidance of social situations, distress, impairment, and diagnostic comorbidity. Being male, black, Asian, or over 65 years old was

associated with a decreased likelihood of experiencing situational PAs, whereas being unemployed was associated with an increased likelihood. Individuals with situational PAs also exhibited greater fear and avoidance of social situations, impairment, coping-oriented substance use, treatment utilization, and concurrent and longitudinal psychiatric comorbidity. Consistent with most epidemiologic studies, the information collected relied on self-report, and not all participants were available for both waves of assessment. The present findings suggest that SAD-related situational PAs are associated with more severe and complex presentations of SAD. Implications for the assessment and treatment of SAD, as well as for the use of PAs as a descriptive specified for SAD, are discussed.

Correlates of Hospital Use in Homeless and Unstably Housed Women: The Role of Physical Health and Pain Doran KM, Shumway M, Hoff RA, Blackstock OJ, Dilworth SE, Riley ED. Womens Health Issues. 2014; 24(5): 535-541.
The aim of this study was to examine correlates of emergency department (ED) use and hospitalizations in a community-based cohort of homeless and unstably housed women, with a focus on the role of physical health and pain. The authors conducted a cross-sectional analysis of baseline survey results from a study of homeless and unstably housed women in San Francisco. Primary outcomes were any self-reported ED visit and inpatient hospitalization over the prior 6ýýmonths. Primary independent variables of interest were self-reported physical health status, as measured by the Short Form-12 (SF-12), and bodily pain. Other potential covariates were organized using the Gelberg-Andersen Behavioral Model for Vulnerable Populations. Standard bivariate and multivariable logistic regression techniques were used. Three hundred homeless and unstably housed women were included in the study, of whom 37.7% reported having an ED visit and 23.0% reported being hospitalized in the prior 6ýýmonths. Mean SF-12 physical health scores indicated poorer than average health compared with the U.S. norm. Most women (79.3%) reported at least some limitation in their daily activities owing to pain. In adjusted analyses, moderate and high levels of bodily pain were significantly correlated with ED visits (odds ratio [OR], 2.92 and OR, 2.57) and hospitalizations (OR, 6.13 and OR, 2.49). As SF-12 physical health scores decreased, indicating worse health, the odds of ED use increased. Predisposing, enabling, and additional need factors did not mediate these associations. Physical health and bodily pain are important correlates of ED visits and hospitalizations among homeless and unstably housed women. Interventions to reduce ED use among women who are homeless should address the high levels of pain in this population.

Rural/Urban Residence, Access, and Perceived Need for Treatment among African American Cocaine Users Borders TF, Booth BM, Stewart KE, Cheney AM, Curran GM. J Rural Health. 2014.
The purpose of this study was to examine how rural/urban residence, perceived access, and other factors impede or facilitate perceived need for drug use treatment, a concept closely linked to treatment utilization. Two hundred rural and 200 urban African American cocaine users who were not receiving treatment were recruited via Respondent-Driven Sampling and completed a structured in-person interview. Bivariate and multivariate analyses were conducted to test the associations between perceived need and rural/urban residence, perceived access, and other predisposing (eg, demographics), enabling (eg, insurance), and health factors (eg, psychiatric distress).In bivariate analyses, rural relative to urban cocaine users reported lower perceived treatment need (37% vs 48%), availability, affordability, overall ease of access, and effectiveness, as well as lower perceived acceptability of residential, outpatient, self-help, and hospital-based services. In multivariate analyses, there was a significant interaction between rural/urban residence and the

acceptability of religious counseling. At the highest level of acceptability, rural users had lower odds of perceived need (OR = 0.21); at the lowest level, rural users had higher odds of perceived need (OR = 3.97) than urban users. Among rural users, the acceptability of religious counseling was negatively associated with perceived need (OR = 0.65). Ease of access was negatively associated (OR = 0.71) whereas local treatment effectiveness (OR = 1.47) and the acceptability of hospital-based treatment (OR = 1.29) were positively associated with perceived need among all users. Our findings suggest rural/urban disparities in perceived need and access to drug use treatment. Among rural and urban cocaine users, improving perceptions of treatment effectiveness and expanding hospital-based services could promote treatment seeking.

Recent Violence in a Community-based Sample of Homeless and Unstably Housed Women with High Levels of Psychiatric Comorbidity Riley ED, Cohen J, Knight KR, Decker A, Marson K, Shumway M. Am J Public Health. 2014; 104(9): 1657-1663.
The authors determined associations between co-occurring psychiatric conditions and violence against homeless and unstably housed women. Between 2008 and 2010, they interviewed homeless and unstably housed women recruited from community venues about violence, socioeconomic factors, and psychiatric conditions. They used multivariable logistic regression to determine independent correlates of violence. Among 291 women, 97% screened positive for 1 or more psychiatric conditions. Types of violence perpetrated by primary partners and persons who were not primary partners (non-primary partners) included emotional violence (24% vs 50%; P < .01), physical violence (11% vs 19%; P < .01), and sexual violence (7% vs 22%; P < .01). The odds of primary partner and non-primary partner violence increased with each additional psychiatric diagnosis and decreasing levels of social isolation. All types of violence were more commonly perpetrated by non-primary partners, suggesting that an exclusive focus on domestic violence screening in health care or social service settings will miss most of the violence in this population. Contrary to some previous studies, the odds of violence decreased as social isolation increased, suggesting that social isolation may be protective in homeless and unstably housed communities with high levels of comorbidity and limited options.

The Association of Interpersonal Trauma with Somatic Symptom Severity in a Primary Care Population with Chronic Pain: Exploring the Role of Gender and the Mental Health Sequelae of Trauma S McCall-Hosenfeld J, Winter M, Heeren T, Liebschutz JM. J Psychosom Res. 2014; 77(3): 196-204.
Female trauma survivors develop somatic symptoms more frequently than males. The authors propose a model for somatic symptom development among trauma survivors, focusing on gender. Among 597 urban primary care patients with chronic pain, they examined the association between somatic symptom severity and three interpersonal trauma types: 1) sexual trauma (ST), 2) intimate partner violence (IPV), and 3) childhood trauma history (≥3 adverse childhood experiences (3+ACE)). The authors developed a structural equation model in which PTSD, depression, and substance abuse were evaluated as potential mediators of the path between trauma exposure and somatic symptom severity, and explored the role of gender in this model.350 (59%) respondents were female; the mean age was 47. Women reported significantly more somatic symptoms than men, although somatic symptoms were increased among all interpersonal trauma survivors. In models in which the potential intervening variables are considered in aggregate, the authors did not find a significant interaction between gender and trauma on somatic symptom severity, with the exception of 3+ACEs. A structural equation model showed depression and substance abuse, for men, and depression, for women, were associated with somatic symptom severity. PTSD was not associated with somatic symptom severity. Paths from trauma exposures to mental health sequel

were stronger for men. Women have more severe somatic symptoms. With the exception of 3+ACEs, the association between trauma and somatic symptoms is amplified in both genders. Structural equation models showed the pathways differed by gender in function and strength of association.

Pain is Associated with Risky Drinking Over Time among HIV-infected Persons in St. Petersburg, Russia Tsui JI, Cheng DM, Coleman SM, Lira MC, Blokhina E, Bridden C, Krupitsky E, Samet JH. Drug Alcohol Depend. 2014.
Pain is highly prevalent among persons with HIV. Alcohol may be used to "self-medicate" pain. This study examined the association between pain and risky alcohol use over time in a cohort of HIV-infected Russian drinkers. This secondary analysis utilized longitudinal data from a randomized trial of a behavioral intervention. Subjects included HIV-infected adults who reported past 6-month risky drinking and unprotected sex and were recruited from HIV and addiction treatment sites in St. Petersburg, Russia. The main independent variable was pain that at least moderately interfered with daily living. The primary outcome was past month risky drinking amounts based on NIAAA guidelines. General estimating equations (GEE) logistic regression models were used to calculate odds ratios and 95% confidence intervals for the association between pain and risky drinking over time (i.e., baseline, 6 and 12 months), adjusting for potential confounders. Baseline characteristics of participants (n=699) were mean age of 30 (SD 5) years, 41% female, and 22% <9th grade education. Nearly one quarter (24%) had a CD4 cell count <200cells/*l, and only 17% were on antiretroviral therapy. Nearly half (46%) reported at least moderate pain interference in the past month and 81% were drinking risky amounts. In adjusted longitudinal GEE models, pain was significantly associated with greater odds of repo,rting past month risky drinking (AOR=1.34, 95% CI: 1.05-1.71, p value=0.02).Among a cohort of HIV-infected Russian drinkers, pain that at least moderately interfered with daily living was associated with higher odds of reporting risky drinking amounts over time.

Process Monitoring of an HIV Treatment as Prevention Program in British Columbia, Canada Lourenco L, Lima VD, Heath K, Nosyk B, Gilbert M, Colley G, Consolacion T, Barrios R, Hogg R, Krajden M, Konrad S, Murti M, Nelson J, May-Hadford J, Haggerstone J, Pick N, Gustafson R, Rusch M, Day I, Montaner JSG. J Acquir Immune Defic Syndr. 2014; 67(3): e94-e109.
In light of accumulated scientific evidence of the secondary preventive benefits of antiretroviral therapy, a growing number of jurisdictions worldwide have formally started to implement HIV Treatment as Prevention (TasP) programs. To date, no gold standard for TasP program monitoring has been described. Here, the authors describe the design and methods applied to TasP program process monitoring in British Columbia (BC), Canada. Monitoring indicators were selected through a collaborative and iterative process by an interdisciplinary team including representatives from all 5 regional health authorities, the BC Centre for Disease Control (BCCDC), and the BC Centre for Excellence in HIV/AIDS (BC-CfE). An initial set of 36 proposed indicators were considered for inclusion. These were ranked on the basis of 8 criteria: data quality, validity, and scientific evidence, informative power of the indicator, feasibility, confidentiality, accuracy, and administrative requirement. The consolidated list of indicators was included in the final monitoring report, which was executed using linked population-level data. A total of 13 monitoring indicators were included in the BC TasP Monitoring Report. Where appropriate, indicators were stratified by subgroups of interest, including HIV risk group and demographic characteristics. Six Monitoring Reports are generated quarterly: 1 for each of the regional health authorities and a consolidated provincial report. We have developed a comprehensive TasP process monitoring strategy using

evidence-based HIV indicators derived from linked population-level data. Standardized longitudinal monitoring of TasP program initiatives is essential to optimize individual and public health outcomes and to enhance program efficiencies.

Hepatotoxicity in A 52-week Randomized Trial of Short-term Versus Long-term Treatment with Buprenorphine/naloxone in HIV-negative Injection Opioid Users in China and Thailand

Lucas GM, Young A, Donnell D, Richardson P, Aramrattana A, Shao Y, Ruan Y, Liu W, Fu L, Ma J, Celentano DD, Metzger D, Jackson J B, Burns D, HPTN 058 study group. Drug Alcohol Depend. 2014; 142: 139-145.

Buprenorphine/naloxone (BUP/NX), an effective treatment for opioid dependence, has been implicated in hepatic toxicity. However, as persons taking BUP/NX have multiple hepatic risk factors, comparative data are needed to quantify the risk of hepatoxicity with BUP/NX. The authors compared rates of alanine aminotransferase (ALT) elevation grade 3 (ALT≥5.1 times the upper limit of normal) and graded bilirubin elevations in HIV-negative opioid injectors randomized to long-term (52 weeks) or short-term (18 days) medication assisted treatment (LT-MAT and ST-MAT, respectively) with BUP/NX in a multisite trial conducted in China and Thailand. ALT and bilirubin were measured at baseline, 12, 26, 40 and 52 weeks, times temporally remote from BUP/NX exposure in the ST-MAT participants. Among1036 subjects with at least one laboratory follow-up measurement, 76 (7%) participants experienced ALT elevation ≥ grade 3. In an intent-to-treat analysis, the risk of ALT events was similar in participants randomized to LT-MAT compared with ST-MAT (adjusted hazard ratio 1.25, 95% confidence interval 0.79 to 1.98). This finding was supported by an as-treated analysis, in which actual exposure to BUP/NX was considered. Hepatitis C serocon version during follow-up was strongly associated with ALT events. Bilirubin elevations ≥ grade 2 occurred in 2% of subjects, with no significant difference between arms. Over 52-week follow-up, the risk of hepatotoxicity was similar in opioid injectors receiving brief and prolonged treatment with BUP/NX. These data suggest that most hepatotoxic events observed during treatment with BUP/NX are due to other factors.

Costs of Care For Persons with Opioid Dependence in Commercial Integrated Health Systems

Lynch FL, McCarty D, Mertens J, Perrin NA, Green CA, Parthasarathy S, Dickerson JF, Anderson BM, Pating D. Addiction Science & Clinical Practice. 2014; 9:16.

When used in general medical practices, buprenorphine is an effective treatment for opioid dependence, yet little is known about how use of buprenorphine affects the utilization and cost of health care in commercial health systems. The objective of this retrospective cohort study was to examine how buprenorphine affects patterns of medical care, addiction medicine services, and costs from the health system perspective. Individuals with two or more opioid-dependence diagnoses per year, in two large health systems (System A: n = 1836; System B: n = 4204) over the time span 2007–2008 were included. Propensity scores were used to help adjust for group differences. Patients receiving buprenorphine plus addiction counseling had significantly lower total health care costs than patients with little or no addiction treatment (mean health care costs with buprenorphine treatment = $13,578; vs. mean health care costs with no addiction treatment = $31,055; $p < .0001$), while those receiving buprenorphine plus addiction counseling and those with addiction counseling only did not differ significantly in total health care costs (mean costs with counseling only: $17,017; $p = .5897$). In comparison to patients receiving buprenorphine plus counseling, those with little or no addiction treatment had significantly greater use of primary care ($p < .001$), other medical visits ($p = .001$), and emergency services ($p = .020$). Patients with counseling only (compared to patients with buprenorphine plus counseling) used less inpatient detoxification ($p < .001$), and had significantly more PC visits ($p = .001$), other medical visits ($p = .005$), and mental health visits ($p =$

.002). Buprenorphine is a viable alternative to other treatment approaches for opioid dependence in commercial integrated health systems, with total costs of health care similar to abstinence-based counseling. Patients with buprenorphine plus counseling had reduced use of general medical services compared to the alternatives.

Oregon's Strategy to Confront Prescription Opioid Misuse: A Case Study McCarty D, Bovett R, Burns T, Cushing J, Glynn ME, Kruse J, Millet LM, Shames J. J Subst Abuse Treat. 2014.
Governor John Kitzhaber appointed a Prescription Drug Taskforce to address Oregon's opioid epidemic. This case study reviews the Taskforce's participation in the National Governors Association State Policy Academy on Reducing Prescription Drug Abuse. To address the challenge of the misuse and abuse of prescription opioids, the Taskforce developed a strategy for practice change, community education and enhanced access to safe opioid disposal using stakeholder meetings, consensus development, and five action steps: (1) fewer pills in circulation, (2) educate prescribers and the public on the risks of opioid use, (3) foster safe disposal of unused medication, (4) provide treatment for opioid dependence, and (5) continued leadership from the Governor, health plans and health professionals. Although the story is ongoing, there are lessons for leadership in other states and for public health and medical practitioners throughout the country.

Comparing the Life Concerns of Prescription Opioid and Heroin Users Stein MD, Anderson BJ, Thurmond P, Bailey GL. J Subst Abuse Treat. 2014.
This study explored life concerns of prescription opioid (PO) and heroin users. Persons entering opioid detoxification rated their level of concern about 43 health and welfare items. Using exploratory factor analysis and conceptual rationale, we identified ten areas of concern. Participants (N=529) were 69.9% male, 87.5% non-Hispanic Caucasian, and 24.2% PO users. Concern about drug problems was perceived as the most serious concern, followed by money problems, relationship problems, mental health, and cigarette smoking. PO users expressed significantly lower concern about drug problems ($p=.017$) and transmissible diseases ($p<.001$), but were more concerned about alcohol use ($p<.001$) than heroin users. There were no significant differences with regard to the other 7 areas of concern. Recognition of the daily worries of opioid dependent persons could allow providers to better tailor their services to the context of their patients' lives.

Screening and Assessment Tools For Measuring Adolescent Client Needs and Functioning in Substance Abuse Treatment Knight DK, Becan JE, Landrum B, Joe GW, Flynn PM. Subst Use Misuse. 2014; 49(7): 902-918.
The purpose of this study is to establish the psychometric properties of a noncommercial, publicly available, modular screening and assessment system for adolescents in substance abuse treatment. Data were collected in 2011-2012 from 1,189 adolescents admitted to eight residential treatment programs in urban and rural locations in the United States. Results from three sets of analyses documented the instruments to be reliable. Females reported more problems than males, and younger adolescents reported more problems than older youth. Implications and limitations are discussed, and suggestions for future research are provided.

Test-retest Reliability of a Self-administered Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) in Primary Care Patients McNeely J, Strauss SM, Wright S, Rotrosen J, Khan R, Lee JD, Gourevitch MN. J Subst Abuse Treat. 2014; 47(1): 93-101.
The time required to conduct drug and alcohol screening has been a major barrier to its implementation in mainstream healthcare settings. Because patient self-administered tools are potentially more efficient, the authors translated the Alcohol, Smoking and Substance Involvement

Screening Test (ASSIST) into an audio guided computer assisted self-interview (ACASI) format. This study reports on the test-retest reliability of the ACASI ASSIST in an adult primary care population. Adult primary care patients completed the ACASI ASSIST, in English or Spanish, twice within a 1-4 week period. Among the 101 participants, there were no significant differences between test administrations in detecting moderate to high risk use for tobacco, alcohol, or any other drug class. Substance risk scores from the two administrations had excellent concordance (90-98%) and high correlation (ICC 0.90-0.97) for tobacco, alcohol, and drugs. The ACASI ASSIST has good test-retest reliability, and warrants additional study to evaluate its validity for detecting unhealthy substance use.

Characterizing Longitudinal Health State Transitions among Heroin, Cocaine, and Methamphetamine Users Nosyk B, Li L, Evans E, Huang D, Min J, Kerr T, Brecht ML, Hser YI. Drug Alcohol Depend. 2014; 140: 69-77.

Of this study was to characterize longitudinal patterns of drug use careers and identify determinants of drug use frequency across cohorts of primary heroin, (MA) and cocaine users. This was a pooled analysis of prospective cohort studies. Participants were Illicit drug users recruited from community, criminal justice and drug treatment settings in California, USA. The authors used longitudinal data on from five observational cohort studies featuring primary users of heroin (N=629), cocaine (N=694) and methamphetamine (N=474). The mean duration of follow-up was 20.9 years. Monthly longitudinal data was arranged according to five health states (incarceration, drug treatment, abstinence, non-daily and daily use). The authors fitted proportional hazards (PH) frailty models to determine independent differences in successive episode durations. They then executed multi-state Markov (MSM) models to estimate probabilities of transitioning between health states, and the determinants of these transitions. Across primary drug use types, PH frailty models demonstrated durations of daily use diminished in successive episodes over time. MSM models revealed primary stimulant users had more erratic longitudinal patterns of drug use, transitioning more rapidly between periods of treatment, abstinence, non-daily and daily use. MA users exhibited relatively longer durations of high-frequency use. Criminal engagement had a destabilizing effect on health state durations across drug types. Longer incarceration histories were associated with delayed transitions toward cessation.PH frailty and MSM modeling techniques provided complementary information on longitudinal patterns of drug abuse. This information can inform clinical practice and policy, and otherwise be used in health economic simulation models, designed to inform resource allocation decisions.

Willingness to Use HIV Pre-Exposure Prophylaxis among Opiate Users Stein M, Thurmond P, Bailey G. AIDS Behav. 2014; 18(9): 1694-1700.

Few studies of pre-exposure prophylaxis (PrEP) to prevent HIV infection have focused on drug users. Between February to September 2013, the authors asked 351 opiate injectors entering detoxification treatment about HIV risk, knowledge about PrEP, and willingness to use a once daily PrEP pill under one of two randomly assigned effectiveness scenarios-40% (low) or 90% (high) effective in reducing HIV risk. Participants were 70% male and 87% non-Hispanic White. Only 7% had heard of a drug to reduce HIV risk, yet once informed, 47% would be willing to take such a pill [35% of those in the low effectiveness scenario and 58% in the high group ($p<0.001$)]. Higher perceived HIV risk was associated with greater willingness to take medication. Increasing knowledge of PrEP and the rate of HIV reduction-effectiveness promised will influence its use among targeted high-risk drug users.

Sleep Disturbances and Pain among Individuals with Prescription Opioid Dependence
Hartwell EE, Pfeifer JG, McCauley JL, Moran-Santa Maria M, Back SE. Addict Behav. 2014; 39(10): 1537-1542.
Poor sleep quality has been observed in individuals with substance use disorders and is often a trigger for relapse. To date, little research has investigated sleep quality among individuals with prescription opioid (PO) dependence. The present study aimed to address this gap in the literature by examining subjective and objective sleep disturbances among PO dependent individuals. Subjects were 68 non-treatment seeking individuals (33 PO dependent, 35 healthy controls). Subjective sleep was assessed with the Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI). Subjects were admitted for an overnight inpatient hospital stay during which objective sleep data was collected using an actigraphy device. Self-report pain was measured with the Brief Pain Inventory. Significant group differences in subjective sleep quality were revealed in the PSQI ($p<0.01$) and ISI ($p<0.01$). Poor sleep quality (i.e., PSQI total score>5) was identified in 80.6% of the PO group, as compared to 8.8% of the control group ($p<.001$). Significant group differences in sleep quality were identified in five of six actigraphy variables: total time asleep, sleep efficiency, latency of onset of sleep, total time awake and time mobile. Furthermore, significant associations between pain severity and sleep quality were observed. Results indicate high rates of sleep impairment and poor sleep quality among PO dependent individuals. Pain severity was significantly correlated with sleep quality. Although preliminary, the findings highlight the importance of assessing and treating sleep disturbances, as well as pain, among patients with PO dependence.

The Relationship between Recovery and Health-related Quality of Life Garner BR, Scott CK, Dennis ML, Funk RR. J Subst Abuse Treat. 2014; 47(4): 293-298.
Building upon recommendations to broaden the conceptualization of recovery and to assess its relationship with health-related quality of life (HRQoL), this study addressed three primary aims. These included: 1) testing the model fit of a hypothesized latent measure of recovery, 2) examining the extent to which this multidimensional measure of recovery was associated with concurrently measured HRQoL, and 3) examining the extent to which this multidimensional measure of recovery predicted changes in HRQoL during the subsequent year. Data were from 1,008 adults who completed follow-up assessments at 15 and 16 years post-intake. Confirmatory factor analysis indicated a good fit for a hypothesized recovery measure (CFI=.98; RMSEA=.06). Additionally, structural equation modeling suggested that this recovery measure was not only concurrently associated with HRQoL ($\beta=.78$, $p<.001$), but was also a significant predictor of changes in HRQoL during the subsequent year ($\beta=.25$, $p<.001$).

Legal Factors Associated with Change in Alcohol Use and Partner Violence among Offenders
Crane CA, Schlauch RC, Hawes SW, Mandel DL, Easton CJ. J Subst Abuse Treat. 2014; 47(2): 151-159.
Intimate partner violence (IPV) is a pervasive social concern that may be exacerbated by high rates of alcohol dependence among perpetrators. Society has attempted to combat IPV through various legal interventions, but the effects of specific legal factors on behavioral change and treatment compliance remain largely unexamined. The primary focus of the current study was to comprehensively evaluate the impact of various legal factors (i.e., judicial mandate, judicial monitoring, stage of change, and stake in conformity) on mandatory treatment compliance and behavioral change over a 12 week post-adjudication period among a high-risk sample of alcohol dependent IPV offenders (N = 60). Growth curve analyses revealed effects of judicial monitoring and stage of change such that participants reporting low perceived judicial monitoring and early

stages of change reported higher initial levels and a more rapid reduction in IPV than those reporting high perceived judicial monitoring and late stages of change, who reported consistently low IPV. Although we found that legal factors were poor predictors of treatment compliance and alcohol use during treatment, the association between alcohol and IPV was moderated by the legal factors. Stake in conformity was negatively associated with IPV among low alcohol users and positively associated among high alcohol users whereas stage of change was negatively associated with IPV among high alcohol users. The current results suggest that pretreatment legal factors may represent an important consideration in reducing IPV among alcohol dependent offenders. Further research is required to determine the efficacy of legal factors in isolation of treatment as well as methods of manipulating these factors to optimally compliment a prescribed course of treatment.

Extended-Release Naltrexone for Alcohol and Opioid Dependence: A Meta-analysis of Healthcare Utilization Studies Hartung DM, McCarty D, Fu R, Wiest K, Chalk M, Gastfriend DR. J Subst Abuse Treat. 2014; 47(2): 113-121.
Through improved adherence, once-monthly injectable extended-release naltrexone (XR-NTX) may provide an advantage over other oral agents approved for alcohol and opioid dependence treatment. The objective of this study was to evaluate cost and utilization outcomes between XR-NTX and other pharmacotherapies for treatment of alcohol and opioid dependence. Published studies were identified through comprehensive search of two electronic databases. Studies were included if they compared XR-NTX to other approved medicines and reported economic and healthcare utilization outcomes in patients with opioid or alcohol dependence. The authors identified five observational studies comparing 1,565 patients using XR-NTX to other therapies over 6 months. Alcohol dependent XR-NTX patients had longer medication refill persistence versus acamprosate and oral naltrexone. Healthcare utilization and costs was generally lower or as low for XR-NTX-treated patients relative to other alcohol dependence agents. Opioid dependent XR-NTX patients had lower inpatient substance abuse-related utilization versus other agents and $8170 lower total cost versus methadone.

Aberrant Drug-Related Behaviors: A Qualitative Analysis of Medical Record Documentation in Patients Referred to an HIV/Chronic Pain Clinic Merlin JS, Turan JM, Herbey I, Westfall AO, Starrels JL, Kertesz SG, Saag MS, Ritchie CS. Pain Med. 2014.
Due to rising rates of opioid addiction and overdose among individuals on chronic opioid therapy, aberrant drug-related behaviors (ADRBs) are an important and challenging issue. The authors' objective was to qualitatively investigate the documentation of ADRBs in the medical record. Manually abstracted provider notes from an HIV primary care clinic were analyzed using content analysis methods. Categories of ADRBs identified included patients requesting opioids, obtaining non-prescribed opioids, and becoming emotional about opioids. The authors also identified several types of provider language used when documenting ADRBs, including purely descriptive language and emotional language such as labeling, frustration, and concern, and responses such as setting conditions for opioid prescription and action-oriented language. The impact of including emotional language in the medical record is unknown. Development of instruments that can be used to facilitate ADRB documentation, as well as evidence-based approaches to addressing ADRBs, is needed.

Parenting and Concerns of Pregnant Women in Buprenorphine Treatment Rizzo RA, Neumann AM, King SOC, Hoey, RF; Finnell DS, Blondell RD. MCN Am J Matern Child Nurs. 2014; 39(5): 319-324.
Opioid-dependent pregnant women are characterized by drug use during pregnancy and deficits in knowledge of newborn care and feeding, and of child development. The authors assessed parenting skills and concerns among pregnant women in buprenorphine treatment for prescription opioid dependence. They interviewed 32 pregnant women who received buprenorphine treatment for prescription opioid dependence in a primary care setting and administered questionnaires, including the Adult-Adolescent Parenting Inventory version 2 (AAPI-2) and Childhood Experience of Care and Abuse Questionnaire.AAPI-2 scores revealed medium risk of abuse for all five scales: inappropriate expectations of the child, low level of empathy, strong belief in corporal punishment, reversal of parent-child roles, and oppression of children's power and independence. Primary concerns of participants were neonatal abstinence syndrome (NAS) and their child's health. Pregnant women who received buprenorphine for treatment of prescription opioid dependence showed a lack of appropriate parenting skills, but did not express concern about their ability to parent. These findings suggest a need for nurses to assist prescription opioid-dependent pregnant women in acquiring additional parenting skills, to refer for educational parenting intervention, and to educate patients about NAS.

Effect of the Affordable Care Act's Young Adult Insurance Expansions on Hospital-Based Mental Health Care Golberstein E, Busch SH, Zaha R, Greenfield SF, Beardslee WR, Meara E. Am J Psychiatry. 2014.
Insurance coverage for young adults has increased since 2010, when the Affordable Care Act (ACA) required insurers to permit children to remain on parental policies until age 26 as dependents. This study estimated the association between the dependent coverage provision and changes in young adults' use of hospital-based services for substance use disorders and non-substance use psychiatric disorders. The authors conducted a quasi-experimental comparison of a national sample of non-childbirth-related inpatient admissions to general hospitals (a total of 2,670,463 admissions, 430,583 of which had primary psychiatric diagnoses) and California emergency department visits with psychiatric diagnoses (N=11,139,689), using data spanning 2005 to 2011. Analyses compared young adults who were targeted by the ACA dependent coverage provision (19- to 25-year-olds) and those who were not (26- to 29-year-olds), estimating changes in utilization before and after implementation of the dependent coverage provision. Primary outcome measures included quarterly inpatient admissions for primary diagnoses of any psychiatric disorder per 1,000 populations; emergency department visits with any psychiatric diagnosis per 1,000 populations; and payer source. Dependent coverage expansion was associated with 0.14 more inpatient admissions for psychiatric diagnoses per 1,000 for 19- to 25-year-olds (targeted by the ACA) than for 26- to 29-year-olds (not targeted by the ACA). The coverage expansion was associated with 0.45 fewer psychiatric emergency department visits per 1,000 in California. The probability that inpatient admissions nationally and emergency department visits in California were uninsured decreased significantly. ACA dependent coverage provisions produced modest increases in general hospital psychiatric inpatient admissions and higher rates of insurance coverage for young adults nationally. Lower rates of emergency department visits were observed in California.

CLINICAL TRIALS NETWORK-RELATED RESEARCH

Brief Intervention for Patients With Problematic Drug Use Presenting in Emergency Departments: A Randomized Clinical Trial. Bogenschutz MP, Donovan DM, Mandler RN, Perl HI, Forcehimes AA, Crandall C, Lindblad R, Oden NL, Sharma G, Metsch L, Lyons MS, McCormack R, Konstantopoulos WM, Douaihy A. JAMA Intern Med. 2014 Nov 1;174(11):1736-1745.

Medical treatment settings such as emergency departments (EDs) present important opportunities to address problematic substance use. Currently, EDs do not typically intervene beyond acute medical stabilization. The objective of this study was to contrast the effects of a brief intervention with telephone boosters (BI-B) with those of screening, assessment, and referral to treatment (SAR) and minimal screening only (MSO) among drug-using ED patients. Between October 2010 and February 2012, 1285 adult ED patients from 6 US academic hospitals, who scored 3 or greater on the 10-item Drug Abuse Screening Test (indicating moderate to severe problems related to drug use) and who were currently using drugs, were randomized to MSO (n=431), SAR (n=427), or BI-B (n=427). Follow-up assessments were conducted at 3, 6, and 12 months by blinded interviewers. Following screening, MSO participants received only an informational pamphlet. The SAR participants received assessment plus referral to addiction treatment if indicated, and the BI-B participants received assessment and referral as in SAR, plus a manual-guided counseling session based on motivational interviewing principles and up to 2 "booster" sessions by telephone during the month following the ED visit. Outcomes evaluated at follow-up visits included self-reported days using the patient-defined primary problem drug, days using any drug, days of heavy drinking, and drug use based on analysis of hair samples. The primary outcome was self-reported days of use of the patient-defined primary problem drug during the 30-day period preceding the 3-month follow-up. Follow-up rates were 89%, 86%, and 81% at 3, 6, and 12 months, respectively. For the primary outcome, estimated differences in number of days of use (95% CI) were as follows: MSO vs BI-B, 0.72 (-0.80 to 2.24), P (adjusted)=.57; SAR vs BI-B, 0.70 (-0.83 to 2.23), P (adjusted).57; SAR vs MSO, -0.02 (-1.53 to 1.50), P (adjusted)=.98. There were no significant differences between groups in self-reported days using the primary drug, days using any drug, or heavy drinking days at 3, 6, or 12 months. At the 3-month follow-up, participants in the SAR group had a higher rate of hair samples positive for their primary drug of abuse (265 of 280 [95%]) than did participants in the MSO group (253 of 287 [88%]) or the BI-B group (244 of 275 [89%]). Hair analysis differences between groups at other time points were not significant. In this sample of drug users seeking emergency medical treatment, a relatively robust brief intervention did not improve substance use outcomes. More work is needed to determine how drug use disorders may be addressed effectively in the ED. Trial Registration: clinicaltrials.gov Identifier: NCT01207791.

The Multi-site Prescription Opioid Addiction Treatment Study: 18-month Outcomes Potter JS, Dreifuss JA, Marino EN, Provost SE, Dodd DR, Rice LS, Fitzmaurice GM, Griffin ML, Weiss RD. J Subst Abuse Treat. 2015 Jan;48(1):62-69. Epub 2014 Aug 2.

Despite the high prevalence of prescription opioid dependence in the U.S., little is known about the course of this disorder and long-term response to treatment. The authors therefore examined 18-month post-randomization outcomes of participants in the Prescription Opioid Addiction Treatment Study, a multi-site, randomized controlled trial examining varying durations of buprenorphine-naloxone treatment and different intensities of counseling for prescription opioid dependence. Thus the current follow-up study provides a unique contribution to the field by reporting longer-term outcomes of a well-characterized population of treatment-seeking prescription opioid dependent patients. Participants from the treatment trial (N=252/653) completed an 18-month follow-up

telephone assessment. Multivariable analyses examined associations between participant characteristics and key indicators of month-18 status: opioid abstinence, DSM-IV opioid dependence, and opioid agonist treatment. Overall, participants showed improvement from baseline to month 18: 49.6% were abstinent in the previous 30days, with only 16.3% opioid-dependent. Some participants, however, had initiated past-year heroin use (n=9) or opioid injection (n=17). Most participants (65.9%) engaged in substance use disorder treatment during the past year, most commonly opioid agonist therapy (48.8%). Of particular interest in this population, multivariable analysis showed that greater pain severity at baseline was associated with opioid dependence at 18months. In conclusion, although opioid use outcomes during the treatment trial were poor immediately following a buprenorphine-naloxone taper compared to those during 12 weeks of buprenorphine-naloxone stabilization, opioid use outcomes at 18-month follow-up showed substantial improvement over baseline and were comparable to the rate of successful outcomes during buprenorphine-naloxone stabilization in the treatment trial.

Cost-effectiveness of Rapid HCV Testing and Simultaneous Rapid HCV and HIV Testing in Substance Abuse Treatment Programs Schackman BR, Leff JA, Barter DM, DiLorenzo MA, Feaster DJ, Metsch LR, Freedberg KA, Linas BP. Addiction. 2014 Oct 8. [Epub ahead of print].
He ais of this study were to evaluate the cost-effectiveness of rapid hepatitis C virus (HCV) and simultaneous HCV/HIV antibody testing in substance abuse treatment programs. The authors used a decision analytic model to compare the cost-effectiveness of no HCV testing referral or offer, off-site HCV testing referral, on-site rapid HCV testing offer, and on-site rapid HCV and HIV testing offer. Base case inputs included 11% undetected chronic HCV, 0.4% undetected HIV, 35% HCV co-infection among HIV-infected, 53% linked to HCV care after testing antibody positive, and 67% linked to HIV care. Disease outcomes were estimated from established computer simulation models of HCV (HEP-CE) and HIV (CEPAC). Data on test acceptance and costs were from a national randomized trial of HIV testing strategies conducted at 12 substance abuse treatment programs in the USA. Mearures obtained included lifetime costs (2011 US dollars) and quality-adjusted life years (QALYs) discounted at 3% annually; incremental cost-effectiveness ratios (ICERs) On-site rapid HCV testing had an ICER of $18,300/QALY compared with no testing, and was more efficient than (dominated) off-site HCV testing referral. On-site rapid HCV and HIV testing had an ICER of $64,500/QALY compared with on-site rapid HCV testing alone. In one and two-way sensitivity analyses, the ICER of on-site rapid HCV and HIV testing remained <$100,000/QALY, except when undetected HIV prevalence was <0.1% or when we assumed frequent HIV testing elsewhere. The ICER remained <$100,000/QALY in approximately 90% of probabilistic sensitivity analyses. On-site rapid hepatitis C virus and HIV testing in substance abuse treatment programs is cost-effective at a <$100,000/ quality-adjusted life years threshold.

Uptake of HIV Testing in Substance Use Disorder Treatment Programs That Offer On-Site Testing. Kyle TL, Horigian VE, Tross S, Gruber VA, Pereyra M, Mandler RN, Feaster DJ, Metsch LR. AIDS Behav. 2014 Jul 30. [Epub ahead of print].
Increasing rates of HIV testing within substance use disorder (SUD) treatment clients is an important public health strategy for reducing HIV transmission rates. The present study examined uptake of HIV testing among 1,224 clients in five SUD treatment units that offered on-site testing in Florida, New York, and California. Nearly one-third (30 %) of the participants, who had not previously tested positive, reported not having been tested for HIV within the past 12 months. Women, African Americans, and injection drug users had a higher likelihood of having been tested within the past 12 months. The SUD treatment program was the most frequently identified location of participants' last HIV test. Despite the availability of free, on-site testing, a substantial proportion

of clients were not tested, suggesting that strategies to increase uptake of testing should include addressing barriers not limited to location and cost.

A 'Missing Not at Random' (MNAR) and 'Missing at Random' (MAR) Growth Model Comparison with a Buprenorphine/Naloxone Clinical Trial McPherson S, Barbosa-Leiker C, Mamey MR, McDonell M, Enders CK, Roll J. Addiction. 2015 Jan;110(1):51-8. Epub 2014 Oct 16.

The aims of this study were to compare three missing data strategies: 1) Latent growth model that assumes the data are missing at random (MAR) model, 2) Diggle-Kenward missing not at random (MNAR) model where dropout is a function of previous/concurrent urinalysis (UA) submissions, and 3) Wu-Carroll MNAR model where dropout is a function of the growth factors.

This was a secondary data analysis of a National Drug Abuse Treatment Clinical Trials Network trial that examined a 7-day versus 28-day taper (i.e., stepwise decrease in buprenorphine/ naloxone) on the likelihood of submitting an opioid-positive UA during treatment, The study setting comprised 11 outpatient treatment settings in 10 US cities and examined 516 opioid dependent participants. Measurements taken were opioid UAs provided across the 4-week treatment period. The MAR model showed a significant effect (B=-0.45, $p < 0.05$) of trial arm on the opioid-positive UA slope (i.e., 28-day taper participants were less likely to submit a positive UA over time) with a small effect size (d=0.20). The MNAR Diggle-Kenward model demonstrated a significant (B=-0.64, $p<0.01$) effect of trial arm on the slope with a large effect size (d=0.82). The MNAR Wu-Carroll model evidenced a significant (B=-0.41, $p<0.05$) effect of trial arm on the UA slope that was relatively small (d=0.31). This performance comparison of three missing data strategies (latent growth model, Diggle-Kenward selection model, Wu-Carrol selection model) on sample data indicates a need for increased use of sensitivity analyses in clinical trial research. Given the potential sensitivity of the trial arm effect to missing data assumptions, it is critical for researchers to consider whether the assumptions associated with each model are defensible.

Opioid Withdrawal, Craving, and Use During and After Outpatient Buprenorphine Stabilization and Taper: A Discrete Survival and Growth Mixture Model. Northrup TF, Stotts AL, Green C, Potter JS, Marino EN, Walker R, Weiss RD, Trivedi M. Addict Behav. 2015 Feb;41:20-8. Epub 2014 Sep 28.

Most patients relapse to opioids within one month of opioid agonist detoxification, making the antecedents and parallel processes of first use critical for investigation. Craving and withdrawal are often studied in relationship to opioid outcomes, and a novel analytic strategy applied to these two phenomena may indicate targeted intervention strategies. Specifically, this secondary data analysis of the Prescription Opioid Addiction Treatment Study used a discrete-time mixture analysis with time-to-first opioid use (survival) simultaneously predicted by craving and withdrawal growth trajectories. This analysis characterized heterogeneity among prescription opioid-dependent individuals (N=653) into latent classes (i.e., latent class analysis [LCA]) during and after buprenorphine/naloxone stabilization and taper. A 4-latent class solution was selected for overall model fit and clinical parsimony. In order of shortest to longest time-to-first use, the 4 classes were characterized as 1) high craving and withdrawal, 2) intermediate craving and withdrawal, 3) high initial craving with low craving and withdrawal trajectories and 4) a low initial craving with low craving and withdrawal trajectories. Odds ratio calculations showed statistically significant differences in time-to-first use across classes. Generally, participants with lower baseline levels and greater decreases in craving and withdrawal during stabilization combined with slower craving and withdrawal rebound during buprenorphine taper remained opioid-free longer. This exploratory work expanded on the importance of monitoring craving and withdrawal during buprenorphine induction,

stabilization, and taper. Future research may allow individually tailored and timely interventions to be developed to extend time-to-first opioid use.

Denial of Urinalysis-confirmed Opioid Use in Prescription Opioid Dependence. Hilario EY, Griffin ML, McHugh RK, McDermott KA, Connery HS, Fitzmaurice GM, Weiss RD. J Subst Abuse Treat. 2015 Jan;48(1):85-90. Epub 2014 Jul 18.
Although research has generally supported the validity of substance use self-reports, some patients deny urine-verified substance use. The authors examined the prevalence and patterns of denying urinalysis-confirmed opioid use in a sample of prescription opioid dependent patients. They also identified characteristics associated with denial in this population of increasing public health concern. Opioid use self-reports were compared with weekly urinalysis results in a 12-week multi-site treatment study for prescription opioid dependence. Among those who used opioids during the trial (n=246/360), 44.3% (n=109) denied urinalysis-confirmed opioid use, although usually only once (78%). Overall, 22.9% of opioid-positive urine tests (149/650) were denied on self-report. Multivariable analysis found that initially using opioids to relieve pain was associated with denying opioid use. These findings support the use of both self-reports and urine testing in treating prescription opioid dependence.

Association between Hepatitis C Virus and Opioid Use while in Buprenorphine Treatment: Preliminary Findings Murphy SM, Dweik D, McPherson S, Roll JM. Am J Drug Alcohol Abuse. 2015 Jan;41(1):88-92.
The prevalence of hepatitis-C-virus (HCV) infections is high among opioid-dependent individuals. Prior research on the simultaneous treatment of both conditions has primarily assessed success as it pertains to HCV. However, it has been noted that favorable substance use therapy outcomes may improve the likelihood of HCV-treatment initiation and success. Therefore, current guidelines for the treatment of HCV among illicit drug users suggest that treatment for addiction be given the highest priority. The objectives of this study were to determine whether opioid-dependent participants in a clinical trial of buprenorphine-treatment tapering regimens, who tested positive for the HCV antibody, experienced significantly different levels of opioid abstinence than those not infected. Data came from the National Drug Abuse Treatment Clinical Trial Network study 0003. 516 eligible opioid-dependent participants were randomized to either a 7-day or 28-day buprenorphine tapering schedule following a 4-week buprenorphine stabilization period. Generalized estimating equations were used to test the research question. Participants with the HCV antibody were significantly less likely to submit opioid-negative urine analyses during and/or immediately following active treatment [OR=0.69; CI=0.51-0.93], indicating a higher rate of opioid use among this group. Individualized opioid-dependence treatment strategies may be required for opioid-dependent individuals who test positive for the HCV antibody in order to ensure resources for both opioid-dependence and HCV therapies are used efficiently.

Assessing Craving and Its Relationship to Subsequent Prescription Opioid Use among Treatment-seeking Prescription Opioid Dependent Patients. McHugh RK, Fitzmaurice GM, Carroll KM, Griffin ML, Hill KP, Wasan AD, Weiss RD. Drug Alcohol Depend. 2014 Dec 1;145:121-6. Epub 2014 Oct 16.
Craving is viewed as a core feature of substance use disorders and has been shown to predict future drug use, particularly over the short term. Accordingly, craving is often assessed in treatment settings as a marker of risk for subsequent drug use. The identification of the briefest measure that maintains predictive validity is of particular value for both clinical and research settings to minimize assessment burden while maintaining utility for the prediction of use.

Data from a multi-site clinical trial of treatment for prescription opioid dependence were examined to evaluate whether a brief, 3-item craving scale administered each week predicted urine-confirmed self report of prescription opioid use in the subsequent week. Logistic regression models examining the association between craving and presence or absence of opioid use in the following week were conducted, controlling for opioid use in the previous week, treatment condition, and lifetime history of heroin use. Greater craving was associated with a higher odds of prescription opioid use in the following week. For each one-unit increase on this 10-point scale, the odds of using opioids in the subsequent week was 17% higher. In addition to an item assessing urges, items assessing cue-induced craving and perceived likelihood of relapse in an environment where drugs were previously used contributed uniquely to this association.
A brief measure of prescription opioid craving predicted prescription opioid use among individuals in treatment. This measure offers an efficient strategy to inform the assessment of risk for use in this population.

Self-rated Measure of Pain Frequency, Intensity, and Burden: Psychometric Properties of a New Instrument for the Assessment of Pain Dela Cruz AM, Bernstein IH, Greer TL, Walker R, Rethorst CD, Grannemann B, Carmody T, Trivedi MH. J Psychiatr Res. 2014 Dec;59:155-60. Epub 2014 Aug 27.
A brief, self-administered measurement of pain frequency, intensity, and burden is desirable in both research and clinical settings. The authors describe the development and initial psychometric properties of a new instrument, the Pain Frequency, Intensity, and Burden Scale (P-FIBS). The P-FIBS was administered to all participants (N = 302) with psychostimulant use disorders in the National Institute on Drug Abuse Clinical Trials Network's STRIDE (Stimulant Reduction Intervention using Dose Exercise) multisite trial. The four items on the P-FIBS demonstrate high item-total correlations (range 0.70-0.85) with a high Cronbach's alpha (0.90). The P-FIBS demonstrated a strong negative correlation with the bodily pain sub-score of the Short Form Health Survey ($r = -0.76$, $p < 0.0001$) and did not correlate with a measure of cocaine ($r = 0.09$, $p = 0.12$) or methamphetamine ($r = -0.06$, $p = 0.33$) craving. The P-FIBS demonstrates good psychometric properties. This brief measure can be used to assess pain in research settings or as a screen in clinical settings. Further research is needed to assess the measure's sensitivity to change with treatment.

Applying an Ensemble Classification Tree Approach to the Prediction of Completion of a 12-Step Facilitation Intervention With Stimulant Abusers Doyle SR, Donovan DM. Psychol Addict Behav. 2014 Dec;28(4):1127-43. Epub 2014 Aug 18.
The purpose of this study was to explore the selection of predictor variables in the evaluation of drug treatment completion using an ensemble approach with classification trees. The basic methodology is reviewed, and the subagging procedure of random subsampling is applied. Among 234 individuals with stimulant use disorders randomized to a 12-step facilitative intervention shown to increase stimulant use abstinence, 67.52% were classified as treatment completers. A total of 122 baseline variables were used to identify factors associated with completion. The number of types of self-help activity involvement prior to treatment was the predominant predictor. Other effective predictors included better coping self-efficacy for substance use in high-risk situations, more days of prior meeting attendance, greater acceptance of the Disease model, higher confidence for not resuming use following discharge, lower Addiction Severity Index (ASI) Drug and Alcohol composite scores, negative urine screens for cocaine or marijuana, and fewer employment problems. The application of an ensemble subsampling regression tree method utilizes the fact that classification trees are unstable but, on average, produce an improved prediction of the completion

of drug abuse treatment. The results support the notion there are early indicators of treatment completion that may allow for modification of approaches more tailored to fitting the needs of individuals and potentially provide more successful treatment engagement and improved outcomes.

Patient Perspectives on Buprenorphine/Naloxone: A Qualitative Study of Retention During the Starting Treatment with Agonist Replacement Therapies (START) Study Teruya C, Schwartz RP, Mitchell SG, Hasson AL, Thomas C, Buoncristiani SH, Hser YI, Wiest K, Cohen AJ, Glick N, Jacobs P, McLaughlin P, Ling W. J Psychoactive Drugs. 2014 November-December;46(5):412-426.

This study examines the barriers and facilitators of retention among patients receiving buprenorphine/naloxone at eight community-based opioid treatment programs across the United States. Participants (n = 105) were recruited up to three and a half years after having participated in a randomized clinical trial comparing the effect of buprenorphine/naloxone and methadone on liver function. Semi-structured interviews were conducted with 67 patients provided with buprenorphine/naloxone who had terminated early and 38 patients who had completed at least 24 weeks of the trial. Qualitative data were analyzed using the constant comparison method. Barriers to buprenorphine/naloxone retention that emerged included factors associated with: (1) the design of the clinical trial; (2) negative medication or treatment experience; and (3) personal circumstances. The facilitators comprised: (1) positive experience with the medication; (2) personal determination and commitment to complete; and (3) staff encouragement and support. The themes drawn from interviews highlight the importance of considering patients' prior experience with buprenorphine/naloxone and methadone, medication preference, personal circumstances, and motivation to abstain from illicit use or misuse of opioids, as these may influence retention. Ongoing education of patients and staff regarding buprenorphine/naloxone, especially in comparison to methadone, and support from staff and peers are essential.

Lessons Learned for Follow-up Phone Booster Counseling Calls with Substance Abusing Emergency Department Patients Donovan DM, Hatch-Maillette MA, Phares MM, McGarry E, Peavy KM, Taborsky JJ Subst Abuse Treat. 2014 Nov 5. pii: S0740-5472(14)00224-4. [Epub ahead of print].

Post-visit "booster" sessions have been recommended to augment the impact of brief interventions delivered in the Emergency Department (ED). This paper, which focuses on implementation issues, presents descriptive information and interventionists' qualitative perspectives on providing brief interventions over the phone, challenges, "lessons learned", and recommendations for others attempting to implement adjunctive booster calls. Attempts were made to complete two 20-minute telephone "booster" calls within a week following a patient's ED discharge with 425 patients who screened positive for and had recent problematic substance use other than alcohol or nicotine. Over half (56.2%) of participants completed the initial call; 66.9% of those who received the initial call also completed the second call. Median number of attempts to successfully contact participants for the first and second calls was 4 and 3, respectively. Each completed call lasted an average of about 22 minutes. Common challenges/ barriers identified by booster callers included unstable housing, limited phone access, unavailability due to additional treatment, lack of compensation for booster calls, and booster calls coming from an area code different than the participants' locale and from someone other than ED staff. Specific recommendations are presented with respect to implementing a successful centralized adjunctive booster call system. Future use of booster calls might be informed by research on contingency management (e.g., incentivizing call completions), smoking cessation quitlines, and phone-based continuing care for substance abuse patients. Future research

needs to evaluate the incremental benefit of adjunctive booster calls on outcomes over and above that of brief motivational interventions delivered in the ED setting.

Client and Provider Views on Access to Care for Substance-using American Indians: Perspectives from a Northern Plains Urban Clinic Kropp F, Lilleskov M, Richards J, Somoza E, On Behalf Of The CTN0033-Ot-4 Team. Am Indian Alsk Native Ment Health Res. 2014;21(2):43-65.
In addition to disparities in rates of substance use problems, American Indians (AIs) report multiple barriers to receiving treatment services. The present study utilized intake questionnaire data and focus groups to gain perspectives from 152 clients (65% male, 35% female; mean age 30 years) and 6 female providers on access to treatment for Northern Plains AIs in an urban, non-Native program. AI clients acknowledged the need for treatment more often than did substance users in general, but faced greater resource barriers. Both clients and providers offered specific recommendations for improving access to substance use treatment for AI populations in the Northern Plains.

Achieving Cannabis Cessation - Evaluating N-acetylcysteine Treatment (ACCENT): Design and Implementation of a Multi-site, Randomized Controlled Study in the National Institute on Drug Abuse Clinical Trials Network McClure EA, Sonne SC, Winhusen T, Carroll KM, Ghitza UE, McRae-Clark AL, Matthews AG, Sharma G, Van Veldhuisen P, Vandrey RG, Levin FR, Weiss RD, Lindblad R, Allen C, Mooney LJ, Haynes L, Brigham GS, Sparenborg S, Hasson AL, Gray KM. Contemp Clin Trials. 2014 Nov;39(2):211-23. Epub 2014 Aug 30.
Despite recent advances in behavioral interventions for cannabis use disorders, effect sizes remain modest, and few individuals achieve long-term abstinence. One strategy to enhance outcomes is the addition of pharmacotherapy to complement behavioral treatment, but to date no efficacious medications targeting cannabis use disorders in adults through large, randomized controlled trials have been identified. The National Institute on Drug Abuse Clinical Trials Network (NIDA CTN) is currently conducting a study to test the efficacy of N-acetylcysteine (NAC) versus placebo (PBO), added to contingency management, for cannabis cessation in adults (ages 18-50). This study was designed to replicate positive findings from a study in cannabis-dependent adolescents that found greater odds of abstinence with NAC compared to PBO. This paper describes the design and implementation of an ongoing 12-week, intent-to-treat, double-blind, randomized, placebo-controlled study with one follow-up visit four weeks post-treatment. Approximately 300 treatment-seeking cannabis-dependent adults will be randomized to NAC or PBO across six study sites in the United States. The primary objective of this 12-week study is to evaluate the efficacy of twice-daily orally-administered NAC (1200mg) versus matched PBO, added to contingency management, on cannabis abstinence. NAC is among the first medications to demonstrate increased odds of abstinence in a randomized controlled study among cannabis users in any age group. The current study will assess the cannabis cessation efficacy of NAC combined with a behavioral intervention in adults, providing a novel and timely contribution to the evidence base for the treatment of cannabis use disorders.

The Relationship of Therapeutic Alliance and Treatment Delivery Fidelity With Treatment Retention in a Multisite Trial of Twelve-Step Facilitation Campbell BK, Guydish J, Le T, Wells EA, McCarty D. Psychol Addict Behav. 2014 Aug 18. [Epub ahead of print].
This study examined associations of therapeutic alliance and treatment delivery fidelity with treatment retention in Stimulant Abusers to Engage in Twelve-Step (STAGE-12), a community-based trial of 12-Step Facilitation (TSF) conducted within the National Drug Abuse Treatment Clinical Trials Network (CTN). The STAGE-12 trial randomized 234 stimulant abusers enrolled in

10 outpatient drug treatment programs to an eight-session, group and individual TSF intervention. During the study, TSF participants rated therapeutic alliance using the Helping Alliance questionnaire-II. After the study, independent raters evaluated treatment delivery fidelity of all TSF sessions on adherence, competence, and therapist empathy. Poisson regression modeling examined relationships of treatment delivery fidelity and therapeutic alliance with treatment retention (measured by number of sessions attended) for 174 participants with complete fidelity and alliance data. Therapeutic alliance ($p = .005$) and therapist competence ($p = .010$) were significantly associated with better treatment retention. Therapist adherence was associated with poorer retention in a nonsignificant trend ($p = .061$). In conclusion, stronger therapeutic alliance and higher therapist competence in the delivery of a TSF intervention were associated with better treatment retention whereas treatment adherence was not. Training and fidelity monitoring of TSF should focus on general therapist skills and therapeutic alliance development to maximize treatment retention.

Total Antioxidant Capacity is Significantly Lower in Cocaine-dependent and Methamphetamine-dependent Patients Relative to Normal Controls: Results from a Preliminary Study Walker J, Winhusen T, Storkson JM, Lewis D, Pariza MW, Somoza E, Somoza V. Hum Psychopharmacol. 2014 Aug 4. [Epub ahead of print].

Oxidative stress can result in damage to the brain and other organs. To protect from oxidative damage, the human body possesses molecular defense systems, based on the activity of antioxidants, and enzymatic defense systems, including the enzymes catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px). Although pre-clinical research has shown that stimulant use is associated with oxidative damage, oxidative stress and the antioxidant defense systems have not been evaluated in clinical samples of stimulant-dependent patients. This study aimed to investigate the link between stimulant dependence and oxidative stress. Peripheral blood samples from 174 methamphetamine (n=48) and/or cocaine-dependent (n=126) participants as well as 30 normal control participants were analyzed for the enzyme activities of CAT, SOD, and GSH-Px in the erythrocytes and the total antioxidant capacity and the malondialdehyde concentration in the plasma. The authors could show an association of stimulant dependence with a depletion of total antioxidant capacity to 54.6±4.7%, which correlates with a reduced activity of the SOD to 71.3±0.03% compared with healthy control participants (100%). Stimulant-dependent patients had significantly lower antioxidant capacity relative to controls, suggesting that they may be at greater risk for oxidative damage to the brain and other organs.

Characteristics of Mexican and Mexican American Adolescents in Treatment for "Cheese" Heroin Use Walker R, Maxwell JC, Adinoff B, Carmody T, Coton CE, Tirado CF. J Ethn Subst Abuse. 2014;13(3):258-272.

Clinical and cultural characteristics of Hispanic adolescent heroin users are not well described. The current exploratory study was conducted to describe a sample of in-treatment Hispanic adolescents with opioid dependence, specifically, cheese heroin. Mexican and Mexican American adolescents with heroin dependence (N = 72) in three treatment programs were interviewed and completed self-report measures. Participants reported, on average, first using cheese heroin at age 13.5 years and daily use at age 14.2 years. The majority (74%) reported a previous overdose. Adolescents being raised by caregivers other than both biological parents, who used drugs with relatives, and whose immediate family members have documentation to be in the United States fared worse on several indicators of drug use severity and other risky behaviors. The self-reported brief time period from first use to daily use strongly suggests the need for early prevention efforts. Additional research is needed to add to these preliminary results and inform prevention efforts.

WOMEN & GENDER DIFFERENCES RESEARCH

Gender Differences in Clinical Outcomes for Cocaine Dependence: Randomized Clinical Trials of Behavioral Therapy and Disulfiram DeVito EE, Babuscio TA, Nich C, Ball SA, Carroll KM. Drug and Alcohol Dependence. 2014; 145, 156-167.

Despite extensive research on gender differences in addiction, there are relatively few published reports comparing treatment outcomes for women versus men based on evidence-based treatments evaluated in randomized clinical trials. An aggregate sample comprised of data from five randomized clinical trials of treatment for cocaine dependence (N = 434) was evaluated for gender differences in clinical outcomes. Secondary analyses compared gender differences in outcome by medication condition (disulfiram versus no medication) and across multiple behavioral treatment conditions. Women, compared with men, had poorer treatment outcomes on multiple measures of cocaine use during treatment and at post-treatment follow-up. These results appear to be primarily accounted for by disulfiram being less effective in women compared with men. There was no evidence of meaningful gender differences in outcome as a function of the behavioral therapies evaluated. These findings suggest that women and men may benefit to similar degrees from some empirically validated behavioral treatments for addiction. Conversely, some addiction pharmacotherapies, such as disulfiram, may be associated with poorer outcomes among women relative to men and point to the need for careful assessment of pharmacological treatments in both sexes prior to widespread clinical implementation.

The Effect of Combination Oral Contraceptives on Smoking-related Symptomatology during Short-term Smoking Abstinence Hinderaker K, Allen AM, Tosun N, al'Absi M, Hatsukami D, Allen SS. Addict Behav. 2014 Oct 23; [Epub ahead of print].

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

Sexual Orientation, Adult Connectedness, Substance Use, and Mental Health Outcomes Among Adolescents: Findings From the 2009 New York City Youth Risk Behavior Survey

Seil KS, Desai MM, Smith MV. Am J Public Health. 2014 Oct; 104(10):1950-1956.

The authors examined associations between identifying as lesbian, gay, or bisexual (LGB) and lacking a connection with an adult at school on adolescent substance use and mental health outcomes including suicidality. Methods: They analyzed data from the 2009 New York City Youth Risk Behavior Survey (n=8910). Outcomes of interest included alcohol use, marijuana use, illicit drug use, depressive symptomatology, suicide ideation, and suicide attempt. The prevalence of each outcome was significantly higher among LGB adolescents than heterosexual adolescents and among those who lacked an adult connection at school than among those who did have such a connection. Even when LGB adolescents had an adult connection at school, their odds of most outcomes were significantly higher than for heterosexual adolescents. Those LGB adolescents who lacked a school adult connection had the poorest outcomes (about 45% reported suicide ideation; 31% suicide attempt). The authors conclude that adolescents who are LGB, particularly those who lack a connection with school adults, are at high risk for substance use and poorer mental health outcomes. Interventions should focus on boosting social support and improving outcomes for this vulnerable group.

Gender Differences in the Impact of Stressful Life Events on Changes in Body Mass Index

Udo T, Grilo CM, McKee SA. Prev Med. 2014 Sep 7; 69C:49-53.

The positive association between stress and weight has been consistently demonstrated, particularly in women. The effect of stress on changes in weight, however, is less clear. A total of 33,425 participants in Wave 1 and Wave 2 surveys of the National Epidemiologic Survey on Alcohol and Related Condition (NESARC) were included in this study. The study examined the relationship between stressful life events during the 12months prior to the Wave 2 interview and changes in body mass index (BMI) between Wave 1 and Wave 2 interviews. Women reported significantly greater increases in BMI than men. Stressful life events, particularly job-related changes, legal problems, and death of family or friends, were associated significantly with increases in BMI among women but not men. In a nationally representative sample, stressful life events were associated with greater weight gain in women. Prevention of weight gain in women should focus on the behavioral and physiological mechanisms underlying female-specific effects of stressful l

SCIENCE POLICY AND COMMUNICATIONS RESEARCH

The Impact of Science Education Games on Prescription Drug Abuse Attitudes Among Teens: A Case Study Klisch Y, Bowling KG, Miller LM, Ramos MA, Journal of Drug Education 2014; 43(3): 255-275.
Two online science education games, in which players learn about the risks of prescription drug abuse in the context of investigating crimes, were evaluated to determine shifts of prescription drug abuse attitudes attributable to game exposure. High school students from grades 11 and 12 (n = 179) were assigned to one of the games and participated in a pretest, two game-play sessions, and a delayed posttest. Students in both groups demonstrated more negative attitudes toward prescription drug abuse after playing the game, driven by changes of students' normative beliefs and their ability to make the connection between prescription drug abuse and illicit drugs. A secondary aim was to assess gains in science knowledge; however, due to low internal consistency reliabilities of content measures, students' knowledge acquisition could not be determined.

Explain the Brain: Websites to Help Scientists Teach Neuroscience to the General Public Chudler EH, Bergsman KC, CBE-Life Science Education 2014; 13: 577-583.
This Feature showcases Internet-based resources to help neuroscientists explain their work to the general public and K12 audiences. These Internet resources feature videos, images, animations, and other outreach tools that are accessible to lay audiences and that speakers can adapt for their own presentations.

Ethanol and Cocaine: Environmental Place Conditioning, Stereotypy, and Synergism in Planarians Tallarida CS, Bires K, Avershal J, Tallarida RJ, Seo S, Rawls SM, Alcohol 2014 Sep;48(6):579-586.
More than 90% of individuals who use cocaine also report concurrent ethanol use, but only a few studies, all conducted with vertebrates, have investigated pharmacodynamic interactions between ethanol and cocaine. Planaria, a type of flatworm often considered to have the simplest 'brain,' is an invertebrate species especially amenable to the quantification of drug-induced behavioral responses and identification of conserved responses. Here, the authors investigated stereotypical and environmental place conditioning (EPC) effects of ethanol administered alone and in combination with cocaine. The observed effect for the combination was enhanced compared to its predicted effect, indicating synergism for the interaction. The synergy with ethanol was specific for cocaine, as related experiments revealed that combinations of ethanol and nicotine did not result in synergy. Evidence from planarians that ethanol produces place-conditioning effects and motor dysfunction, and interacts synergistically with cocaine, suggests that aspects of ethanol neuropharmacology are conserved across species.

The Impact of Science Education Games on Prescription Drug Abuse Attitudes among Teens: A Case Study Klisch Y, Bowling KG, Miller LM, Ramos MA, Journal of Drug Education 2014; 43(3): 255-275.
Two online science education games, in which players learn about the risks of prescription drug abuse in the context of investigating crimes, were evaluated to determine shifts of prescription drug abuse attitudes attributable to game exposure. High school students from grades 11 and 12 (n=179) were assigned to one of the games and participated in a pretest, two game-play sessions, and a delayed posttest. Students in both groups demonstrated more negative attitudes toward prescription drug abuse after playing the game, driven by changes of students' normative beliefs and their ability to make the connection between prescription drug abuse and illicit drugs.

INTRAMURAL RESEARCH

Molecular Targets and Medications Discovery Research Branch

Drug Design and Synthesis Section

Synthesis and Immunological Effects Of Heroin Vaccines Li F, Cheng K, Antoline JF, Iyer MR, Matyas GR, Torres OB, Jalah R, Beck Z, Alving CR, Parrish DA, Deschamps JR, Jacobson AE, Rice KC. Org Biomol Chem, 2014, 12(37), 7211-7232. Issue cover and Featured Article.
Three haptens have been synthesized with linkers for attachment to carrier macromolecules at either the piperidino-nitrogen or via an introduced 3-amino group. Two of the haptens, with a 2-oxopropyl functionality at either C6, or at both the C3 and C6 positions on the 4,5-epoxymorphinan framework, as well as the third hapten (DiAmHap) with diamido moieties at both the C3 and C6 positions, should be much more stable in solution, or in vivo in a vaccine, than a hapten with an ester in one of those positions, as found in many heroin-based haptens. A "classical" opioid synthetic scheme enabled the formation of a 3-amino-4,5-epoxymorphinan which could not be obtained using palladium chemistry. The authors' vaccines are aimed at the reduction of the abuse of heroin and, as well, at the reduction of the effects of its predominant metabolites, 6-acetylmorphine and morphine. One of the haptens, DiAmHap, has given interesting results in a heroin vaccine and is clearly more suited for the purpose than the other two haptens.

Characterization Of A Shortened Model Of Diet Alternation In Female Rats: Effects Of the CB1 Receptor Antagonist Rimonabant On Food Intake and Anxiety-Like Behavior Blasio A, Rice KC, Sabino V, Cottone P. Behav Pharmacol. 2014; 25(7): 609-617.
The prevalence of eating disorders and obesity in western societies is epidemic and increasing in severity. Preclinical research has focused on the development of animal models that can mimic the maladaptive patterns of food intake observed in certain forms of eating disorders and obesity. This study was aimed at characterizing a recently established model of palatable diet alternation in female rats. For this purpose, females rats were fed either continuously with a regular chow diet (Chow/Chow) or intermittently with a regular chow diet for 2 days and a palatable, high-sucrose diet for 1 day (Chow/Palatable). Following diet cycling, rats were administered rimonabant (0, 0.3, 1, 3mg/kg intraperitoneally) during access to either palatable diet or chow diet and were assessed for food intake and body weight. Finally, rats were pretreated with rimonabant (0, 3mg/kg, intraperitoneally) and tested in the elevated plus maze during withdrawal from the palatable diet. Female rats with alternating access to palatable food cycled their intake, overeating during access to the palatable diet and undereating upon returning to the regular chow diet. Rimonabant treatment resulted in increased chow hypophagia and anxiety-like behavior in Chow/Palatable rats. No effect of drug treatment was observed on the compulsive eating of palatable food in the diet-cycled rats. The results of this study suggest that withdrawal from alternating access to the palatable diet makes individuals vulnerable to the anxiogenic effects of rimonabant and provides etiological factors potentially responsible for the emergence of severe psychiatric side-effects following rimonabant treatment in obese patients.

Sustained Pain-Related Depression Of Behavior: Effects Of Intraplantar Formalin and Complete Freund's Adjuvant On Intracranial Self-Stimulation (ICSS) and Endogenous Kappa Opioid Biomarkers In Rats Leitl MD, Potter DN, Cheng K, Rice KC, Carlezon WA Jr, Negus SS. Mol Pain, 2014, epub Sep 23, 2014.

Intraplantar administration of complete Freund's adjuvant (CFA) and formalin are two noxious stimuli commonly used to produce sustained pain-related behaviors in rodents for research on neurobiology and treatment of pain. One clinically relevant manifestation of pain is depression of behavior and mood. This study compared effects of intraplantar CFA and formalin on depression of positively reinforced operant behavior in an assay of intracranial self-stimulation (ICSS) in rats. Effects of CFA and formalin on other physiological and behavioral measures, and opioid effects on formalin-induced depression of ICSS, were also examined. There were four main findings. First, consistent with previous studies, both CFA and formalin produced similar paw swelling and mechanical hypersensitivity. Second, CFA produced weak and transient depression of ICSS, whereas formalin produced a more robust and sustained depression of ICSS that lasted at least 14 days. Third, formalin-induced depression of ICSS was reversed by morphine doses that did not significantly alter ICSS in saline-treated rats, suggesting that formalin effects on ICSS can be interpreted as an example of pain-related and analgesic-reversible depression of behavior. Finally, formalin-induced depression of ICSS was not associated with changes in central biomarkers for activation of endogenous kappa opioid systems, which have been implicated in depressive-like states in rodents, nor was it blocked by the kappa antagonist norbinaltorphimine. These results suggest differential efficacy of sustained pain stimuli to depress brain reward function in rats as assessed with ICSS. Formalin-induced depression of ICSS does not appear to engage brain kappa opioid systems.

The Inverse Agonist Of CB1 Receptor SR141716 Blocks Compulsive Eating Of Palatable Food Dore R, Valenza M, Wang X, Rice KC, Sabino V, Cottone P. Addict Biol. 2014; 19(5): 849-861.

Dieting and the increased availability of highly palatable food are considered major contributing factors to the large incidence of eating disorders and obesity. This study was aimed at investigating the role of the cannabinoid (CB) system in a novel animal model of compulsive eating, based on a rapid palatable diet cycling protocol. Male Wistar rats were fed either continuously a regular chow diet (Chow/Chow, control group) or intermittently a regular chow diet for 2 days and a palatable, high-sucrose diet for 1 day (Chow/Palatable). Chow/Palatable rats showed spontaneous and progressively increasing hypophagia and body weight loss when fed the regular chow diet, and excessive food intake and body weight gain when fed the palatable diet. Diet-cycled rats dramatically escalated the intake of the palatable diet during the first hour of renewed access (7.5-fold compared to controls), and after withdrawal, they showed compulsive eating and heightened risk-taking behavior. The inverse agonist of the CB1 receptor, SR141716 reduced the excessive intake of palatable food with higher potency and the body weight with greater efficacy in Chow/Palatable rats, compared to controls. Moreover, SR141716 reduced compulsive eating and risk-taking behavior in Chow/Palatable rats. Finally, consistent with the behavioral and pharmacological observations, withdrawal from the palatable diet decreased the gene expression of the enzyme fatty acid amide hydrolase in the ventromedial hypothalamus while increasing that of CB1 receptors in the dorsal striatum in Chow/Palatable rats, compared to controls. These findings will help understand the role of the CB system in compulsive eating.

Increased Tau Phosphorylation and Aggregation In the Hippocampus Of Mice Overexpressing Corticotropin-Releasing Factor Campbell SN, Zhang C, Monte L, Roe AD, Rice KC, Taché Y, Masliah E, Rissman RA. J Alzheimers Dis, 2014, epub Aug 13, 2014.
Clinical and basic science research suggests that stress and/or changes in central stress signaling intermediates may be involved in Alzheimer's disease (AD) pathogenesis. Although the links between stress and AD remain unsettled, data from our group and others have established that stress exposure in rodents may confer susceptibility to AD pathology by inducing hippocampal tau phosphorylation (tau-P). Work in the authors' laboratory has shown that stress-induced tau-P requires activation of the type-1 corticotropin-releasing factor receptor (CRFR1). CRF overexpressing (CRF-OE) mice are a model of chronic stress that display cognitive impairment at 9-10 month of age. In this study we used 6-7 month old CRF-OE mice to examine whether sustained exposure to CRF and stress steroids would impact hippocampal tau-P and kinase activity in the presence or absence of the CRFR1-specific antagonist, R121919, given daily for 30 days. CRF-OE mice had significantly elevated tau-P compared to wild type (WT) mice at the AT8 (S202/T204), PHF-1 (S396/404), S262, and S422 sites. Treating CRF-OE mice with R121919 blocked phosphorylation at the AT8 (S202/T204) and PHF-1 (S396/404) sites, but not at the S262 and S422 sites and reduced phosphorylation of c-Jun N Terminal Kinase (JNK). Examination of hippocampal extracts from CRF-OE mice at the ultrastructural level revealed negatively stained round/globular aggregates that were positively labeled by PHF-1. These data suggest critical roles for CRF and CRFR1 in tau-P and aggregation and may have implications for the development of AD cognitive decline.

Linear Pharmacokinetics Of 3,4-Methylenedioxypyrovalerone (MDPV) and Its Metabolites In the Rat: Relationship To Pharmacodynamic Effects Anizan S, Concheiro M, Lehner KR, Bukhari MO, Suzuki M, Rice KC, Baumann MH, Huestis MA. Addict Biol, 2014, epub Dec 5, 2014.
3,4-Methylenedioxypyrovalerone (MDPV) is a commonly abused synthetic cathinone in the United States and is associated with dangerous side effects. MDPV is a dopamine transporter blocker that is 10-fold more potent than cocaine as a locomotor stimulant in rats. Previous in vitro and in vivo metabolism studies identified 3,4-dihydroxypyrovalerone (3,4-catechol-PV) and 4-hydroxy-3-methoxypyrovalerone (4-OH-3-MeO-PV) as the two primary MDPV metabolites. This study examined MDPV pharmacokinetics and metabolism, along with associated pharmacodynamic effects in rats receiving 0.5, 1.0 and 2.0mg/kg subcutaneous (s.c.) MDPV. Blood was collected by an indwelling jugular catheter before dosing and at 10, 20, 30, 60, 120, 240 and 480 minutes thereafter. Plasma specimens were analyzed by liquid chromatography coupled to high-resolution tandem mass spectrometry. Maximum concentrations (Cmax) and area-under-the-curve (AUC) for MDPV and two metabolites increased proportionally with administered dose, showing linear pharmacokinetics. MDPV exhibited the highest Cmax at all doses (74.2-271.3μg/l) and 4-OH-3-MeOH-PV the highest AUC (11366-47724 minutes per μg/l), being the predominant metabolite. MDPV time to Cmax (Tmax) was 12.9-18.6 minutes, while 3,4-catechol-PV and 4-OH-3-MeO-PV peaked later with Tmax 188.6-240 minutes after s.c. dosing. Horizontal locomotor activity (HLA) and stereotypy correlated positively with plasma MDPV concentrations, while HLA correlated negatively with MDPV metabolites. These results suggest that the parent compound mediates motor stimulation after systemic MDPV administration, but additionally, metabolites may be inhibitory, may not be active or may not pass the blood brain barrier.

Role Of Bed Nucleus Of the Stria Terminalis Corticotrophin-Releasing Factor Receptors In Frustration Stress-Induced Binge-Like Palatable Food Consumption In Female Rats With A History Of Food Restriction Micioni Di Bonaventura MV, Ciccocioppo R, Romano A, Bossert JM, Rice KC, Ubaldi M, St Laurent R, Gaetani S, Massi M, Shaham Y, Cifani C. J Neurosci, 2014; 34(34): 11316-11324.

The authors developed recently a binge-eating model in which female rats with a history of intermittent food restriction show binge-like palatable food consumption after 15 min exposure to the sight of the palatable food. This "frustration stress" manipulation also activates the hypothalamic-pituitary-adrenal stress axis. Here, the authors determined the role of the stress neurohormone corticotropin-releasing factor (CRF) in stress-induced binge eating in our model. Micioni Di Bonaventura MV, Ciccocioppo R, Romano A, Bossert JM, Rice KC, Ubaldi M, St Laurent R, Gaetani S, Massi M, Shaham Y, Cifani C. J Neurosci, 2014, 34(34), 11316-24.

They also assessed the role of CRF receptors in the bed nucleus of the stria terminalis (BNST), a brain region implicated in stress responses and stress-induced drug seeking, in stress-induced binge eating. They used four groups that were first exposed or not exposed to repeated intermittent cycles of regular chow food restriction during which they were also given intermittent access to high-caloric palatable food. On the test day, they either exposed or did not expose the rats to the sight of the palatable food for 15 min (frustration stress) before assessing food consumption for 2 h. The authors found that systemic injections of the CRF1 receptor antagonist R121919 (2,5-dimethyl-3-(6-dimethyl-4-methylpyridin-3-yl)-7 dipropylamino pyrazolo[1,5-a]pyrimidine) (10-20 mg/kg) and BNST (25-50 ng/side) or ventricular (1000 ng) injections of the nonselective CRF receptor antagonist D-Phe-CRF(12-41) decreased frustration stress-induced binge eating in rats with a history of food restriction. Frustration stress also increased Fos (a neuronal activity marker) expression in ventral and dorsal BNST. Results demonstrate a critical role of CRF receptors in BNST in stress-induced binge eating in our rat model. CRF1 receptor antagonists may represent a novel pharmacological treatment for bingeing-related eating disorders.

Characterization and Optimization Of Heroin Hapten-BSA Conjugates: Method Development For the Synthesis Of Reproducible Hapten-Based Vaccines Torres OB, Jalah R, Rice KC, Li F, Antoline JF, Iyer MR, Jacobson AE, Boutaghou MN, Alving CR, Matyas GR. Anal Bioanal Chem, 2014, 406(24), 5927-5937.

A potential new treatment for drug addiction is immunization with vaccines that induce antibodies that can abrogate the addictive effects of the drug of abuse. One of the challenges in the development of a vaccine against drugs of abuse is the availability of an optimum procedure that gives reproducible and high yielding hapten-protein conjugates. In this study, a heroin/morphine surrogate hapten (MorHap) was coupled to bovine serum albumin (BSA) using maleimide-thiol chemistry. MorHap-BSA conjugates with 3, 5, 10, 15, 22, 28, and 34 haptens were obtained using different linker and hapten ratios. Using this optimized procedure, MorHap-BSA conjugates were synthesized with highly reproducible results and in high yields. The number of haptens attached to BSA was compared by 2,4,6-trinitrobenzenesulfonic acid (TNBS) assay, modified Ellman's test and matrix assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). Among the three methods, MALDI-TOF MS discriminated subtle differences in hapten density. The effect of hapten density on enzyme-linked immunosorbent assay (ELISA) performance was evaluated with seven MorHap-BSA conjugates of varying hapten densities, which were used as coating antigens. The highest antibody binding was obtained with MorHap-BSA conjugates containing 3-5 haptens. This is the first report that rigorously analyzes, optimizes and characterizes the conjugation of haptens to proteins that can be used for vaccines against drugs of abuse. The

effect of hapten density on the ELISA detection of antibodies against haptens demonstrates the importance of careful characterization of the hapten density by the analytical techniques described.

Glial TLR4 Signaling Does Not Contribute To Opioid-Induced Depression Of Respiration Zwicker JD, Zhang Y, Ren J, Hutchinson MR, Rice KC, Watkins LR, Greer JJ, Funk GD. J Appl Physiol, 2014, 117(8), 857-868.

Opioids activate glia in the central nervous system in part by activating the toll-like receptor 4 (TLR4)/myeloid differentiation 2 (MD2) complex. TLR4/MD2-mediated activation of glia by opioids compromises their analgesic actions. Glial activation is also hypothesized as pivotal in opioid-mediated reward and tolerance and as a contributor to opioid-mediated respiratory depression. The authors tested the contribution of TLR4 to opioid-induced respiratory depression using rhythmically active medullary slices that contain the pre-Bötzinger Complex (preBötC, an important site of respiratory rhythm generation) and adult rats in vivo. Injection with DAMGO (μ-opioid receptor agonist; 50 μM) or bath application of DAMGO (500 nM) or fentanyl (1 μM) slowed frequency recorded from XII nerves to 40%, 40%, or 50% of control, respectively. This DAMGO-mediated frequency inhibition was unaffected by preapplication of lipopolysaccharides from Rhodobacter sphaeroides (a TLR4 antagonist, 2,000 ng/ml) or (+)naloxone (1-10 μM, a TLR4-antagonist). Bath application of (-)naloxone (500 nM; a TLR4 and μ-opioid antagonist), however, rapidly reversed the opioid-mediated frequency decrease. The authors also compared the opioid-induced respiratory depression in slices in vitro in the absence and presence of bath-applied minocycline (an inhibitor of microglial activation) and in slices prepared from mice injected (ip) 18 h earlier with minocycline or saline. Minocycline had no effect on respiratory depression in vitro. Finally, the respiratory depression evoked in anesthetized rats by tail vein infusion of fentanyl was unaffected by subsequent injection of (+)naloxone, but completely reversed by (-)naloxone. These data indicate that neither activation of microglia in preBötC nor TLR4/MD2-activation contribute to opioid-induced respiratory depression.

Activation Of Adult Rat CNS Endothelial Cells By Opioid-Induced Toll-Like Receptor 4 (TLR4) Signaling Induces Proinflammatory, Biochemical, Morphological, And Behavioral Sequelae Grace PM, Ramos KM, Rodgers KM, Wang X, Hutchinson MR, Lewis MT, Morgan KN, Kroll JL, Taylor FR, Strand KA, Zhang Y, Berkelhammer D, Huey MG, Greene LI, Cochran TA, Yin H, Barth DS, Johnson KW, Rice KC, Maier SF, Watkins LR. Neuroscience, 2014; 280: 299-317.

CNS immune signaling contributes to deleterious opioid effects including hyperalgesia, tolerance, reward, and dependence/withdrawal. Such effects are mediated by opioid signaling at toll-like receptor 4 (TLR4), presumptively of glial origin. Whether CNS endothelial cells express TLR4 is controversial. If so, they would be well positioned for activation by blood-borne opioids, contributing to opioid-induced pro-inflammatory responses. These studies examined adult primary rat CNS endothelial cell responses to (-)-morphine or its mu opioid receptor (MOR)-inactive metabolite morphine-3-glucuronide (M3G), both known TLR4 agonists. The authors demonstrate that adult rat CNS endothelial cells express functional TLR4. M3G activated nuclear factor kappaB (NF-κB), increased tumor necrosis factor-α (TNFα) and cyclooxygenase-2 (COX2) mRNAs, and released prostaglandin E2 (PGE2) from these cells. (-)-Morphine-induced upregulation of TNFα mRNA and PGE2 release were unmasked by pre-treatment with nalmefene, a MOR antagonist without TLR4 activity (unlike CTAP, shown to have both MOR- and TLR4-activity), suggestive of an interplay between MOR and TLR4 co-activation by (-)-morphine. In support, MOR-dependent Protein Kinase A (PKA) opposed TLR4 signaling, as PKA inhibition (H-89) also unmasked (-)-morphine-induced TNFα and COX2 mRNA upregulation. Intrathecal injection of CNS endothelial

cells, stimulated in vitro with M3G, produced TLR4-dependent tactile allodynia. Further, cortical suffusion with M3G in vivo induced TLR4-dependent vasodilation. Finally, endothelial cell TLR4 activation by lipopolysaccharide and/or M3G was blocked by the glial inhibitors AV1013 and propentofylline, demonstrating endothelial cells as a new target of such drugs. These data indicate that (-)-morphine and M3G can activate CNS endothelial cells via TLR4, inducing proinflammatory, biochemical, morphological, and behavioral sequelae. CNS endothelial cells may have previously unanticipated roles in opioid-induced effects, in phenomena blocked by presumptive glial inhibitors, as well as TLR4-mediated phenomena more broadly.

3,4-Methylenedioxypyrovalerone (MDPV)-Induced Conditioned Taste Avoidance In the F344/N And LEW Rat Strains King HE, Wetzell B, Rice KC, Riley AL. Pharmacol Biochem Behav, 2014;126:163-169.

The inbred Fischer (F344) and Lewis (LEW) rats, while originally developed as animal models for cancer and tissue transplantation research, have since been used to study genetic differences in a variety of physiological and behavioral endpoints. In this context, LEW rats show greater sensitivity to the aversive effects of cocaine as compared to F344 rats in a conditioned taste avoidance procedure. Like cocaine, 3,4-methylenedioxypyrovalerone (MDPV; "bath salts") acts as a dopamine transport blocker and possesses aversive properties, making it a good candidate for assessing whether the aforementioned strain differences with cocaine would generalize to drugs with similar biochemical action. Accordingly, male F344 and LEW rats were exposed to a novel saccharin solution followed by injections of one of four doses of MDPV in a taste avoidance procedure. Over the four saccharin/MDPV pairings during conditioning, core body temperatures were also assessed. Similar to previous research, MDPV induced robust dose-dependent taste avoidance, although no effect of strain was observed. MDPV also produced hyperthermia that was independent of strain and unrelated to the conditioned taste avoidance. These findings argue for a complex influence of multiple (and likely interacting) monoaminergic systems mediating MDPV-induced taste avoidance in the two strains and suggest different mechanisms of avoidance learning for cocaine and MDPV.

Select Steroid Hormone Glucuronide Metabolites Can Cause Toll-Like Receptor 4 Activation and Enhanced Pain Lewis SS, Hutchinson MR, Frick MM, Zhang Y, Maier SF, Sammakia T, Rice KC, Watkins LR. Brain Behav Immun. 2014, epub Sep 16, 2014.

The authors have recently shown that several classes of glucuronide metabolites, including the morphine metabolite morphine-3-glucuronide and the ethanol metabolite ethyl glucuronide, cause toll like receptor 4 (TLR4)-dependent signaling in vitro and enhanced pain in vivo. Steroid hormones, including estrogens and corticosterone, are also metabolized through glucuronidation. Here the authors demonstrate that in silico docking predicts that corticosterone, corticosterone-21-glucuronide, estradiol, estradiol-3-glucuronide and estradiol-17-glucuronide all dock with the MD-2 component of the TLR4 receptor complex. In addition to each docking with MD-2, the docking of each was altered by pre-docking with (+)-naloxone, a TLR4 signaling inhibitor. As agonist versus antagonist activity cannot be determined from these in silico interactions, an in vitro study was undertaken to clarify which of these compounds can act in an agonist fashion. Studies using a cell line transfected with TLR4, necessary co-signaling molecules, and a reporter gene revealed that only estradiol-3-glucuronide and estradiol-17-glucuronide increased reporter gene product, indicative of TLR4 agonism. Finally, in in vivo studies, each of the 5 drugs was injected intrathecally at equimolar doses. In keeping with the in vitro results, only estradiol-3-glucuronide and estradiol-17-glucuronide caused enhanced pain. For both compounds, pain enhancement was blocked by the TLR4 antagonist lipopolysaccharide from Rhodobacter sphaeroides, evidence for the involvement in TLR4 in the resultant pain enhancement. These findings have implications for

several chronic pain conditions, including migraine and temporomandibular joint disorder, in which pain episodes are more likely in cycling females when estradiol is decreasing and estradiol metabolites are at their highest.

An Assessment Of MDPV-Induced Place Preference In Adult Sprague-Dawley Rats King HE, Wetzell B, Rice KC, Riley AL. Drug Alcohol Depend, 2014, epub Nov 12, 2014.
Most drugs of abuse have both aversive and rewarding effects, and the use and abuse potential of such drugs is thought to be a function of a balance of these affective properties. Characterizing these effects and their relative balance may provide insight into abuse vulnerability. One drug that has received recent attention is methylenedioxypyrovalerone (MDPV), a monoamine transport inhibitor similar to, but significantly more potent than, cocaine. MDPV is self-administered and has been shown to produce aversive and rewarding effects in adult rats. The present study extended this characterization of the affective properties of MDPV by examining its ability to support place conditioning at a range of doses known to produce taste avoidance. Male Sprague-Dawley rats were injected with MDPV (1, 1.8 or 3.2mg/kg) or saline and placed on the non-preferred side of a place conditioning apparatus for 30min. On the next day, they were given an injection of saline and placed on the preferred side. This was repeated three times for a total of four conditioning cycles, and side preference was assessed on a final test. All doses of MDPV produced significant increases in time spent in the drug-paired chamber, an effect not seen in vehicle-treated animals.
That the same doses of MDPV induced both taste avoidance and place preference allows assessments of how other factors might impact these effects and how they may, in turn, contribute to its abuse liability.

Effects Of Mu Opioid Receptor Agonists In Assays Of Acute Pain-Stimulated and Pain-Depressed Behavior In Rats: Role Of Mu Agonist Efficacy and Noxious Stimulus Intensity
Altarifi A, Negus SS, Rice KC. J Pharmacol Exp Ther, 2014, epub Nov 18, 2014.
Pain is associated with stimulation of some behaviors and depression of others, and mu opioid receptor agonists are among the most widely used analgesics for treatment of pain. The present study used parallel assays of pain-stimulated and pain-depressed behavior in male Sprague-Dawley rats to compare antinociception profiles for six mu opioid analgesics that varied in efficacy at mu opioid receptors (in order from highest to lowest efficacy: methadone, fentanyl, morphine, hydrocodone, buprenorphine, nalbuphine). Intraperitonial injection of dilute lactic acid served as an acute, chemical noxious stimulus to either stimulate a stretching response or depress operant responding maintained by electrical brain stimulation in an intracranial self-stimulation (ICSS) procedure. All mu agonists blocked both stimulation of stretching and depression of ICSS produced by 1.8% lactic acid. The high-efficacy mu agonists methadone and fentanyl were more potent to block acid-induced depression of ICSS than acid-stimulated stretching, whereas lower efficacy agonists displayed similar potency across assays. All mu agonists except morphine also facilitated ICSS in the absence of the noxious stimulus at doses similar to those that blocked acid-induced depression of ICSS. The potency of the low-efficacy mu agonist nalbuphine, but not the high-efficacy mu agonist methadone, to block acid-induced depression of ICSS was significantly reduced by increasing the intensity of the noxious stimulus to 5.6% acid. These results demonstrate sensitivity of acid-induced depression of ICSS to a range of clinically effective mu opioid analgesics and reveal distinctions between opioids based on efficacy at the mu receptor.

Medicinal Chemistry Section

Dopamine D1 and D3 Receptors Mediate Reconsolidation Of Cocaine Memories In Mouse Models Of Drug Self-Administration Yan Y, Newman AH, Xu M. Neuroscience 2014; 278: 154-164.

Memories of drug experience and drug-associated environmental cues can elicit drug-seeking and taking behaviors in humans. Disruption of reconsolidation of drug memories dampens or even erases previous memories and therefore may provide a useful way to treat drug abuse. The authors and others previously demonstrated that dopamine D1 and D3 receptors play differential roles in acquiring cocaine-induced behaviors. Moreover, D3 receptors contribute to the reconsolidation of cocaine-induced conditioned place preference. In the present study, the authors examined effects of manipulating D1 or D3 receptors on reconsolidation of cocaine memories in mouse models of drug self-administration. They found that pharmacological blockade of dopamine D1 receptors or a genetic mutation of the D3 receptor gene attenuated reconsolidation that lasted for at least 1 week after the retrieval. In contrast, with no memory retrieval, pharmacological antagonism of D1 receptors or the D3 receptor gene mutation did not significantly affect the reconsolidation of cocaine memories. Pharmacological blockade of D3 receptors also attenuated reconsolidation in wild-type mice but not in D3 receptor mutant mice that lasted for at least 1 week after the retrieval. These results suggest that dopamine D1 and D3 receptors play key roles in the reconsolidation of cocaine memories in mice, and that these receptors may serve as novel targets for the treatment of cocaine abuse in humans.

Computational and Biochemical Docking Of The Irreversible Cocaine Analog RTI 82 Directly Demonstrates Ligand Positioning In the Dopamine Transporter Central Substrate Binding Site Dahal RA, Pramod AB, Sharma B, Krout D, Foster JD, Cha JH, Cao J, Newman AH, Lever JR, Vaughan RA, Henry LK J Biol Chem 2014; 289(43): 29712-29727, Issue cover and Featured Article.

The dopamine transporter (DAT) functions as a key regulator of dopaminergic neurotransmission via re-uptake of synaptic dopamine (DA). Cocaine binding to DAT blocks this activity and elevates extracellular DA, leading to psychomotor stimulation and addiction, but the mechanisms by which cocaine interacts with DAT and inhibits transport remain incompletely understood. Here, the authors addressed these questions using computational and biochemical methodologies to localize the binding and adduction sites of the photoactivatable irreversible cocaine analog 3-(p-chlorophenyl)tropane-2-carboxylic acid, 4'-azido-3'-iodophenylethyl ester ([125I]RTI 82). Comparative modeling and small molecule docking indicated that the tropane pharmacophore of RTI 82 was positioned in the central DA active site with an orientation that juxtaposed the aryliodoazide group for cross-linking to rat DAT Phe-319. This prediction was verified by focused methionine substitution of residues flanking this site followed by cyanogen bromide mapping of the [125I]RTI 82-labeledmutants and by the substituted cysteine accessibility method protection analyses. These findings provide positive functional evidence linking tropane pharmacophore interaction with the core substrate binding site and support a competitive mechanism for transport inhibition. This synergistic application of computational and biochemical methodologies overcomes many uncertainties inherent in other approaches and furnishes a schematic framework for elucidating the ligand-protein interactions of other classes of DA transport inhibitors.

Effects Of Buspirone and the Dopamine D3 Receptor Compound PG 619 On Cocaine and Methamphetamine Self-Administration In Rhesus Monkeys Using the Food-Drug Choice Paradigm John WS, Banala AK, Newman AH, Nader MA Psychopharmacology, 2014, e-pub Oct. 21, 2014.

The dopamine (DA)D2 and D3 receptors have been associated with cocaine abuse. A recent study with the D3 receptor (D3R) partial agonist PG619 found that it attenuated cocaine-induced reinstatement and the D2-like receptor antagonist buspirone has shown positive outcomes in two studies of cocaine abuse in monkeys. However, a recent clinical trial indicated that buspirone did not improve abstinence in treatment-seeking cocaine abusers. The objective of the study was to examine PG619 and buspirone under a food-drug choice paradigm in order to better model the clinical findings. In addition, the authors extended the characterization of both compounds to include methamphetamine (MA) self-administration (SA). Six adult male rhesus monkeys were trained to respond under a concurrent food (1.0-g pellets) and drug (0.01–0.3 mg/kg/injection cocaine or MA) choice paradigm in which complete SA dose-response curves were determined each session (N=3/group). Monkeys received 5 days of treatment with either PG619 (0.1–3.0 mg/kg, i.v.) or buspirone (0.01–1.0 mg/kg, i.m.). In a follow-up study, the SA doses were reduced (0.003–0.1 mg/kg/injection) to increase reinforcement frequency and buspirone was retested. PG619 did not affect cocaine or MA choice, while buspirone increased low-dose cocaine choice. Changing the SA doses increased the number of reinforcers received each session, but buspirone did not decrease drug choice. Consistent with clinical findings, these results do not support the use of buspirone for psychostimulant abuse and suggest that food-drug choice paradigms may have greater predictive validity than the use of other schedules of reinforcement.

Designer Drug Research Unit

Baths Salts, Spice, and Related Designer Drugs: The Science Behind the Headlines (Review) Baumann MH, Solis E Jr, Watterson LR, Marusich JA, Fantegrossi WE, Wiley JL. J Neurosci 2014; 34: 15150-15158.

The abuse of synthetic psychoactive substances known as "designer drugs," or "new psychoactive substances" (NPS), is increasing at an alarming rate. NPS are purchased as alternatives to traditional illicit drugs of abuse and are manufactured to circumvent laws regulating the sale and use of controlled substances. Synthetic cathinones (i.e., "bath salts") and synthetic cannabinoids (i.e., "spice") are two types of NPS that have received substantial media attention. Although low recreational doses of bath salts or spice compounds can produce desirable effects, high doses or chronic exposure often leads to dangerous medical consequences, including psychosis, violent behaviors, tachycardia, hyperthermia, and even death. Despite the popularity of NPS, there is a paucity of scientific data about these drugs. Here the authors provide a brief up-to-date review describing the mechanisms of action and neurobiological effects of synthetic cathinones and cannabinoids.

Awash In A Sea Of 'Bath Salts': Implications For Biomedical Research and Public Health (Editorial) Baumann MH. Addiction 2014; 109: 1577-1579.

The emergence of “bath salts” products containing synthetic cathinones represents a global public health threat. Synthetic cathinones have significant abuse potential, and the effects of high-dose administration can be life-threatening. More preclinical and human research is needed to understand the complex pharmacology and toxicology of these substances.

Interaction Of Psychoactive Tryptamines With Biogenic Amine Transporters and Serotonin Receptor Subtypes Blough BE, Landavazo A, Decker AM, Partilla JS, Baumann MH, Rothman RB. Psychopharmacology (Berl) 2014; 231: 4135.

Synthetic hallucinogenic tryptamines, especially those originally described by Alexander Shulgin, continue to be abused. The range of subjective experiences produced by different tryptamines suggests that multiple neurochemical mechanisms are involved in their actions, in addition to the established role of agonist activity at serotonin 2A (5-HT2A) receptors. This study evaluated the interaction of a series of synthetic tryptamines with biogenic amine neurotransmitter transporters and with serotonin (5-HT) receptor subtypes implicated in psychedelic effects. Neurotransmitter transporter activity was determined in rat brain synaptosomes. Receptor activity was determined using calcium mobilization and DiscoveRx PathHunter assays in HEK293, Gα16-CHO, and CHOk1 cells transfected with human receptors. Twenty-one tryptamines were analyzed in transporter uptake and release assays, and 5-HT2A, serotonin 1A (5-HT1A), and 5-HT2A β-arrestin functional assays. Eight of the compounds were found to have 5-HT-releasing activity. Thirteen compounds were found to be 5-HT uptake inhibitors or were inactive. All tryptamines were 5-HT2A agonists with a range of potencies and efficacies, but only a few compounds were 5-HT1A agonists. Most tryptamines recruited β-arrestin through 5-HT2A activation. All psychoactive tryptamines are 5-HT2A agonists, but 5-HT transporter (SERT) activity may contribute significantly to the pharmacology of certain compounds. The in vitro transporter data confirm structure-activity trends for releasers and uptake inhibitors whereby releasers tend to be structurally smaller compounds. Interestingly, two tertiary amines were found to be selective substrates at SERT, which dispels the notion that 5-HT-releasing activity is limited only to primary or secondary amines.

Pharmacology Of Novel Synthetic Stimulants Structurally Related To the "Bath Salts" Constituent 3,4-Methylenedioxypyrovalerone (MDPV) Marusich JA, Antonazzo KR, Wiley JL, Blough BE, Partilla JS, Baumann MH. Neuropharmacology 2014; 87: 206-213.

There has been a dramatic rise in the abuse of synthetic cathinones known as "bath salts," including 3,4-methylenedioxypyrovalerone (MDPV), an analog linked to many adverse events. MDPV differs from other synthetic cathinones because it contains a pyrrolidine ring which gives the drug potent actions as an uptake blocker at dopamine and norepinephrine transporters. While MDPV is now illegal, a wave of "second generation" pyrrolidinophenones has appeared on the market, with α-pyrrolidinovalerophenone (α-PVP) being most popular. Here, the authors sought to compare the in vitro and in vivo pharmacological effects of MDPV and its congeners: α-PVP, α-pyrrolidinobutiophenone (α-PBP), and α-pyrrolidinopropiophenone (α-PPP). They examined effects of test drugs in transporter uptake and release assays using rat brain synaptosomes, then assessed behavioral stimulant effects in mice. They found that α-PVP is a potent uptake blocker at dopamine and norepinephrine transporters, similar to MDPV. α-PBP and α-PPP are also catecholamine transporter blockers but display reduced potency. All of the test drugs are locomotor stimulants, and the rank order of in vivo potency parallels dopamine transporter activity, with MDPV > α-PVP > α-PBP > α-PPP. Motor activation produced by all drugs is reversed by the dopamine receptor antagonist SCH23390. Furthermore, results of a functional observational battery show that all test drugs produce typical stimulant effects at lower doses and some drugs produce bizarre behaviors at higher doses. Taken together, our findings represent the first evidence that second generation analogs of MDPV are catecholamine-selective uptake blockers which may pose risk for addiction and adverse effects in human users.

Molecular Targets and Medications Discovery Branch

Medication Development Program

Preference For Distinct Functional Conformations Of the Dopamine Transporter Alters the Relationship Between Subjective Effects Of Cocaine and Stimulation Of Mesolimbic Dopamine Kohut SJ, Hiranita T, Hong S-K, Ebbs AL, Tronci V, Green J, Garcés-Ramírez L, Chun LE, Mereu M, Newman AH, Katz JL, Tanda G. Biol Psychiatry. 2014; 76(10): 802-809.
Different conformational equilibria of the DAT regulate differences in extracellular DA, and related cocaine-like subjective effects induced by structurally diverse typical and atypical DA uptake inhibitors (DUI), some of which are in clinical use, or have been suggested, as ADHD medications. Standard but not atypical-DUIs produced a linear, time-independent, relationship between cocaine-like subjective effects and stimulation of DA-levels. Dopamine uptake is the target of several drugs for treating neuropsychiatric disorders, such as ADHD. The authors' results help to identify safe and effective medications with minimal cocaine-like subjective effects that contribute to abuse liability.

Optogenetics and Transgenic Technology Core and Glia-Neuron Interactions Lab, Office of the Scientific Director

Sercamp: A Carboxy-Terminal Protein Modification That Enables Monitoring Of ER Calcium Homeostasis Henderson MJ, Wires ES, Trychta KA, Richie CT, Harvey BK. Mol Biol Cell. 2014 Sep 15;25(18):2828-2839.
Endoplasmic reticulum (ER) calcium homeostasis is disrupted in diverse pathologies, including neurodegeneration, cardiovascular diseases, and diabetes. Temporally defining calcium dysregulation during disease progression, however, has been challenging. Here the authors describe secreted ER calcium-monitoring proteins (SERCaMPs), which allow for longitudinal monitoring of ER calcium homeostasis. They identified a carboxy-terminal modification that is sufficient to confer release of a protein specifically in response to ER calcium depletion. A Gaussia luciferase (GLuc)-based SERCaMP provides a simple and sensitive method to monitor ER calcium homeostasis in vitro or in vivo by analyzing culture medium or blood. GLuc-SERCaMPs revealed ER calcium depletion in rat primary neurons exposed to various ER stressors. In vivo, ER calcium disruption in rat liver was monitored over several days by repeated sampling of blood. The results suggest that SERCaMPs will have broad applications for the long-term monitoring of ER calcium homeostasis and the development of therapeutic approaches to counteract ER calcium dysregulation.

Methamphetamine Induces A Rapid Increase Of Intracellular Ca++ Levels In Neurons Overexpressing Gcamp5 Yu SJ, Wu KJ, Bae EK, Hsu MJ, Richie CT, Harvey BK, Wang Y. Addict Biol. 2014 Nov 6. doi: 10.1111/adb.12193. [Epub ahead of print].
In this study, methamphetamine (Meth)- and glutamate (Glu)-mediated intracellular Ca++ (Ca++ i) signals were examined in real time in primary cortical neurons overexpressing an intracellular Ca++ probe, GCaMP5, by adeno-associated viral (AAV) serotype 1. Binding of Ca++ to GCaMP increased green fluorescence intensity in cells. Both Meth and Glu induced a rapid increase in Ca++ i, which was blocked by MK801, suggesting that Meth enhanced Ca++ i through Glu receptor in neurons. The Meth-mediated Ca++ signal was also blocked by Mg++, low Ca++ or the L-type Ca++ channel inhibitor nifedipine. The ryanodine receptor inhibitor dantrolene did not alter the initial Ca++ influx but partially reduced the peak of Ca++ i. These data suggest that Meth enhanced

Ca++ influx through membrane Ca++ channels, which then triggered the release of Ca++ from the endoplasmic reticulum in the cytosol. AAV-GCaMP5 was also injected to the parietal cortex of adult rats. Administration of Meth enhanced fluorescence in the ipsilateral cortex. Using immunohistochemistry, Meth-induced green fluorescence was found in the NeuN-containing cells in the cortex, suggesting that Meth increased Ca++ in neurons in vivo. In conclusion, we have used in vitro and in vivo techniques to demonstrate a rapid increase of Ca++ i by Meth in cortical neurons through overexpression of GCaMP5. As Meth induces behavioral responses and neurotoxicity through Ca++ i, modulation of Ca++ i may be useful to reduce Meth-related reactions.

PDYN, A Gene Implicated In Brain/Mental Disorders, Is Targeted By REST In the Adult Human Brain Henriksson R, Bäckman CM, Harvey BK, Kadyrova H, Bazov I, Shippenberg TS, Bakalkin G. Biochim Biophys Acta. 2014 Nov;1839(11):1226-1232.
The dynorphin κ-opioid receptor system is implicated in mental health and brain/mental disorders. However, despite accumulating evidence that PDYN and/or dynorphin peptide expression is altered in the brain of individuals with brain/mental disorders, little is known about transcriptional control of PDYN in humans. In the present study, the authors show that PDYN is targeted by the transcription factor REST in human neuroblastoma SH-SY5Y cells and that that interfering with REST activity increases PDYN expression in these cells. They also show that REST binding to PDYN is reduced in the adult human brain compared to SH-SY5Y cells, which coincides with higher PDYN expression. This may be related to MIR-9 mediated down-regulation of REST as suggested by a strong inverse correlation between REST and MIR-9 expression. These results suggest that REST represses PDYN expression in SH-SY5Y cells and the adult human brain and may have implications for mental health and brain/mental disorders.

AAV-Mediated Targeting Of Gene Expression To the Peri-Infarct Region In Rat Cortical Stroke Model Mätlik K, Abo-Ramadan U, Harvey BK, Arumäe U, Airavaara M. J Neurosci Methods. 2014 Oct 30;236:107-113.Mätlik K, Abo-Ramadan U, Harvey BK, Arumäe U, Airavaara M. J Neurosci Methods. 2014 Oct 30;236:107-113.
For stroke patients the recovery of cognitive and behavioral functions is often incomplete. Functional recovery is thought to be mediated largely by connectivity rearrangements in the peri-infarct region. A method for manipulating gene expression in this region would be useful for identifying new recovery-enhancing treatments. The authors have characterized a way of targeting adeno-associated virus (AAV) vectors to the peri-infarct region of cortical ischemic lesion in rats 2days after middle cerebral artery occlusion (MCAo). They used magnetic resonance imaging (MRI) to show that the altered properties of post-ischemic brain tissue facilitate the spreading of intrastriatally injected nanoparticles toward the infarct. They show that subcortical injection of green fluorescent protein-encoding dsAAV7-GFP resulted in transduction of cells in and around the white matter tract underlying the lesion, and in the cortex proximal to the lesion. A similar result was achieved with dsAAV7 vector encoding the cerebral dopamine neurotrophic factor (CDNF), a protein with therapeutic potential. Viral vector-mediated intracerebral gene delivery has been used before in rodent models of ischemic injury. However, the method of targeting gene expression to the peri-infarct region, after the initial phase of ischemic cell death, has not been described before. The authors demonstrate a straightforward and robust way to target AAV vector-mediated over-expression of genes to the peri-infarct region in a rat stroke model. This method will be useful for studying the action of specific proteins in peri-infarct region during the recovery process.

Hypothalamic Prolyl Endopeptidase (PREP) Regulates Pancreatic Insulin and Glucagon Secretion In Mice Kim JD, Toda C, D'Agostino G, Zeiss CJ, DiLeone RJ, Elsworth JD, Kibbey RG, Chan O, Harvey BK, Richie CT, Savolainen M, Myöhänen T, Jeong JK, Diano S. Proc Natl Acad Sci U S A. 2014 Aug 12;111(32):11876-11881.
Prolyl endopeptidase (PREP) has been implicated in neuronal functions. Here we report that hypothalamic PREP is predominantly expressed in the ventromedial nucleus (VMH), where it regulates glucose-induced neuronal activation. PREP knockdown mice (Prep(gt/gt)) exhibited glucose intolerance, decreased fasting insulin, increased fasting glucagon levels, and reduced glucose-induced insulin secretion compared with wild-type controls. Consistent with this, central infusion of a specific PREP inhibitor, S17092, impaired glucose tolerance and decreased insulin levels in wild-type mice. Arguing further for a central mode of action of PREP, isolated pancreatic islets showed no difference in glucose-induced insulin release between Prep(gt/gt) and wild-type mice. Furthermore, hyperinsulinemic euglycemic clamp studies showed no difference between Prep(gt/gt) and wild-type control mice. Central PREP regulation of insulin and glucagon secretion appears to be mediated by the autonomic nervous system because Prep(gt/gt) mice have elevated sympathetic outflow and norepinephrine levels in the pancreas, and propranolol treatment reversed glucose intolerance in these mice. Finally, re-expression of PREP by bilateral VMH injection of adeno-associated virus-PREP reversed the glucose-intolerant phenotype of the Prep(gt/gt) mice. Taken together, our results unmask a previously unknown player in central regulation of glucose metabolism and pancreatic function.

The Beneficial Effect Of A Prolyl Oligopeptidase Inhibitor, KYP-2047, On Alpha-Synuclein Clearance and Autophagy In A30P Transgenic Mouse Savolainen MH, Richie CT, Harvey BK, Männistö PT, Maguire-Zeiss KA, Myöhänen TT. Neurobiol Dis. 2014 Aug; 68: 1-15.
The misfolding and aggregation of α-synuclein (aSyn) eventually lead to an accumulation of toxic forms that disturb normal neuronal function and result in cell death. aSyn rich inclusions are seen in Parkinson's disease, dementia with Lewy bodies and other synucleinopathies. Prolyl oligopeptidase (PREP) can accelerate the aggregation process of aSyn and the inhibition of PREP leads to a decreased amount of aggregated aSyn in cell models and in aSyn transgenic mice. In this study, the authors investigated the effect of 5- and 28-day PREP inhibitor (KYP-2047) treatments on a mouse strain carrying a point mutation in the aSyn coding gene. Following PREP inhibition, they found a decrease in high molecular-weight oligomeric aSyn and a concomitant increase in the amount of the autophagosome marker, LC3BII, suggesting enhanced macroautophagy (autophagy) and aSyn clearance by KYP-2047. Moreover, 28-day treatment with KYP-2047 caused significant increases in striatal dopamine levels. In cell culture, overexpression of PREP reduced the autophagy. Furthermore, the inhibition of PREP normalized the changes on autophagy markers (LC3BII and p62) caused by an autophagy inhibition or aSyn overexpression, and induced the expression of beclin 1, a positive regulator of autophagy. Taken together, these results suggest that PREP inhibition accelerates the clearance of protein aggregates via increased autophagy and thus normalizes the cell functions in vivo and in vitro. Therefore, PREP inhibition may have future potential in the treatment of synucleinopathies.

MANF Is Indispensable For the Proliferation and Survival Of Pancreatic B Cells Lindahl M, Danilova T, Palm E, Lindholm P, Võikar V, Hakonen E, Ustinov J, Andressoo JO, Harvey BK, Otonkoski T, Rossi J, Saarma M. Cell Rep. 2014 Apr 24;7(2): 366-375.
All forms of diabetes mellitus (DM) are characterized by the loss of functional pancreatic β cell mass, leading to insufficient insulin secretion. Thus, identification of novel approaches to protect and restore β cells is essential for the development of DM therapies. Mesencephalic astrocyte-

derived neurotrophic factor (MANF) is an endoplasmic reticulum (ER)-stress-inducible protein, but its physiological role in mammals has remained obscure. The authors generated MANF-deficient mice that strikingly develop severe diabetes due to progressive postnatal reduction of β cell mass, caused by decreased proliferation and increased apoptosis. Additionally, they show that lack of MANF in vivo in mouse leads to chronic unfolded protein response (UPR) activation in pancreatic islets. Importantly, MANF protein enhanced β cell proliferation in vitro and overexpression of MANF in the pancreas of diabetic mice enhanced β cell regeneration. The authors demonstrate that MANF specifically promotes β cell proliferation and survival, thereby constituting a therapeutic candidate for β cell protection and regeneration.

Clinical Pharmacology and Therapeutics Branch

Treatment Section

Substance Use and Hepatitis C: An Ecological Momentary Assessment Study Phillips KA, Epstein DH, Vahabzadeh M, Mezghanni M, Lin J-L, Preston KL. Health Psychology, 2014 Jul; 33(7): 710-719.
The objective of this study was to assess craving and mood related to opioid and cocaine use among asymptomatic hepatitis C virus (HCV)+ and HCV– methadone patients who have not started antiviral treatment. In this 28-week prospective ecological momentary assessment (EMA) study, 114 methadone-maintained, heroin- and cocaine-abusing individuals reported from the field in real time on their mood, craving, exposure to drug-use triggers, and drug use via handheld computers. Sixty-one percent were HCV+; none were overtly symptomatic or receiving HCV treatment. HCV status was not associated with age, sex, race, or past-30-day or lifetime heroin or cocaine use. In event-contingent EMA entries, HCV+ individuals more often attributed use to having been bored, worried, or sad; feeling uncomfortable; or others being critical of them compared with HCV– participants. In randomly prompted EMA entries, HCV+ participants reported significantly more exposure to drug-use triggers, including handling at least $10 in cash, seeing cocaine or heroin, seeing someone being offered/use cocaine or heroin, being tempted to use cocaine, and wanting to see what would happen if they used just a little cocaine or heroin. HCV+ individuals experienced more negative moods and more often cited these negative moods as causes for drug use. HCV+ individuals reported greater exposure to environmental drug-use triggers, but they did not more frequently cite these as causes for drug use. The EMA data reported here suggest that HCV+ intravenous drug users may experience more labile mood and more reactivity to mood than HCV– intravenous drug users. The reason for the difference is not clear, but HCV status may be relevant to tailoring of treatment.

Identifying Drug (Cocaine) Intake Events From Acute Physiological Response In the Presence Of Free-Living Physical Activity Hossain SM, Ali AA, Rahman MM, Ertin E, Epstein D, Kennedy A, Preston K, Umbricht A, Chen Y, Kumar S. Proc. ACM/IEEE International Conference on Information Processing in Sensor Networks (IPSN), Berlin, Germany, 2014.
A variety of health and behavioral states can potentially be inferred from physiological measurements that can now be collected in the natural free-living environment. The major challenge, however, is to develop computational models for automated detection of health events that can work reliably in the natural field environment. In this paper, the authors develop a physiologically-informed model to automatically detect drug (Cocaine) use events in the free-living environment of participants from their electrocardiogram (ECG) measurements. The key to reliably

detecting drug use events in the field is to incorporate the knowledge of autonomic nervous system (ANS) behavior in the model development so as to decompose the activation effect of Cocaine from the natural recovery behavior of the parasympathetic nervous system. The authors collect 89 days worth of data in two residential lab environments and 922 days of data in the field environment with illicit drug users, for a total of 11,000+ hours. They use the data collected in the lab environments to develop a model that tracks the recovery by the parasympathetic nervous system and then estimates the dampening caused to the recovery by the metabolism of Cocaine and consequent activation of the sympathetic nervous system. With appropriate data cleaning and screening procedures, the authors develop an efficient model that can quickly identify candidate windows of data to assess for potential drug use, and then apply the model on the recovery segments from these windows. The model keeps the false positive rate to 0.87/day (for 9+ hours/day of ECG data) in the lab and to 1.13/day (for 11+ hours/day of ECG data) in the field, both for 100% true positive rate.

Psychostimulant Addiction Treatment Phillips KA, Epstein DH, Preston KL. Neuropharmacology, 2014 Apr 12. pii: S0028-3908(14)00128-2. doi: 10.1016/j.neuropharm.2014.04.002.
Treatment of psychostimulant addiction has been a major, and not fully met, challenge. For opioid addiction, there is strong evidence for the effectiveness of several medications. For psychostimulants, there is no corresponding form of agonist maintenance that has met criteria for regulatory approval or generally accepted use. Stimulant-use disorders remain prevalent and can result in both short-term and long-term adverse consequences. The mainstay of treatment remains behavioral interventions. In this paper, the authors discuss those interventions and some promising candidates in the search for pharmacological interventions. This article is part of the Special Issue entitled 'CNS Stimulants'.

Integrative Neuroscience Research Branch

Neuronal Networks Section

Single Rodent Mesohabenular Axons Release Glutamate and GABA Phillips KA, Epstein DH, Preston KL. Neuropharmacology, 2014 Apr 12. pii: S0028-3908(14)00128-2. doi: 10.1016/j.neuropharm.2014.04.002.
The lateral habenula (LHb) is involved in reward, aversion, addiction and depression through descending interactions with several brain structures, including the ventral tegmental area (VTA). The VTA provides reciprocal inputs to LHb, but their actions are unclear. Here the authors show that the majority of rat and mouse VTA neurons innervating LHb coexpress markers for both glutamate signaling (vesicular glutamate transporter 2; VGluT2) and GABA signaling (glutamic acid decarboxylase; GAD, and vesicular GABA transporter; VGaT). A single axon from these mesohabenular neurons coexpresses VGluT2 protein and VGaT protein and, surprisingly, establishes symmetric and asymmetric synapses on LHb neurons. In LHb slices, light activation of mesohabenular fibers expressing channelrhodopsin2 driven by VGluT2 (Slc17a6) or VGaT (Slc32a1) promoters elicits release of both glutamate and GABA onto single LHb neurons. In vivo light activation of mesohabenular terminals inhibits or excites LHb neurons. These findings reveal an unanticipated type of VTA neuron that cotransmits glutamate and GABA and provides the majority of mesohabenular inputs.

Role Of Glutamatergic Projections From Ventral Tegmental Area To Lateral Habenula In Aversive Conditioning Root DH, Mejias-Aponte CA, Qi J, Morales M. J Neurosci. 2014 Oct 15;34(42):13906-13910.

The dopamine transporter (DAT) functions as a key The ventral tegmental area (VTA) plays roles in both reward and aversion. The participation of VTA in diverse behaviors likely reflects its heterogeneous neuronal phenotypes and circuits. Recent findings indicate that VTA GABAergic neurons that coexpress tyrosine hydroxylase (TH) projecting to lateral habenula (LHb) play a role in reward. In addition to these mesohabenular TH-GABAergic neurons, the VTA has many neurons expressing vesicular glutamate transporter 2 (VGluT2) that also project to LHb. To determine the behavioral role of mesohabenular VGluT2 neurons, the authors targeted channelrhodopsin2 to VTA VGluT2 neurons of VGluT2::Cre mice. These mice were tested in an apparatus where moving into one chamber stimulated VTA VGluT2 projections within the LHb, and exiting the chamber inactivated the stimulation. The authors found that mice spent significantly less time in the chamber where VGluT2 mesohabenular fiber stimulation occurred. Mice that received injections of mixed AMPA and NMDA glutamate receptor antagonists in LHb were unresponsive to VGluT2-mesohabenular fiber stimulation, demonstrating the participation of LHb glutamate receptors in mesohabenular stimulation-elicited aversion. In the absence of light stimulation, mice showed a conditioned place aversion to the chamber that was previously associated with VGluT2-mesohabenular fiber stimulation. The authors conclude that there is a glutamatergic signal from VTA VGluT2-mesohabenular neurons that plays a role in aversion by activating LHb glutamatergic receptors.

A Glutamatergic Reward Input From the Dorsal Raphe To Ventral Tegmental Area Dopamine Neurons Qi J, Zhang S, Wang HL, Wang H, de Jesus Aceves Buendia J, Hoffman AF, Lupica CR, Seal RP, Morales M. Nat Commun. 2014 Nov 12;5:5390.

Electrical stimulation of the dorsal raphe (DR) and ventral tegmental area (VTA) activates the fibres of the same reward pathway but the phenotype of this pathway and the direction of the reward-relevant fibres have not been determined. Here the authors report rewarding effects following activation of a DR-originating pathway consisting of vesicular glutamate transporter 3 (VGluT3) containing neurons that form asymmetric synapses onto VTA dopamine neurons that project to nucleus accumbens. Optogenetic VTA activation of this projection elicits AMPA-mediated synaptic excitatory currents in VTA mesoaccumbens dopaminergic neurons and causes dopamine release in nucleus accumbens. Activation also reinforces instrumental behaviour and establishes conditioned place preferences. These findings indicate that the DR-VGluT3 pathway to VTA utilizes glutamate as a neurotransmitter and is a substrate linking the DR-one of the most sensitive reward sites in the brain-to VTA dopaminergic neurons.

Glutamate Neurons Within the Midbrain Dopamine Regions Morales M, Root DH. Neuroscience. 2014 May 27;282C: 60-68.

Midbrain dopamine systems play important roles in Parkinson's disease, schizophrenia, addiction, and depression. The participation of midbrain dopamine systems in diverse clinical contexts suggests these systems are highly complex. Midbrain dopamine regions contain at least three neuronal phenotypes: dopaminergic, GABAergic, and glutamatergic. Here, the authors review the locations, subtypes, and functions of glutamatergic neurons within midbrain dopamine regions. Vesicular glutamate transporter 2 (VGluT2) mRNA-expressing neurons are observed within each midbrain dopamine system. Within rat retrorubral field (RRF), large populations of VGluT2 neurons are observed throughout its anteroposterior extent. Within rat substantia nigra pars compacta (SNC), VGluT2 neurons are observed centrally and caudally, and are most dense within

the laterodorsal subdivision. RRF and SNC rat VGluT2 neurons lack tyrosine hydroxylase (TH), making them an entirely distinct population of neurons from dopaminergic neurons. The rat ventral tegmental area (VTA) contains the most heterogeneous populations of VGluT2 neurons. VGluT2 neurons are found in each VTA subnucleus but are most dense within the anterior midline subnuclei. Some subpopulations of rat VGluT2 neurons co-express TH or glutamic acid decarboxylase (GAD), but most of the VGluT2 neurons lack TH or GAD. Different subsets of rat VGluT2-TH neurons exist based on the presence or absence of vesicular monoamine transporter 2, dopamine transporter, or D2 dopamine receptor. Thus, the capacity by which VGluT2-TH neurons may release dopamine will differ based on their capacity to accumulate vesicular dopamine, uptake extracellular dopamine, or be autoregulated by dopamine. Rat VTA VGluT2 neurons exhibit intrinsic VTA projections and extrinsic projections to the accumbens and to the prefrontal cortex. Mouse VTA VGluT2 neurons project to accumbens shell, prefrontal cortex, ventral pallidum, amygdala, and lateral habenula. Given their molecular diversity and participation in circuits involved in addiction, we hypothesize that individual VGluT2 subpopulations of neurons play unique roles in addiction and other disorders.

Structural Biology Unit

Chronic Ethanol Consumption Profoundly Alters Regional Brain Ceramide and Sphingomyelin Content In Rodents Roux A, Muller L, Jackson SN, Baldwin K, Womack V, Pagiazitis J, O'Rourke JR, Thanos PK, Balaban C, Schultz JA, Volkow ND, Woods AS. ACS Chem Neurosci. 2014 Dec 1, 2014 [Epub ahead of print].
Ceramides (CER) are involved in alcoholinduced neuroinflammation. In a mouse model of chronic alcohol exposure, 16 CER and 18 sphingomyelin (SM) concentrations from whole brain lipid extracts were measured using electrospray mass spectrometry. All 18 CER concentrations in alcohol exposed adults increased significantly (range: 25−607%); in juveniles, 6 CER decreased (range: −9 to −37%). In contrast, only three SM decreased in adult and one increased significantly in juvenile. Next, regional identification at 50 μm spatial resolution from coronal sections was obtained with matrix implanted laser desorption/ionization mass spectrometry imaging (MILDI-MSI) by implanting silver nanoparticulate matrices followed by focused laser desorption. Most of the CER and SM quantified in whole brain extracts were detected in MILDI images. Coronal sections from three brain levels show qualitative regional changes in CER-SM ion intensities, as a function of group and brain region, in cortex, striatum, accumbens, habenula, and hippocampus. Highly correlated changes in certain white matter CER-SM pairs occur in regions across all groups, including the hippocampus and the lateral (but not medial) cerebellar cortex of adult mice. These data provide the first microscale MS evidence of regional lipid intensity variations induced by alcohol.

Complex Molecular and Cellular Mechanisms Regulate G-Protein-Coupled Receptors (Gpcrs) and Influence Their Plasticity Tovo-Rodrigues L, Roux A, Hutz MH, Rhode LA, Woods AS. Neuroscience 2014;277: 764-779.
It is suggested that proteins intrinsically disordered regions (IDRs) play a role in GPCR's intra and extracellular regions plasticity, due to their potential for post-translational modification and interaction with other proteins. These regions are defined as lacking a stable three-dimensional (3D) structure. They are rich in hydrophilic and charged, amino acids and are capable to assume different conformations which allow them to interact with multiple partners. In this study the authors analyzed 75 GPCR involved in synaptic transmission using computational tools for sequence-based

prediction of IDRs within a protein. They also evaluated putative ligand-binding motifs using receptor sequences. The disorder analysis indicated that neurotransmitter GPCRs have a significant amount of disorder in their N-terminus, third intracellular loop (3IL) and C-terminus. About 31%, 39% and 53% of human GPCR involved in synaptic transmission are disordered in these regions. Thirty-three percent of receptors show at least one predicted PEST motif, this being statistically greater than the estimate for the rest of human GPCRs. About 90% of the receptors had at least one putative site for dimerization in their 3IL or C-terminus. ELM instances sampled in these domains were 14-3-3, SH3, SH2 and PDZ motifs. In conclusion, the increased flexibility observed in GPCRs, added to the enrichment of linear motifs, PEST and heteromerization sites, may be critical for the nervous system's functional plasticity.

Cellular Pathobiology Section

Bcl-2 Family In Inter-Organelle Modulation Of Calcium Signaling; Roles In Bioenergetics and Cell Survival Lewis A, Hayashi T, Su T-P, Betenbaugh MJ. J Bioenerg Biomembr 2014; 46: 1–15.

Bcl-2 family proteins, known for their apoptosis functioning at the mitochondria, have been shown to localize to other cellular compartments to mediate calcium (Ca2+) signals. Since the proper supply of Ca2+ in cells serves as an important mechanism for cellular survival and bioenergetics, we propose an integrating role for Bcl-2 family proteins in modulating Ca2+ signaling. The endoplasmic reticulum (ER) is the main Ca2+ storage for the cell and Bcl-2 family proteins competitively regulate its Ca2+ concentration. Bcl-2 family proteins also regulate the flux of Ca2+ from the ER by physically interacting with inositol 1,4,5-trisphosphate receptors (IP3Rs) to mediate their opening. Type 1 IP3Rs reside at the bulk ER to coordinate cytosolic Ca2+ signals, while type 3 IP3Rs reside at mitochondria-associated ER membrane (MAM) to facilitate mitochondrial Ca2+ uptake. In healthy cells, mitochondrial Ca2+ drives pyruvate into the citric acid (TCA) cycle to facilitate ATP production, while a continuous accumulation of Ca2+ can trigger the release of cytochrome c, thus initiating apoptosis. Since multiple organelles and Bcl-2 family proteins are involved in Ca2+ signaling, the authors aim to clarify the role that Bcl-2 family proteins play in facilitating Ca2+ signaling and how mitochondrial Ca2+ is relevant in both bioenergetics and apoptosis. They also explore how these insights could be useful in controlling bioenergetics in apoptosis-resistant cell lines.

Morphine Drives Internal Ribosome Entry Site-Mediated Hnrnp K Translation In Neurons Through Opioid Receptor-Dependent Signaling Lee PT, Chao PK, Ou LC, Chuang JY, Lin YC, Chen SC, Chang HF, Law PY, Loh HH, Chao YS, Su TP, Yeh SH. Nucleic Acids Research 2014; 42 (21):13012-13025.

Heterogeneous nuclear ribonucleoprotein K (hnRNP K) binds to the promoter region of mu-opioid receptor (MOR) to regulate its transcriptional activity. How hnRNP K contributes to the analgesic effects of morphine, however, is largely unknown. The authors provide evidence that morphine increases hnRNP K protein expression via MOR activation in rat primary cortical neurons and HEK-293 cells expressing MORs, without increasing mRNA levels. Using the bicistronic reporter assay, they examined whether morphine-mediated accumulation of hnRNP K resulted from translational control. They identified potential internal ribosome entry site elements located in the 5' untranslated regions of hnRNP K transcripts that were regulated by morphine. This finding suggests that internal translation contributes to the morphine-induced accumulation of hnRNP K protein in regions of the central nervous system correlated with nociceptive and antinociceptive modulatory

systems in mice. Finally, they found that downregulation of hnRNP K mediated by siRNA attenuated morphine-induced hyperpolarization of membrane potential in AtT20 cells. Silencing hnRNP K expression in the spinal cord increased nociceptive sensitivity in wild-type mice, but not in MOR-knockout mice. Thus, these findings identify the role of translational control of hnRNP K in morphine-induced analgesia through activation of MOR.

Sigma-1 Receptor Chaperones In Neurodegenerative and Psychiatric Disorders Tsai SY, Pokrass MJ, Klauer NR, De Credico NE, Su TP. Expert Opinion on Therapeutic Targets, 2014; 18(12):1461-1476.
Sigma-1 receptors (Sig-1Rs) are molecular chaperones that reside mainly in the endoplasmic reticulum (ER) but exist also in the proximity of the plasma membrane. Sig-1Rs are highly expressed in the CNS and are involved in many cellular processes including cell differentiation, neuritogenesis, microglia activation, protein quality control, calcium-mediated ER stress and ion channel modulation. Disturbance in any of the above cellular processes can accelerate the progression of many neurological disorders; therefore, the Sig-1R has been implicated in several neurological diseases. This review broadly covers the functions of Sig-1Rs including several neurodegenerative disorders in humans and drug addiction associated neurological disturbance in the case of HIV infection. The authors discuss how several Sig-1R ligands could be utilized in therapeutic approaches to treat those disorders. Emerging understanding of the cellular functions of this unique transmembrane chaperone may lead to the use of new agents or broaden the use of certain available ligands as therapeutic targets in those neurological disorders.

Molecular Neuropsychiatry Research Branch

Differential Effects Of Binge Methamphetamine Injections On the mRNA Expression Of Histone Deacetylases (HDACs) In the Rat Striatum Omonijo O, Wongprayoon P, Ladenheim B, McCoy MT, Govitrapong P, Jayanthi S, Cadet JL. Neurotoxicology. 2014 Oct 27;45C:178-184.
Methamphetamine use disorder is characterized by recurrent binge episodes. Humans addicted to methamphetamine experience various degrees of cognitive deficits and show evidence of neurodegenerative processes in the brain. Binge injections of METH to rodents also cause significant toxic changes in the brain. In addition, this pattern of METH injections can alter gene expression in the dorsal striatum. Gene expression is regulated, in part, by histone deacetylation. The authors thus tested the possibility that METH toxic doses might cause changes in the mRNA levels of histone deacetylases (HDACs). They found that METH did produce significant decreases in the mRNA expression of HDAC8, which is a class I HDAC. METH also decreased expression of HDAC6, HDAC9, and HDAC10 that are class II HDACs. The expression of the class IV HDAC, HDAC11, was also suppressed by METH. The expression of Sirt2, Sirt5, and Sirt6 that are members of class III HDACs was also downregulated by METH injections. These findings implicate changes in HDAC expression may be an early indicator of impending METH-induced neurotoxicity in the striatum. This idea is consistent with the accumulated evidence that some HDACs are involved in neurodegenerative processes in the brain.

Differential Effects Of Environment-Induced Changes In Body Temperature On Modafinil's Actions Against Methamphetamine-Induced Striatal Toxicity In Mice Raineri M1, González B, Rivero-Echeto C, Muñiz JA, Gutiérrez ML, Ghanem CI, Cadet JL, García-Rill E, Urbano FJ, Bisagno V. Neurotox Res. 2014 Sep 27. [Epub ahead of print].
Methamphetamine (METH) exposure can produce hyperthermia that might lead to toxicity and

death. Modafinil is a wake-promoting compound that is also been prescribed off-label to treat METH dependence. Modafinil has shown neuroprotective properties against METH harmful effects in animal models. The goal of the present study was to test if the prevention of hyperthermia might play a role on the neuroprotective actions of modafinil against METH toxicity using various ambient temperatures. METH was administered to female C57BL/6 mice in a binge regimen: 4 × 5 mg/kg, 2 h apart; modafinil (90 mg/kg) was injected twice, 1 h before first and fourth METH injections. Drugs were given at cold ambient temperature (14 °C) or hot ambient temperature (29 °C). Body temperature was measured during treatments. Brains were dissected out 6 days after treatments and processed for tyrosine hydroxylase (TH), dopamine transporter (DAT), GFAP and c-Fos immunohistochemistry. Exposure to hot ambient temperature exacerbated METH toxicity evidenced by striatal reductions in TH and DAT and increased GFAP immmunoreactivity. Modafinil counteracted reductions in TH and DAT, but failed to block astroglial activation. At both ambient temperatures tested modafinil did induce increments in GFAP, but the magnitude was significantly lower than the one induced by METH. Both drugs induced increases in c-Fos positive nuclei; modafinil did not block this effect. These results suggest that protective effects of modafinil against METH-induced neurotoxicity may be dependent, in part, to its hypothermic effects. Nevertheless, modafinil maintained some protective properties on METH-induced alterations in the striatum at different ambient temperatures.

Glial-Neuronal Ensembles: Partners In Drug Addiction-Associated Synaptic Plasticity Cadet JL, Bisagno V. Front Pharmacol. 2014 Sep 2; 5: 204.

Drug addiction is manifested by a compulsive drive to take licit or illicit substances despite repeated severe adverse consequences (Volkow et al., 2012). Addiction is also accompanied by a vicious cycle of binges, abstinence, and relapses. Almost all drugs of abuse trigger euphoric feelings consequent to a rapid increase of dopamine levels in the mesolimbic system. Even after long periods of abstinence, addicts remain vulnerable to drug craving and/or relapses that can be triggered by stimuli previously associated with drugs (Koob and Volkow,2010). These features of addiction suggest that drugs might cause a form of persistent neuroplasticity that is acutely responsive to environmental stimuli, with consequent compulsive drug-seeking and taking behaviors. Neural functions require the coordinated interactions of multiple neuronal cell types and a diverse population of glial cells. The three major glial cell types in the brain, astrocytes, oligodendrocytes, and microglia, communicate with each other and with neurons by using neurotransmitters, other small molecules, and gap junctions (Araque et al., 2014). Oligodendrocytes increase the speed of electrical transmission through nerve axons by forming the axonal myelin sheath and clustering ion channels at nodes of Ranvier (Nave, 2010). Microglia prune synapses in part by monitoring synaptic transmission (Schafer et al., 2013; Wake et al., 2013). Astrocytes can regulate synaptic transmission between neurons by modifying the concentration of extracellular potassium, controlling local blood flow, by releasing and/or taking up neurotransmitters or neuromodulators, by delivering nutrients to neurons, and by altering the geometry and volume of the brain extracellular space (Araque et al., 2014). This brief summary of glial functions suggests that these cells might play important roles in the long-term manifestations of substance use disorders, both in terms of addiction to these agents and their long-term neuropsychiatric consequences. In what follows, we discuss some recent findings that support the thesis that glial cells are part and parcel of the plastic mechanisms that are induced by drugs of abuse.

Behavioral Neuroscience Section

A New Brain Site and Time For Late-Term Consolidation (Or Reconsolidation) Of Cocaine Memories Kramar, CP, Chefer, VI, Wise, RA, Medina, JH, Barbano, MF. Neuropsychopharmacology, 2014; 39(7):1645-1653.
Cocaine is thought to be addictive because it elevates dopamine levels in the striatum, reinforcing drug-seeking habits. Cocaine also elevates dopamine levels in the hippocampus, a structure involved in contextual conditioning as well as in reward function. Hippocampal dopamine promotes the late phase of consolidation of an aversive step-down avoidance memory. Here, the authors examined the role of hippocampal dopamine function in the persistence of the conditioned increase in preference for a cocaine-associated compartment. Blocking dorsal hippocampal D1-type receptors (D1Rs) but not D2-type receptors (D2Rs) 12 h after a single training trial extended persistence of the normally short-lived memory; conversely, a general and a specific phospholipase C-coupled D1R agonist (but not a D2R or adenylyl cyclase-coupled D1R agonist) decreased the persistence of the normally long-lived memory established by three-trial training. These effects of D1 agents were opposite to those previously established in a step-down avoidance task, and were here also found to be opposite to those in a lithium chloride-conditioned avoidance task. After returning to normal following cocaine injection, dopamine levels in the dorsal hippocampus were found elevated again at the time when dopamine antagonists and agonists were effective: between 13 and 17 h after cocaine injection. These findings confirm that, long after the making of a cocaine-place association, hippocampal activity modulates memory consolidation for that association via a dopamine-dependent mechanism. They suggest a dynamic role for dorsal hippocampal dopamine in this late-phase memory consolidation and, unexpectedly, differential roles for late consolidation of memories for places that induce approach or withdrawal because of a drug association.

Cholinergic PPTg Lesions Unexpectedly Fail To Alter Cocaine Or Heroin Self-Administration Or Conditioned Place Preference Steidl, S, Wang, H, Wise, RA. PLoS One, 2014; 9: e84412.
Cholinergic input to the ventral tegmental area (VTA) is known to contribute to reward. Although it is known that the pedunculopontine tegmental nucleus (PPTg) provides an important source of excitatory input to the dopamine system, the specific role of PPTg cholinergic input to the VTA in cocaine reward has not been previously determined. The authors used a diphtheria toxin conjugated to urotensin-II (Dtx::UII), the endogenous ligand for urotensin-II receptors expressed by PPTg cholinergic but not glutamatergic or GABAergic cells, to lesion cholinergic PPTg neurons. Dtx::UII toxin infusion resulted in the loss of 95.78 (±0.65)% of PPTg cholinergic cells but did not significantly alter either cocaine or heroin self-administration or the development of cocaine or heroin conditioned place preferences. Thus, cholinergic cells originating in PPTg do not appear to be critical for the rewarding effects of cocaine or of heroin.

Neuroimaging Research Branch

Low- But Not High-Frequency LFP Correlates With Spontaneous BOLD Fluctuations In Rat Whisker Barrel Cortex Lu H, Wang L, Rea WW, Brynildsen JK, Jaime S, Zuo Y, Stein EA, Yang Y.Cerebral Cortex. 2014 Oct 20. pii: bhu248. [Epub ahead of print].
Resting-state magnetic resonance imaging (rsMRI) is thought to reflect ongoing spontaneous brain activity. However, the precise neurophysiological basis of rsMRI signal remains elusive. Converging evidence supports the notion that local field potential (LFP) signal in the high-frequency range correlates with fMRI response evoked by a task (e.g., visual stimulation). It

remains uncertain whether this relationship extends to rsMRI. In this study, the authors systematically modulated LFP signal in the whisker barrel cortex (WBC) by unilateral deflection of rat whiskers. Results show that functional connectivity between bilateral WBC was significantly modulated at the 2 Hz, but not at the 4 or 6 Hz, stimulus condition. Electrophysiologically, only in the low-frequency range (<5 Hz) was the LFP power synchrony in bilateral WBC significantly modulated at 2 Hz, but not at 4- or 6-Hz whisker stimulation, thus distinguishing these 2 experimental conditions, and paralleling the findings in rsMRI. LFP power synchrony in other frequency ranges was modulated in a way that was neither unique to the specific stimulus conditions nor parallel to the fMRI results. These results support the hypothesis that emphasizes the role of low-frequency LFP signal underlying rsMRI.

Complexity Of Oxytocin′s Effects In A Chronic Cocaine Dependent Population Lee MR, Glassman M, King-Casas B, Kelly DL, Stein EA, Schroeder J, Salmeron BJ. European Neuropsychopharmacology 2014 Sep;24(9):1483-1491.
Behavioral and neuroplastic changes occurring in the development of addiction parallel those that occur in social bonding. This has led to speculation that drugs of abuse co-opt systems that subserve social attachment to shift attachment to drugs of abuse. Oxytocin, a neuropeptide that is important in social bonding, has been shown in rodents to decrease psychostimulant self-administration, locomotor activity, and conditioned place preference, it is unclear what role it may play in human drug addiction. In this double-blind, placebo-controlled crossover study, 23 cocaine-dependent inpatients in court-ordered treatment completed 4 task sessions measuring desire to use cocaine, cue-induced craving, monetary reward decisions and social cognition. Before each session, subjects administered 24 IU of intranasal oxytocin or placebo. Oxytocin increased desire to use cocaine and cue-induced excitability with no effect on cue-induced desire to use. Oxytocin also removed the effect of state anger on several measures of cue reactivity. Response to monetary reward increased under oxytocin and measures of social cognition worsened. The significant increase in the desire for drug and monetary reward as well as the significant decrease in measures of social cognition was small but warrant further study of the effect of oxytocin′s effect in cocaine dependent subjects. The effect of oxytocin to modulate the relationship between state anger and cue reactivity should be explored further for potential therapeutic use of oxytocin in cocaine dependent patients. These findings are discussed in light of the human and rodent oxytocin literature.

Abstinence From Cocaine and Sucrose Self-Administration Reveals Altered Mesocortico-limbic Circuit Connectivity By Resting State MRI Lu H, Zou Q, Chefer S, Ross TJ, Vaupel DB, Guillem K, Rea WP, Yang Y, Peoples LL, Stein EA. Brain Connectivity 2014 Sep;4(7):499-510.
Previous preclinical studies have emphasized that drugs of abuse, through actions within and between mesocorticolimbic (MCL) regions, usurp learning and memory processes normally involved in the pursuit of natural rewards. To distinguish MCL circuit pathobiological neuroadaptations that accompany addiction from general learning processes associated with natural reward, the authors trained two groups of rats to self-administer either cocaine (IV) or sucrose (orally) followed by an identically enforced 30 day abstinence period. These procedures are known to induce behavioral changes and neuroadaptations. A third group of sedentary animals served as a negative control group for general handling effects. The authors examined low-frequency spontaneous fluctuations in the functional magnetic resonance imaging (fMRI) signal, known as resting-state functional connectivity (rsFC), as a measure of intrinsic neurobiological interactions between brain regions. Decreased rsFC was seen in the cocaine-SA compared with both sucrose-SA and housing control groups between prelimbic (PrL) cortex and entopeduncular nucleus and between nucleus accumbens core (AcbC) and dorsomedial prefrontal cortex (dmPFC). Moreover,

individual differences in cocaine SA escalation predicted connectivity strength only in the Acb-dmPFC circuit. These data provide evidence of fronto-striatal plasticity across the addiction trajectory, which are consistent with Acb-PFC hypoactivity seen in abstinent human drug addicts, indicating potential circuit level biomarkers that may inform therapeutic interventions. They further suggest that available data from cross-sectional human studies may reflect the consequence of rather a predispositional predecessor to their dependence.

Temporal Difference Error Prediction Signal Dysregulation In Cocaine Dependence Stein EA. Neuropsychopharmacology. 2014 Jun; 39(7):1732-1742.
Cocaine dependence impacts drug-related, dopamine-dependent reward processing, yet its influence on non-drug reward processing is unclear. Here, the author investigated cocaine-mediated effects on reward learning using a natural food reinforcer. Cocaine-dependent subjects (N = 14) and healthy controls (N = 14) learned to associate a visual cue with a juice reward. In subsequent functional imaging sessions they were exposed to trials where juice was received as learned, withheld (negative temporal difference error (NTDE)), or received unexpectedly (positive temporal difference error (PTDE)). Subjects were scanned twice in sessions that were identical, except that cocaine-dependent participants received cocaine or saline 10 min before task onset. In the insula, precentral and postcentral gyri NTDE signals were greater, and PTDE-related function was reduced in cocaine-dependent subjects. Compared with healthy controls, in the cocaine-dependent group PTDE signals were also reduced in medial frontal gyrus and reward-related function, irrespective of predictability, was reduced in the putamen. Group differences in error-related activity were predicted by the time as last self-administered cocaine use, but TDE function was not influenced by acute cocaine. Thus, cocaine dependence seems to engender increased responsiveness to unexpected negative outcomes and reduced sensitivity to positive events in dopaminergic reward regions. Although it remains to be established if these effects are a consequence of or antecedent to cocaine dependence, they likely have implications for the high-cocaine use recidivism rates by contributing to the drive to consume cocaine, perhaps via influence on dopamine-related reward computations. The fact that these effects do not acquiesce to acute cocaine administration might factor in binge-related escalated consumption.

Cellular Neurobiology Research Branch

Behavioral Neurophysiology Research Section

Orbitofrontal Inactivation Restores Insight Lost After Cocaine Use Lucantonio F, Takahashi YK, Hoffman AF, Chang CY, Bali-Chaudhary S, Shaham Y, Lupica CR, Schoenbaum G. Nature Neuroscience. 2014 Aug;17(8):1092-1099.
Addiction is characterized by a lack of insight into the likely outcomes of one's behavior. Insight, or the ability to imagine outcomes, is evident when outcomes have not been directly experienced. Using this concept, work in both rats and humans has recently identified neural correlates of insight in the medial and orbital prefrontal cortices. The authors found that these correlates were selectively abolished in rats by cocaine self-administration. Their abolition was associated with behavioral deficits and reduced synaptic efficacy in orbitofrontal cortex, the reversal of which by optogenetic activation restored normal behavior. These results provide a link between cocaine use and problems with insight. Deficits in these functions are likely to be particularly important for problems such as drug relapse, in which behavior fails to account for likely adverse outcomes. As such, our data

provide a neural target for therapeutic approaches to address these defining long-term effects of drug use.

Orbitofrontal Neurons Acquire Responses To 'Valueless' Pavlovian Cues During Unblocking McDannald MA, Esber GR, Wegener MA, Wied HM, Liu TL, Stalnaker TA, Jones JL, Trageser J, Schoenbaum G. Elife. 2014 Jul 18;3:e02653. doi:10.7554/eLife.02653.
The orbitofrontal cortex (OFC) has been described as signaling outcome expectancies or value. Evidence for the latter comes from the studies showing that neural signals in the OFC correlate with value across features. Yet features can co-vary with value, and individual units may participate in multiple ensembles coding different features. Here the authors used unblocking to test whether OFC neurons would respond to a predictive cue signaling a 'valueless' change in outcome flavor. Neurons were recorded as the rats learned about cues that signaled either an increase in reward number or a valueless change in flavor. The authors found that OFC neurons acquired responses to both predictive cues. This activity exceeded that exhibited to a 'blocked' cue and was correlated with activity to the actual outcome. These results show that OFC neurons fire to cues with no value independent of what can be inferred through features of the predicted outcome.

Interneurons Are Necessary For Coordinated Activity During Reversal Learning In Orbitofrontal Cortex Bissonette GB, Schoenbaum G, Roesch MR, Powell EM. Biological Psychiatry. 2014 Epub ahead of print. doi:10.1016/j.biopsych.2014.07.023.
Cerebral cortical gamma-aminobutyric acidergic interneuron dysfunction is hypothesized to lead to cognitive deficits comorbid with human neuropsychiatric disorders, including schizophrenia, autism, and epilepsy. The authors have previously shown that mice that harbor mutations in the Plaur gene, which is associated with schizophrenia, have deficits in frontal cortical parvalbumin-expressing interneurons. Plaur mice have impaired reversal learning, similar to deficits observed in patients with schizophrenia. The authors examined the role of parvalbumin interneurons in orbitofrontal cortex during reversal learning by recording single unit activity from 180 control and 224 Plaur mouse neurons during a serial reversal task. Neural activity was analyzed during correct and incorrect decision choices and reward receipt. Neurons in control mice exhibited strong phasic responses both during discrimination and reversal learning to decisions and rewards, and the strength of the response was correlated with behavioral performance. Although baseline firing was significantly enhanced in Plaur mice, neural selectivity for correct or erroneous decisions was diminished and not correlated with behavior, and reward encoding was downscaled. In addition, Plaur mice showed a significant reduction in the number of neurons that encoded expected outcomes across task phases during the decision period. These data indicate that parvalbumin interneurons are necessary for the representation of outcomes in orbitofrontal cortex. Deficits in inhibition blunt selective neural firing during key decisions, contributing to behavioral inflexibility. These data provide a potential explanation for disorders of cognitive control that accompany the loss of these gamma-aminobutyric acidergic interneurons in human neuropsychiatric disorders, such as autism, epilepsy, and schizophrenia.

The Dorsal Raphe Nucleus Is Integral To Negative Prediction Errors In Pavlovian Fear Berg BA, Schoenbaum G, McDannald MA. European Journal of Neuroscience. 2014 Oct; 40(7): 3096-3101.
Prediction errors are central to modern learning theories. While brain regions contributing to reward prediction errors have been uncovered, the sources of aversive prediction errors remain largely unknown. Here the authors used probabilistic and deterministic reinforcement procedures, followed by extinction, to examine the contribution of the dorsal raphe nucleus to negative, aversive

prediction errors in Pavlovian fear. Rats with dorsal raphe lesions were able to acquire fear and reduce fear to a non-reinforced deterministic cue. However, dorsal raphe lesions impaired the reduction of fear to a probabilistic cue and fear extinction to a deterministic cue, both of which involve the use of negative prediction errors. The results point to an integral role for the dorsal raphe nucleus in negative prediction error signaling in Pavlovian fear.

Clinical Psychoneuroendocrinology and Neuropsychopharmacology Branch

Relationship Between the Thyroid Axisa and Alcohol Craving Aoun EG, Lee MR, Haass-Koffler CL, Swift RM, Addolorato G, Kenna GA, Leggio L. Alcohol Alcohol. 2014 Nov 28. pii: agu085. [Epub ahead of print].
In this study with treatment-seeking alcoholic-patients, the relationship between thyroid hormones and alcohol craving and drinking was investigated. The main findings were a significant positive relationship between fT3 and alcohol craving and a significant effect of alcohol abstinence on TSH levels. This study is important because it replicates previous findings conducted in independent clinical samples and suggests that the thyroid axis might represent a biomarker of alcohol craving and drinking.

Baclofen For the Treatment Of Alcohol Dependence and Possible Role Of Comorbid Anxiety Morley KC, Baillie A, Leung S, Addolorato G, Leggio L, Haber PS. Alcohol Alcohol. 2014 Sep 21. pii: agu062. [Epub ahead of print].
In this analysis of a randomized clinical trial, anxiety comorbidity was used to stratify patients in two subgroups. The study enrolled 42 alcohol-dependent patients randomized to receive placebo, baclofen 30 mg/day or baclofen 60 mg/day for 12 weeks. While main analyses did not detect a medication effect, stratification by anxiety comorbidity revealed a beneficial effect of baclofen 30 mg/day versus placebo on time to lapse and relapse. There was also a beneficial effect for baclofen 60 mg/day relative to placebo on time to relapse in this comorbid group. Albeit preliminary, this study suggests a specific role of baclofen in alcohol-dependent individuals with comorbid anxiety.

Integrative Neurobiology Section

Functional Selectivity Of Allosteric Interactions Within G Protein-Coupled Receptor Oligomers: The Dopamine D1-D3 Receptor Heterotetramer Guitart X, Navarro G, Moreno E, Yano H, Cai NS, Sánchez-Soto M, Kumar-Barodia S, Naidu YT, Mallol J, Cortés A, Lluís C, Canela EI, Casadó V, McCormick PJ, Ferré S. Molecular Pharmacology 2014; 86: 417-429.
The dopamine D1 receptor-D3 receptor (D1R-D3R) heteromer is being considered as a potential therapeutic target for neuropsychiatric disorders. Previous studies suggested that this heteromer could be involved in the ability of D3R agonists to potentiate locomotor activation induced by D1R agonists. It has also been postulated that its overexpression plays a role in L-dopa-induced dyskinesia and in drug addiction. However, little is known about its biochemical properties. By combining bioluminescence resonance energy transfer, bimolecular complementation techniques, and cell-signaling experiments in transfected cells, evidence was obtained for a tetrameric stoichiometry of the D1R-D3R heteromer, constituted by two interacting D1R and D3R homodimers coupled to Gs and Gi proteins, respectively. Coactivation of both receptors led to the canonical negative interaction at the level of adenylyl cyclase signaling, to a strong recruitment of β-arrestin-1, and to a positive cross talk of D1R and D3R agonists at the level of mitogen-activated

protein kinase (MAPK) signaling. Furthermore, D1R or D3R antagonists counteracted β-arrestin-1 recruitment and MAPK activation induced by D3R and D1R agonists, respectively (cross-antagonism). Positive cross talk and cross-antagonism at the MAPK level were counteracted by specific synthetic peptides with amino acid sequences corresponding to D1R transmembrane (TM) domains TM5 and TM6, which also selectively modified the quaternary structure of the D1R-D3R heteromer, as demonstrated by complementation of hemiproteins of yellow fluorescence protein fused to D1R and D3R. These results demonstrate functional selectivity of allosteric modulations within the D1R-D3R heteromer, which can be involved with the reported behavioral synergism of D1R and D3R agonists.

Intracellular Calcium Levels Determine Differential Modulation Of Allosteric Interactions Within G Protein-Coupled Receptor Heteromers Navarro G, Aguinaga D, Moreno E, Hradsky J, Reddy PP, Cortés A, Mallol J, Casadó V, Mikhaylova M, Kreutz MR, Lluís C, Canela EI, McCormick PJ, Ferré S. Chemistry & Biology 2014; 21: 1546-1556.
The pharmacological significance of the adenosine A2A receptor (A2AR)-dopamine D2 receptor (D2R) heteromer is well established and it is being considered as an important target for the treatment of Parkinson's disease and other neuropsychiatric disorders. However, the physiological factors that control its distinctive biochemical properties are still unknown. The authors demonstrate that different intracellular Ca2+ levels exert a differential modulation of A2AR-D2R heteromer-mediated adenylyl-cyclase and MAPK signaling in striatal cells. This depends on the ability of low and high Ca2+ levels to promote a selective interaction of the heteromer with the neuronal Ca2+-binding proteins NCS-1 and calneuron-1, respectively. These Ca2+-binding proteins differentially modulate allosteric interactions within the A2AR-D2R heteromer, which constitutes a unique cellular device that integrates extracellular (adenosine and dopamine) and intracellular (Ca+2) signals to produce a specific functional response.

Synthesis and Biological Evaluation Of A Novel Series Of Heterobivalent Muscarinic Ligands Based On Xanomeline and 1-[3-(4-Butylpiperidin-1-Yl)Propyl]-1,2,3,4-Tetrahydroquinolin-2-One (77-LH-28-1) Bonifazi A, Yano H, Del Bello F, Farande A, Quaglia W, Petrelli R, Matucci R, Nesi M, Vistoli G, Ferré S, Piergentili A. Journal of Medicinal Chemistry 2014; 57: 9065-9077.
Novel bitopic hybrids, based on the M1/M4 muscarinic acetylcholine receptor (mAChR) orthosteric agonist xanomeline (1) and the putative M1 mAChR allosteric agonist 1-[3-(4-butylpiperidin-1-yl)propyl]-1,2,3,4-tetrahydroquinolin-2-one (77-LH-28-1, 3) connected by an aliphatic linker of variable length, were prepared. The novel heterobivalent hybrids 4a-f along with the intermediate alcohols 5a-f were pharmacologically evaluated in radioligand binding assays and some of them for their functional efficacies in bioluminescence resonance energy transfer (BRET)-based assays to give an insight into the structure-activity relationships of bivalent and linker-attached compounds in mAChRs. The hybrid 4d exhibited high efficacy for β-arrestin2 engagement in M1 mAChR and alcohol 5c behaved much like 3 at M1 mAChR and showed full antagonism in both Gi activation and β-arrestin2 engagement at M4 mAChR. Moreover, docking simulations on the M1 mAChR model were performed to elucidate how the binding mode of the proposed compounds is influenced by the linker length.

Comparison Of Caffeine and D-Amphetamine In Cocaine-Dependent Subjects: Differential Outcomes On Subjective and Cardiovascular Effects, Reward Learning, and Salivary Paraxanthine Lane SD, Green CE, Schmitz JM, Rathnayaka N, Fang WB, Ferré S, Moeller FG. Journal of Addiction Research and Therapy 2014; 5: 176.

Due to indirect modulation of dopamine transmission, adenosine receptor antagonists may be useful in either treating cocaine use or improving disrupted cognitive-behavioral functions associated with chronic cocaine use. To compare and contrast the stimulant effects of adenosine antagonism to direct dopamine stimulation, we administered 150 mg and 300 mg caffeine, 20 mg amphetamine, and placebo to cocaine-dependent vs. healthy control subjects, matched on moderate caffeine use. Data were obtained on measures of cardiovascular effects, subjective drug effects (ARCI, VAS, DEQ), and a probabilistic reward-learning task sensitive to dopamine modulation. Levels of salivary caffeine and the primary caffeine metabolite paraxanthine were obtained on placebo and caffeine dosing days. Cardiovascular results revealed main effects of dose for diastolic blood pressure and heart rate; follow up tests showed that controls were most sensitive to 300 mg caffeine and 20 mg amphetamine; cocaine-dependent subjects were sensitive only to 300 mg caffeine. Subjective effects results revealed dose × time and dose × group interactions on the ARCI A, ARCI LSD, and VAS 'elated' scales; follow up tests did not show systematic differences between groups with regard to caffeine or d-amphetamine. Large between-group differences in salivary paraxanthine (but not salivary caffeine) levels were obtained under both caffeine doses. The cocaine-dependent group expressed significantly higher paraxanthine levels than controls under 150 mg and 3-4 fold greater levels under 300 mg at 90 min and 150 min post caffeine dose. However, these differences also covaried with cigarette smoking status (not balanced between groups), and nicotine smoking is known to alter caffeine/paraxanthine metabolism via cytochrome P450 enzymes. These preliminary data raise the possibility that adenosine antagonists may affect cocaine-dependent and non-dependent subjects differently. In conjunction with previous preclinical and human studies, the data suggest that adenosine modulating drugs may have value in the treatment of stimulant use disorders.

EXTRAMURAL POLICIES AND REVIEW ACTIVITIES

Receipt, Referral, and Review

- Total # of grant applications: 1364
- DA primary: 939
- Institute-based reviews: 16 Grant SEPS (116 applications) and 3 Contract SEPS (11 proposals)

Grant Reviews

1. PA-14-015 (T32); Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grants (T32)
2. PAR-13-084 (R25); PAR-13-084: NIDA Research Education Program for Clinical Researchers and Clinicians (R25)
3. PA12-127; Multi-site clinical trials SEP
4. PA-14-042 (Parent K99/R00); NIH Pathway to Independence Award (K99/R00) & PAR-13-163 (K12); NIDA Mentored Clinical Scientists Development Program Award in Drug Abuse and Addiction (K12)
5. PAR-12-066 (R03); NIDA I/START Small Grant Review (R03)
6. PAR-14-010 (UH2/UH3); Identification of Gene Variants for Addiction Related Traits by Next-Gen Sequencing in Model Organisms Selectively Bred for Addiction Traits (UH2/UH3)
7. RFA-DA-15-004 (DP1); FY15 NIDA Avant-Garde Award Program for HIV/AIDS Research
8. PAR-13-270 (U01); GOMED U01: Grand Opportunity in Medications Development for Substance-Related Disorders
9. PAR-12-086 (R21); Cutting-Edge Basic Research Awards (CEBRA) (R21)
10. PAR-13-334 (R01); Strategic Alliances for Medications Development to Treat Substance Use Disorders (R01)
11. RFA-DA-15-005 (R01); Advancing Exceptional Research on HIV/AIDS (R01)
12. PA13-347 (R13); R13 Conference Grant Review (R13)
13. PAR-14-230 & 231; Exploratory Studies of Smoking Cessation Interventions for People with Schizophrenia (R21/R33)
14. PAR-12-199 (R25); Research Education Grants for Statistical and Computational Training in the Genetics of Addiction (R25)
15. RFA-DA-15-009 (U01); Neuroscience Information Framework (U01)
16. PAR-12-297 (R21); Mechanism for Time-Sensitive Drug Abuse Research (R21)

Contract Reviews

1. N01DA-10-9913 (mod 8); Out-Patient Drug Treatment Research Clinic
2. N43DA-15-8921; NIDA E-Cigarettes- SBIR PHASE I (8921)
3. N01DA-15-7793; Production, Analysis and Distribution of Cannabis, MJ (7793)

Certificates of Confidentiality

Between August 6th, 2014 and December 19th, 2014, 101 applications for new and amended Certificates of Confidentiality were processed. During the last Council round, (March 6, 2014 – August 5, 2014), 119 applications for new and amended applications were processed. These

numbers are frequency counts only and do not provide any insight into the complexity of the applications.

Staff Training and Development

Jose Ruiz was accepted and is currently a participant in the NIH Mid-Level Leadership Program – Series 17 (September 26, 2014 – July 17, 2015).

Dr. Yu (Woody) Lin of DCNBR, and a member of Consortium on Minority Affairs of NIDA Office of Diversity and Health Disparity, served at review panel of NIDA Diversity Supplement Program that meets monthly.

CCTN Extramural Policy and Review Activities

The Data and Safety Monitoring Board met

- August 6, 2014 to discuss CTN 0056-Ot, Testing and Linkage to HIV Care in China: a Cluster Randomized Trial
- August 12, 2014 to discuss CTN 0053, Achieving Cannabis Cessation-Evaluating N-Acetylcysteine Treatment (ACCENT)
- October 8, 2014 to discuss CTN 0051, Extended-Release Naltrexone vs. Buprenorphine for Opioid Treatment (X:BOT)
- October 27, 2014 to discuss CTN 0054, Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Dependence (ADAPT-MD)
- December 12, 2014 to discuss CTN 0055, Comparing Treatments for HIV-Positive Opioid Users in an Integrated Care Effectiveness Study (CHOICES)

CONGRESSIONAL AFFAIRS SECTION
(Prepared January 15, 2015)

APPROPRIATIONS

Congress wrapped up its appropriation work in December of last year, passing H.R. 83. NIH received $30.311 billion (excluding special Ebola funding), a 0.5% increase over FY 2014 Enacted levels. NIDA received an appropriation of $1.029 billion, a .31% increase over Enacted FY 2014 levels.

114th CONGRESS

The most relevant committee-related information for NIDA is listed below.
Senate: In the Senate, primary focus is on the

- Committee on Appropriations (Subcommittee on Labor, Health and Human Services, and Education; Financial Services; and Commerce, Justice, Science;
- Committee on Health, Education, Labor, and Pensions (HELP);
- Committee on the Judiciary; and the
- Caucus on International Narcotics Control (this is an officially recognized Caucus, established by law in 1985).

House: In the House, primary focus is on the

- Committee on Appropriations (Subcommittee on Labor, Health and Human Services, Education, and Related Agencies; Financial Services; and Commerce, Justice, Science and Related Agencies);
- Committee on Energy and Commerce (Subcommittee on Health); and the
- Committee on Oversight and Government Reform (Subcommittee on Government Operations OR Subcommittee on Health Care, Benefits, and Administrative Rules[1]).

In both the House and Senate, committee and subcommittee rosters are still being finalized. To present a complete picture, details will be provided in the May Report to Council.

LEGISLATION OF INTEREST

The 114th Congress is in its very early days. We expect to see the reintroduction of legislation proposed in the 113th Congress, focused on issues such as marijuana law reform, prescription drug abuse prevention and treatment, and juvenile and criminal justice system reform. In subsequent reports to Council, we will report on those bills if/when they are introduced.

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

[1] Jurisdictions still under review

INTERNATIONAL ACTIVITIES

NIDA Meetings

U.S. and French Researchers Focus on Binational Collaboration; Announce New NIDA-Inserm Fellows in Drug Abuse Research

Researchers from France and the United States presented research posters and exchanged ideas about binational research during the 2nd Workshop on France-USA Collaborative Initiatives in Addiction. Topics included addiction-related neuroimaging research, marijuana and alcohol research in an era of changing laws and policies, and the potential offered by large biorepositories to expand research into the genetics of addiction. NIDA Director Nora D. Volkow, M.D., and Mohamed Jaber, Ph.D., Laboratoire de Neurosciences Expérimentales et Cliniques, Poitiers, France, co-chaired the round table discussion. Speakers included NIAAA Director George Koob, Ph.D., who discussed the epidemiology of binge drinking among young people, and Jean-Pierre Changeux, Ph.D., Institut Pasteur, who reviewed advances in drug abuse neuroscience research. IP Director Steven W. Gust, Ph.D., and Mireille Guyader, Ph.D., Inserm, introduced the first researchers awarded NIDA-Inserm Postdoctoral Drug Abuse Research Fellowships, which provide 6- to 12-months of rigorous postdoctoral research training in the United States (for French applicants) or France (for U.S. applicants). The meeting was cosponsored by NIDA, NIAAA, Alliance Nationale pour les Sciences de la Vie et de la Sante (Aviesan), and Institut National de la Santé et de la Recherche Médicale (Inserm). In addition, NIDA supported Dr. Changeux's travel. The meeting was held at the Embassy of France on November 18, 2014, in Washington, DC. Other NIDA participants included Joni Rutter, Ph.D., and Jonathan Pollock, Ph.D., DBNBR; Joseph Frascella, Ph.D., DCBNR; Dale Weiss, IP; and Antonello Bonci, M.D., Yavin Shaham, Ph.D., and Amina S. Woods, Ph.D., IRP.

The new NIDA-Inserm Fellows are:

- **Vivien Zell, Ph.D.,** University of Strasbourg, will investigate how glutamate-releasing neurons in the ventral tegmental area contribute to brain function at the molecular, physiological, and behavioral levels and alter the reinforcement mechanisms that contribute to addiction. By identifying and assessing the function of genes enriched in VTA glutamate neurons, his results may suggest new targets or strategies to prevent or treat addiction. Dr. Zell also will investigate whether dopamine and glutamate are released from the same or separate synaptic vesicles, an important concept in presynaptic plasticity of the central nervous system. Dr. Zell's mentor is Thomas Hnasko, Ph.D., University of California, San Diego.

- **Yann Pelloux, Ph.D.,** a postdoctoral researcher at the Centre national de la recherché scientifique (National Center for Scientific Research) at Aix Marseille University. During his postdoctoral research at the University of Cambridge, Dr. Pelloux established an animal model of cocaine seeking and relapse that demonstrated a subset of rats would continue seeking cocaine despite punishment, which mimics human patterns of addiction. Dr. Pelloux will use his NIDA-Inserm fellowship to build on his Cambridge studies that found forebrain differences between compulsive and non-compulsive rats. Dr. Pelloux will use brain imaging and optogenetic techniques to compare neuronal activity in various brain regions and identify the neural networks involved in compulsive cocaine use and context-induced relapse. Dr. Pelloux's mentor is Shaham Yavin, Ph.D., IRP.

- **Andrew F. Scheyer**, Ph.D. candidate, Rosalind Franklin University of Medicine and Science. Mr. Scheyer will study adult rats to examine the consequences of prenatal or adolescent exposure to the primary active ingredient of cannabis, Δ-9 THC. He will investigate whether cannabis exposure disrupts short- and long-term plasticity in the brain and if these functional changes contribute to behaviors that increase addiction vulnerability. Additionally, he will test the viability of interventions using endocannabinoids to correct the behavioral consequences of prenatal and adolescent exposure to Δ-9 THC. Mr. Scheyer's mentor will be 1997 NIDA INVEST Fellow Olivier Manzoni, Ph.D., Institut de Neurobiology de la Mediterranee, in Marseille, France.

NIDA Organizes Symposium at ISAM Meeting

IP Director Steven W. Gust, Ph.D., organized and co-chaired a symposium entitled "Marijuana, Addiction Physicians, and Public Policy" at the International Society of Addiction Medicine (ISAM) meeting. Speakers included Jag H. Khalsa, Ph.D., DPMCDA, who reported on NIDA research into treatment medications, and Vladimir Poznyak, M.D., Ph.D., World Health Organization, who reported on global epidemiology of cannabis use and implications for public health. NIDA grantee Margaret Haney, Ph.D., Columbia University School of Medicine, presented the latest data on cannabinoid formulations, routes of administration, and treatment. Two speakers described the policy issues for addiction physicians in the United States: Stuart Gitlow, M.D., M.P.H., M.B.A., president of the American Society of Addiction Medicine, and Norman Wetterau, M.D., Tricounty Family Medicine and the University of Rochester, N.Y., School of Medicine. Gregory Bunt, M.D., Daytop Village, co-chaired the symposium. NIDA supported Dr. Haney's travel for the symposium. The meeting attracted more than 445 participants from 43 countries. It was held October 2-6, 2014, in Yokohama, Japan.

NIDA Briefs Addiction Research Organizations

IP Director Steven W. Gust, Ph.D., participated in the International Confederation of Alcohol, Tobacco and other Drug Research Associations (ICARA) meeting, which was held in conjunction with the International Society of Addiction Journal Editors (ISAJE) meeting, September 4-5, 2014, in Chicago. Dr. Gust described the productive partnership between the IP and ISAJE that is designed to help scientists from low- and middle-income countries (LMIC) publish their research results in peer-reviewed journals. NIDA has provided partial support for the ISAJE website Publishing Addiction Research Internationally (PARINT.org), an online writing mentor program where addiction journal editors provide one-on-one tutoring for LMIC researchers, and scientific writing workshops where ISAJE members train researchers in a specific country or region. Dr. Gust also summarized NIDA's international mission, funding support, research priorities, and fellowship opportunities. ICARA is an international network of national, regional and international societies that promotes research on alcohol, tobacco and other drugs through professional exchange, collaboration, and advocacy.

2014 Cellular Biology of Addiction Course Features International Opportunities

IP Associate Director Dale S. Weiss discussed opportunities for international research training and funding during a webinar for participants in the 2014 Cellular Biology of Addiction course. Ms. Weiss provided tips for building successful international research collaborations and described the seven NIDA international drug abuse research fellowship programs. She also reviewed NIH and other U.S. funding mechanisms that support international collaborative research. Other NIDA speakers during the webinar included Beth Babecki, M.A. and Jonathan Pollack, Ph.D., DBNBR. NIDA sponsored the course, which was held in Barcelona, Spain, and organized by the University Pompeu Fabra and Cold Spring Harbor Laboratory.

Research Results

International Teams Including Former Fellows Publish Results from Regional HIV Collaborative Research Grants

Former NIDA International fellows and their international partners have published findings from research funded through RFA-DA-10-008, International Research Collaborations on HIV/AIDS and Drug Use. The funding opportunity was issued to stimulate collaborative research among foreign investigators from the same geographic regions to address regional issues on the intersection of HIV/AIDS and drug use in international settings. The articles include:

- Sergei Dvoryak, M.D., Ph.D., a 2001-2001 NIDA Hubert H. Humphrey Drug Abuse Research Fellow and 2010 INVEST/Clinical Trials Network Drug Abuse Research Fellow, is the Ukrainian principal investigator on a grant investigating HIV among prisoners in Ukraine. Dvoryak and colleagues found that half of HIV-positive prisoners were unaware of their status, and that injection drug use, being female, and having been incarcerated previously were all correlated with HIV infection. The team recommends that HIV testing be conducted routinely for prisoners, and that opioid substitution and anti-retroviral therapy be expanded. **Correlates of HIV infection and being unaware of HIV status among soon-to-be-release Ukrainian prisoners** Azbel L, Wickersham JA, Grishaev Y, Dvoryak S, Altice FL. J Int AIDS Soc. 2014 Sep 10;17:19005. doi: 10.7448/IAS.17.1.19005. eCollection 2014.

- An article in the Journal of Addiction was written by researchers from the United States, Russia, and two fellows from the Republic of Georgia, 2003-2004 NIDA Hubert H. Humphrey Drug Abuse Research Fellow David Otiashvili, M.D., and 2014 Distinguished International Scientist Collaboration Awardee Irma Kirtadze, M.D. The authors described a series of preliminary studies conducted as the team began developing a culturally sensitive, women-focused, comprehensive treatment program for Georgian women who inject drugs. The international team concluded that mixed methods research investigating the role of Georgian culture in perceived drug treatment needs and risky drug use and sexual behaviors was a crucial step in designing the feasibility and initial efficacy trials now underway. **Process and product in cross-cultural treatment research: development of a culturally sensitive women-centered substance use intervention in Georgia** Jones HE, Kirtadze I, Otiashvili D, O'Grady KE, Murphy K, Zule W, Krupitsky E, Wechsberg WM. J Addict. 2014; 2014:163603. doi: 10.1155/2014/163603. Epub 2014 Sep 22.

Fellowships

Former NIDA Humphrey Fellows Train Drug Abuse Professionals in Asia

1994-1995 NIDA Humphrey Fellow Tay Bian How, Malaysia, directs the International Centre for Certification and Education of Addiction Professionals (ICCE), the training and credentialing arm of the Colombo Plan Drug Advisory Programme. Funded by the U.S. Department of State, the ICCE program collaborates with the U.S. National Association of Alcohol and Drug Abuse Counselors to train, certify and professionalize the addiction treatment workforce in the Asia-Pacific region. Training programs include Universal Treatment Curricula for Substance Use Disorders, Universal Prevention Curricula for Substance Use, Gender-Responsive Addiction Treatment, and Developing Community-Based Recovery Support Systems. 2009-2010 NIDA Humphrey Fellow Muzafar Mohd Razali, Ph.D., now a visiting scholar at Virginia Commonwealth University, served as an expert consultant for the Universal Prevention Curriculum.

NIDA, ANRS Create Postdoctoral Drug Abuse and HIV Research Fellowship

NIDA and the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) have created a postdoctoral research fellowship to advance scientific understanding of the linkages between drug abuse and HIV while fostering multinational research. The new fellowship is the fifth postdoctoral fellowship program established under the NIDA International Visiting Scientists and Technical Exchange (INVEST) Program. As with other NIDA INVEST fellowships, the new NIDA-ANRS Drug Abuse and HIV Research Fellowship will support 12-month postdoctoral appointments for talented scientists from any nation except the United States. Potential applicants will propose a research plan for working with an expert in HIV-related drug abuse research from a new database of potential mentors, who must be affiliated with a leading institute anywhere in the world. Potential fellows and their mentors will submit the application together. Applications are due April 1, and more details are available at drugabuse.gov/international/fellowships.

NIDA, State Department Welcome Humphrey Fellows

The 11 NIDA Hubert H. Humphrey Drug Abuse Research Fellows for 2014-2015 have began their studies at Virginia Commonwealth University (VCU), met with NIDA officials, and participated in the State Department Global Leadership Forum for Humphrey Fellows. On September 17-18, 2014, NIDA International Program Associate Director Dale Weiss and NIDA International Fellowships Administrator Lisa Jordre briefed the VCU cohort about NIDA's mission, international priorities, and programs to promote collaborative research and scientific exchange about drug abuse and addiction. They also met with each fellow individually to learn about the fellows' goals and to suggest potential professional affiliations. In November, 171 fellows from 98 countries participated in the Global Leadership Forum. During that event, Ms. Weiss led a discussion session about drug abuse and its consequences for health, social, economic, education, and criminal justice systems. Participants included Mr. Brian Morales from the Department of State Bureau of International Narcotics and Law Enforcement Affairs (INL), who invited interested fellows to work with INL's international partners in implementing demand reduction programs.

The 2014-2015 NIDA Hubert H. Humphrey Drug Abuse Research Fellows are:

- **Mariam Abdoh, M.Sc. (Jordan)** Ms. Abdoh is the screening operations for the Jordan Breast Cancer Program in 2014, where she manages the national breast cancer screening and early detection projects for under-privileged communities and non-Jordanian refugees. She has managed public awareness campaigns, medical conferences, and professional training for medical professionals. During her fellowship, Ms. Abdoh will focus on noncommunicable disease prevention, particularly for underserved and minority populations, and on women's health, including nutritional, political and economic issues.
- **Yu Yu Aung, M.B.B.S., M.P.H. (Myanmar)** Dr. Aung has been working in health and development programs addressing HIV/AIDS, reproductive health, adolescent health and development, and capacity building for local nongovernmental organizations and community networks. As an HIV/AIDS National Program Officer in UNESCO, Dr. Aung helped establish the first network of youth at high risk for HIV infection, Myanmar Youth Stars, to prevent HIV transmission. During her fellowship, Dr. Aung will expand her knowledge of the behavioral, social, neurocognitive, and emotional development processes of adolescents; key risk and protective factors affecting health-related behaviors; and designing HIV prevention programs for young people.
- **Nora Binishi, M.Sc. (Kosovo)** An architectural engineer, Ms. Binishi is responsible for promoting hygienic maintenance, safety, and security for government buildings, such as the

University Clinical Center of Kosovo, to ensure a clean and healthy environment for staff and patients. During her fellowship, Ms. Binishi will focus on learning how to raise awareness about the importance of maintaining hospital infrastructure, technical and environmental methods to reduce healthcare-setting acquired infections, and how to transform aging hospital buildings into modern healthcare facilities.

- **Mohammed Magdy Elhamshary, M.D., M.Sc. (Egypt)** A doctoral candidate and an addiction specialist in, Dr. Elhamshary provides psychopharmacological management and counseling for patients with substance use disorders. He is experienced in cognitive behavioral therapy, motivational interviewing and family counseling. Working with nongovernmental organizations, he teaches parents how to detect and manage substance use by their children, trains mental health professionals in addiction medicine, and conducts research. During his fellowship, he will focus primarily on drug abuse prevention and treatment for adolescents in school and community settings.
- **Sylvester Ebenezer Nana Koomson, M.A. (Ghana)** Mr. Koomson is the head of the Greater Accra Regional Office of the Ghana Narcotics Control Board, which coordinates drug law enforcement in Ghana. Prior to his current position, Mr. Koomson lead the International Programs and Information Management section of the Ghana Narcotics Control Board. He focuses on substance abuse education and prevention, especially among youths, communities, and faith-based institutions. During his Fellowship, Mr. Koomson hopes to expand his knowledge of substance abuse education, treatment, and prevention; obtain experience in designing, monitoring, and evaluating effective and efficient interventions; and better understand drug control legislation and policies.
- **Jean-Li Lim, M.D., FRACGP, MAFPM, M. Med (Malaysia)** A primary care physician, Dr. Lim works with indigenous communities in Malaysia promoting Long Acting Reversible Contraception (LARC) to improve maternal health and improve the quality of life among women and their families. During her fellowship, she hopes to learn about assessing unmet health needs in order to design effective programs to improve sexual reproductive health practices among indigenous and marginalized women in Malaysia.
- **Abdul Subor Momand, M.D., M.P.H. (Afghanistan)** In 2008, Dr. Momand was selected as the deputy program coordinator for drug demand reduction in the Afghani Ministry of Public Health. A trainer and supervisor in a community-based mental health program, he has taught healthcare professionals about common mental health and substance use disorders and joined the UNODC Afghan Country Office in 2012 as the national training officer for drug demand reduction. During his fellowship, Dr. Momand wants to learn how to develop and implement more effective drug control policies and strategies and community-based drug abuse prevention and treatment programs, especially for women and children.
- **Farheen Naveed (Pakistan)** A certified substance abuse treatment practitioner, Ms. Naveed serves as a trainer for the Colombo Plan International Center for Certification of Addiction Professionals. She is the managing director of New Horizons Care Center, a pioneer in providing free treatment, rehabilitation and reintegration services to people with substance use disorders, and the founding director of the Drug Free Pakistan Foundation, a nongovernmental organization that provides drug abuse prevention services. In 2009, she successfully convinced the Karachi city district government to launch the Drug Free Karachi program, establishing the largest addiction treatment hospital in Pakistan. Ms. Naveed was nominated as one of the 10 most inspiring women of Pakistan in 2014, and she was recently nominated for an N-Peace Award. Her goals for the fellowship include enhancing her knowledge of evidence-based prevention programs so that she can expand the prevention services available in Pakistan.

- **Francis Kofi Torkornoo, M.A. (Ghana)** Mr. Torkornoo is the director of demand reduction for the Narcotics Control Board, the leading governmental agency in Ghana for drug law enforcement and demand reduction. He has developed a system to monitor precursor chemicals imported, distributed, or used in Ghana; expanded rehabilitation services; and worked on prevention and education programs to detect drug abuse among students in primary and secondary schools. During his fellowship, Mr. Torkornoo plans to study evidence-based substance abuse prevention and rehabilitation programs in the United States.
- **Nanda Myo Aung Wan, M.B.B.S., M. Med. Sc. (Myanmar)** A team leader in drug use prevention and treatment at the Ministry of Health Drug Treatment Hospital Myitkyina, Dr. Wan also provides HIV counseling and testing. He organized a steering committee of representatives from the government, international organizations, and nongovernmental organizations to coordinate harm reduction activities in Kachin State and is a member of the national coordination committee for harm reduction. Dr. Wan is also a monitoring and evaluating officer for methadone maintenance therapy in Kachin State. During his fellowship, Dr. Wan will focus on drug use prevention policy for children and adolescents. He would also like to improve his knowledge of research methodology and develop his ability to conduct a substance use survey among young people.
- **Geraldine Gonzalez Willim, M.S.W. (Paraguay)** A registered private practice social worker, Ms. Willim is designing an educational project to train middle school teachers in drug prevention for the National Anti-Drug Secretariat. She was a director of cooperation at the SENAVITAT, worked at the National Secretariat for Social Action, and served as a qualitative investigation professor at the National University of Asuncion School of Social Work. During her fellowship, Ms. Willim hopes to expand her expertise in substance abuse prevention, treatment, monitoring and research. She also seeks to learn how to design and implement effective prevention programs, especially those programs that train children and teenagers as anti-drug leaders in their communities.

International Visitors

On September 9, 2014 a delegation of high-ranking officials from the China National Narcotics Control Commission, the body responsible for narcotic policies in the Chinese capital visited NIDA. The delegation was led by Li Xianhui the Deputy Secretary-General of the National Narcotics Control Commission. The main purpose of the visit was to learn more about new trends and characteristics regarding drug use in the U.S.

The Guatemalan Drug Commission visited NIDA on November 6, 2014. The commission, whose official name is the National Commission for the Reform of Drug Policy, was appointed by Guatemalan President Otto Perez Molina on October 2013 by executive order. This commission is in charge of revising drug policies and crafting the new antidrug strategy for Guatemala. The visit to NIDA was part of a fact-finding visit to the United States. The NIDA staff participating in the visit included Susan Weiss, Steve Gust, Dale Weiss, Tish Wiley and Maureen Boyle.

Other Activities

Dr. John Satterlee, DBNBR, gave an update on the Roadmap Epigenomics Program at the International Human Epigenome Consortium meeting and gave a presentation entitled "Funding Opportunities at NIDA/NIH" at the Canadian Epigenomics meeting October 7-9, 2014 in Vancouver Canada.

Dr. Jonathan D. Pollock attended the World Congress on Psychiatric Genetics in Copenhagen, Denmark, October 12-18, 2014.

Dr. Cheryl Anne Boyce, DCNBR, is serving as a member of the NIH Caribbean American Planning Committee with the mission: "Promoting science for, by and within the Caribbean" to plan activities including a future distinguished lecture series sponsored by NIH OBSSR. Dr. Jacqueline Lloyd, DESPR, also serves on the committee.

Dr. Ivan Montoya, DPMCDA, was invited to give a plenary lecture titled "Drug Abuse Treatment in Patients with Tuberculosis." at the 45th Union World Conference on Lung Health in Barcelona (Spain) on October 29th, 2014.

Dr. Jag Khalsa, DPMCDA, was sponsored by the Japanese Society on Alcohol-Related Problems to participate in the Annual Conference of the International Society of Addiction Medicine (ISAM), in Yokohama, Japan, October 2-6, 2014. He delivered a plenary lecture titled "Emerging Epidemic of Hepatitis C Infection in Young IDUs'. He also co-chaired with Dr. Greg Bunt, two symposia. One on Food Addiction where he gave a lecture titled 'Role of Nutrition, Nutrigenetics/Nutrigenomics, in Addiction', and another on Marijuana Legalization Policy where he talked about the Medical Consequences of Changes in Marijuana Legalization Policy.

Dr. Marisela Morales, IRP, recently gave invited lectures in Japan, Hungary, and Mexico.

Dr. Amy Newman, IRP, gave an invited lecture at the University of Copenhagen his fall.

Dr. Amy Newman chaired a dopamine transporter session at the 7th SFB35 Transmembrane Transporters in Health and Disease Annual Meeting, in Vienna, September, 2014.

Dr. Geoffrey Schoenbaum's lab helped co-organize and sponsor a meeting on prefrontal function in Whistler, BC: https://sites.google.com/site/prefrontalworkshop/ and has been invited to author reviews on orbitofrontal function by Nature Neuroscience and Current Opinions in Behavioral Neuroscience.

Dr. Yavin Shaham, IRP, gave invited lectures at the University of Cambridge, Tel-Aviv University, the Weizmann Institute, and Hebrew University.

Dr. Jean Lud Cadet, IRP, was the plenary speaker at the Third Symposium of the Latin American Research Network on Drug Addiction (LARNEDA) on November 20, 2014 in San Juan, Puerto Rico. His presentation was titled "Neuropathology of drug abuse disorders".

PROGRAM ACTIVITIES/FOAs

New NIDA RFAs

On January 16, 2015, NIDA issued an RFA entitled **NIDA Translational Avant-Garde Award for Development of Medication to Treat Substance Use Disorders (UH2/UH3)** RFA-DA-15-017. The purpose of this RFA is to support outstanding basic and/or clinical researchers with the vision and expertise to translate research discoveries into medications for the treatment of Substance Use Disorders (SUDs) stemming from tobacco, cannabis, cocaine, methamphetamine, heroin, or prescription opiate use. Eligible applicants must demonstrate the ability to develop molecules with the potential to treat SUDs and advance them in the drug development continuum. The ultimate goal of this FOA is to bring molecules closer to FDA approval. Open date: March 15, 2015. Application due date(s): April 15, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): April 15, 2015, by 5:00 PM local time of applicant organization.

On January 7, 2015, NIDA issued an RFA entitled **Integration of Infectious Diseases and Substance Abuse Intervention Services for Individuals Living with HIV (R01)** RFA-DA-15-013. The goal of this FOA is to develop and test organizational and systems level interventions to determine how best to provide comprehensive, high quality, integrated, sustainable, cost-effective interventions to improve the health outcomes of people living with HIV (PLWH) with substance use disorders and other comorbid conditions. This FOA will support: 1) multidisciplinary research to enhance the adoption and integration of evidence-based screening and treatment of substance abuse in HIV centers and closely related medical settings; and 2) multidisciplinary research to increase the adoption and integration of HIV testing and linkage to HIV care in addiction treatment settings. In both HIV and addiction treatment settings, research to enhance the adoption and integration of treatment services for comorbid conditions (e.g. coinfections, psychiatric disorders) is encouraged. Open date: March 14, 2015. Application due date(s): April 14, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): April 14, 2015, by 5:00 PM local time of applicant organization.

On January 8, 2015, NIDA issued an RFA entitled **Seek, Test, Treat and Retain For Youth and Young Adults Living with or at High Risk for Acquiring HIV (R01)** RFA-DA-15-019. The purpose of this Funding Opportunity Announcement (FOA) is to examine delivery models of HIV-focused services (testing, linkage, engagement and retention in care) for high risk or already HIV+ infected youth and young adults. Applications should incorporate substance use into study aims and service delivery objectives should address access to substance use prevention, screening, and treatment. Applications examining interventions that focus only on individual-level behavior and outcomes will be considered non-responsive, given the systemic and structural determinants of serostatus screening, treatment retention and viral suppression, which are the most striking areas of deficit among youth in the Seek, Test, Treat, and Retain continuum of care. The developmental, structural, and systemic factors related to serving youth need to be clearly incorporated into study aims, rather than simple incremental refocusing of existing interventions to younger people. Open date: March 15, 2015. Application due date(s): April 14, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): April 14, 2015, by 5:00 PM local time of applicant organization.

New NIDA Program Announcements

On January 23, 2015, NIDA issued a PA entitled **Reductions in Illicit Drug Use and Functional Outcomes (R21/R33)** PA-15-099. The purpose of this Funding Opportunity Announcement (FOA) is to encourage applications for Phased Innovation (R21/R33) projects to determine whether reductions in illicit drug use are associated with positive changes in health-related and other functional outcomes in individuals with substance use disorders (SUDs). Functional outcomes include, for example, reductions in morbidity, mortality, criminal justice involvement, overall healthcare expenditures. This FOA provides support for up to two years (R21 phase) for research planning activities and feasibility studies, followed by possible transition to expanded research support (R33 phase). The transition to the R33 phase will be determined by NIH program evaluation of successful achievement of the milestones set for the R21 phase. The ultimate goal of this FOA is to provide evidence that will enable regulatory authorities to accept reductions in illicit drug use as a valid outcome measure in clinical trials of pharmacotherapies for the treatment of SUDs. Open date: May 16, 2015. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On January 9, 2015, NIDA issued a PA entitled **Drug Abuse Prevention Intervention Research (R21)** PA-15-080**, (R03)** PA-15-081**, (R01)** PA-15-082. This Funding Opportunity Announcement (FOA) encourages grant applications for research that will employ rigorous scientific methods to test theoretically derived hypotheses to increase understanding of the science of drug use prevention within diverse populations and settings and across the lifespan. The FOA seeks applications that encompass investigations of cognitive, behavioral, and social processes as they relate to: 1) development of novel prevention approaches; 2) efficacy and effectiveness of prevention interventions or programs; 3) processes that optimize the selection, integration, implementation and sustainability of science-based prevention, including systems-level and health economic factors; and 4) methodologies appropriate for studying complex aspects of prevention science. Open date: May 16, 2015 (R21 and R03), May 5, 2015 (R01). Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On January 8, 2015, NIDA issued a PAR entitled **Cutting-Edge Basic Research Awards (CEBRA) (R21)** PAR-15-079**.** The National Institute on Drug Abuse (NIDA) Cutting-Edge Basic Research Award (CEBRA) is designed to foster highly innovative or conceptually creative research related to drug abuse and addiction and how to prevent and treat them. It supports research that is high-risk and potentially high-impact that is underrepresented or not included in NIDA's current portfolio. The proposed research should: (1) test a highly novel and significant hypothesis for which there are scant precedent or preliminary data and which, if confirmed, would have a substantial impact on current thinking; and/or (2) develop or adapt innovative techniques or methods for addiction research, or that have promising future applicability to drug abuse research. Open date: July 20, 2015. Application due date(s): August 20, 2015; December 18, 2015; August 19, 2016; December 20, 2016; August 18, 2017; and December 20, 2017, by 5:00 PM local time of applicant organization. AIDS application due date(s): August 20, 2015; December 18, 2015; August 19, 2016; December 20, 2016; August 18, 2017; and December 20, 2017, by 5:00 PM local time of applicant organization.

On October 3, 2014, NIDA issued a PA entitled **Epidemiology of Drug Abuse (R01)** PA-15-003, **(R21)** PA-15-001, **(R03)** PA-15-002 **.** This Funding Opportunity Announcement (FOA) is intended to support research projects to enhance our understanding of the nature, extent, distribution, etiology, comorbidities, and consequences of drug use, abuse, and addiction across individuals, families, communities, and diverse population groups. This FOA strongly encourages applications that reflect the breadth of epidemiology research by addressing multiple levels of risk, resilience, and causation across scientific disciplines; by applying novel methods to advance knowledge of the interplay among genetic, environmental, and developmental factors and between social environments and associated health and disease outcomes; and by building on the research investments of NIH and sister HHS agencies to harness existing data on the epidemiology and etiology of drug abuse to improve public health prevention and treatment programs. Open date(s): January 5, 2015 (R01), January 16, 2015 (R21 and R03). Application due date(s) Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply.

New FOAs Issued by NIH Collaborative Research On Addiction (CRAN)

On November 18, 2014, NIDA, in conjunction with NCI and NIAAA, issued a PA entitled **Research Aimed at Novel Behavioral Targets to Improve Adolescent Substance Abuse Treatment and Prevention Interventions (R34)** PA-15-035**, (R01)** PA-15-036**.** This Funding Opportunity Announcement (FOA) is part of a trans-NIH initiative known as Collaborative Research on Addiction at NIH (CRAN). Areas supported by this FOA include research to inform the generation and refinement of novel targets for substance abuse treatment and prevention interventions, modules or adjuncts to existing treatments and prevention interventions that seek to target and modulate behavioral or neurobehavioral processes (e.g., impulsivity, risk-taking propensity, sensation and novelty seeking, distress tolerance, delay discounting, self-regulation, stress reactivity) in adolescents. Additionally, this FOA will encourage studies to include theoretical links that explore the relationship(s) between neural circuitry and treatment and prevention effects, and in particular, how behavioral targets might be affected by treatment and prevention interventions, and how that might be used to improve targeted treatment and prevention development, that translate to reduced morbidity and mortality. Open date(s): January 5, 2015 (R01) and January 16, 2015 (R34). Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

New FOAs Issued by the NIH Roadmap

On January 21, 2015, the NIH Common Fund issued a Roadmap RFA entitled **Metabolomics Core for the Undiagnosed Diseases Network (UDN) (U01) RFA-RM-15-001.** This Funding Opportunity Announcement (FOA) is to establish a Metabolomics Core to augment clinical and laboratory findings of the Undiagnosed Diseases Network (UDN) and to assist the Network in the diagnosis of patients with undiagnosed diseases. Responsive applications will describe a plan to provide comprehensive analytical methods, analyses, technologies, and metabolomics expertise to the UDN to aid in clinical diagnosis and investigate potential mechanisms underlying phenotypic changes in patients. Due to the rare, even unique, disorders of UDN patients, the application should describe the need to develop specialized, "boutique" assays and methods of measurement in

analyses of both normal and abnormal compounds of the diseased metabolome. Open date: March 15, 2015. Application due date(s): April 15, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On January 8, 2015, the NIH Common Fund issued a **Science of Behavior Change: Assay Development and Validation for Stress Reactivity and Stress Resilience Targets (UH2/UH3) RFA-RM-14-019, Science of Behavior Change: Assay Development and Validation for Interpersonal and Social Processes Targets (UH2/UH3) RFA-RM-14-018**, **Science of Behavior Change: Assay Development and Validation for Self-Regulation Targets (UH2/UH3) RFA-RM-14-020.** This Phased Innovation Awards Cooperative Agreement Funding Opportunity Announcement (FOA) solicits applications to support a collaborative research infrastructure involving an interdisciplinary team of basic and clinical scientists to develop the foundation for an experimental medicine approach to behavior change. Research supported by this FOA is meant to support activities focused on behavior change targets in the domain of stress reactivity and stress resilience. Open date: February 20, 2015. Application due date(s): March 20, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On January 8, 2015, the NIH Common Fund issued a Roadmap RFA entitled **NIH Science of Behavior Change Resource and Coordinating Center (U24) RFA-RM-14-017.** This U24 Cooperative Agreement Funding Opportunity Announcement (FOA) will support the NIH Science of Behavior Change (SOBC) Resource and Coordinating Center (RCC), which will coordinate the activities of between five and nine UH2/UH3 Target Validation Projects. The initial UH2/UH3 awards will be made in response to three companion FOAs (RFA-RM-14-018, RFA-RM-14-019, RFA-RM-14-020) that will focus on identifying and validating targets in the three specific behavioral domains of self-regulation, stress reactivity and stress resilience, and interpersonal and social processes. The overall goal of the SOBC Program is to transform behavioral intervention designs by implementing the experimental medicine approach to behavior change research. The overall goal of the RCC will be to provide national leadership for the coordinated efforts of projects and initiatives of SOBC to validate assays for behavior change, with five specific objectives described in this FOA. The RCC will also serve as the central resource for the organization of the meetings and other activities of the SOBC program, including the support of its Steering Committee and External Scientific Panel, and any SOBC steering committee subcommittees that are established. Open date: February 20, 2015. Application due date(s): March 20, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On December 22, 2014, the NIH Common Fund issued a **Nuclear Organization and Function Interdisciplinary Consortium (NOFIC)(U54) RFA-RM-14-030.** This FOA seeks to establish technology-development and data-production centers whose mission will be to develop, benchmark, standardize, and validate the next generation of high-throughput technologies that can produce three dimensional physical and functional maps of mammalian genomes, develop predictive models of mammalian genome structure-function relationships, and test the relevance of new nuclear organizational principles within the context of specific biological paradigms and systems. Open date: January 23, 2015. Application due date(s): February 23, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On November 5, 2014, the NIH Common Fund issued a **Collaborative Activities to Promote Metabolomics Research (Admin Supp) PA-15-030.** This Administrative Supplement funding opportunity is part of the Common Fund Metabolomics Program created to increase and improve

the nation's ability to undertake metabolomics analyses in translational and clinical research. Metabolomics has great potential to advance our understanding of human diseases, but requires specialized expertise in metabolomics study design, technology, and data analysis and interpretation. This FOA supports supplemental funds to current NIH-funded research projects for new interactive collaborations between basic or clinical researchers and metabolomics experts to add a metabolomics approach to the existing Research Strategy for the project. In addition to enhancing the parent grant by adding metabolomics analyses, collaborative projects must include activities to increase the expertise of the biomedical research group in key aspects of metabolomics study design, analysis, and data interpretation. Open date: January 13, 2015. Application due date(s): February 13, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On October 21, 2014, the NIH Common Fund issued a **NIH Director's Early Independence Awards (DP5) RFA-RM-14-004.** The NIH Director's Early Independence Award Program supports exceptional investigators who wish to pursue independent research directly after completion of their terminal doctoral/research degree or clinical residency, thereby forgoing the traditional post-doctoral training period and accelerating their entry into an independent research career. Open date: December 30, 2014. Application due date(s): January 30, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): January 30, 2015, by 5:00 PM local time of applicant organization.

On September 24, 2014, the NIH Common Fund issued a **4D Nucleome Imaging Tools (U01) RFA-RM-14-009.** The purpose of this FOA is to solicit applications that will accelerate the development and validation of imaging technologies for visualizing the structural and functional organization of the mammalian genome and its spatiotemporal dynamics. Projects must propose innovative, high resolution, high throughput, quantitative technologies that can be used to study a statistically significant number of single cells to address critical unmet needs in our understanding of nuclear organization. Open date: January 2, 2015. Application due date(s): February 2, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On September 24, 2014, the NIH Common Fund issued a **Study of Nuclear Bodies and Compartments (U01) RFA-RM-14-008.** The purpose of this FOA is to support projects to develop tools and strategies for studying: 1. the three dimensional architecture of the nucleus in relationship to the topography of nuclear bodies and transcriptional machineries, 2. the structure and function of poorly characterized nuclear structures, or 3. the role of specialized proteins and RNAs in the assembly, organization, and function of nuclear bodies, nuclear structures, and specialized subnuclear domains. Open date: January 2, 2015. Application due date(s): February 2, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On September 24, 2014, the NIH Common Fund issued a **Nucleomics Tools (U01) RFA-RM-14-007.** The purpose of this Funding Opportunity Announcement (FOA) is to solicit applications that propose to develop and validate physical, chemical and biochemical approaches for measuring properties and dynamics of the three-dimensional organization of the genome that cannot be measured adequately using existing methodologies. Open date: January 2, 2015. Application due date(s): February 2, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

New FOAs Issued by the NIH Blueprint for Neuroscience Research

Connectomes Related to Human Disease (U01) PAR-14-281

New FOAs Issued by the BRAIN INITIATIVE

BRAIN Initiative: Development, Optimization, and Validation of Novel Tools and Technologies for Neuroscience Research (SBIR)(R43/R44) PAR-15-091

BRAIN Initiative: Development, Optimization, and Validation of Novel Tools and Technologies for Neuroscience Research (STTR)(R41/R42) PAR-15-090

BRAIN Initiative: Short Courses in Research Tools and Methods (R25) RFA-MH-15-220

BRAIN Initiative: Short Courses in Computational Neuroscience (R25) RFA-MH-15-215

BRAIN Initiative: Development and Validation of Novel Tools to Analyze Cell-Specific and Circuit Specific Processes in the Brain (U01) RFA-MH-15-225

BRAIN Initiative: Planning for Next Generation Human Brain Imaging (R24) RFA-MH-15-200

BRAIN Initiative: Integrated Approaches to Understanding Circuit Function in the Nervous System (U01) RFA-NS-15-005

BRAIN Initiative: Optimization of Transformative Technologies for Large Scale Recording and Modulation in the Nervous System (U01) RFA-NS-15-004

BRAIN Initiative: New Technologies and Novel Approaches for Large-Scale Recording and Modulation in the Nervous System (U01) RFA-NS-15-003

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

NIH Big Data to Knowledge (BD2K) Enhancing Diversity in Biomedical Data Science (R25) RFA-MD-15-005

Biomedical Data Science Training Coordination Center (U24) RFA-ES-15-004

NIH Big Data to Knowledge (BD2K) Initiative Research Education: Open Educational Resources for Sharing, Annotating and Curating Biomedical Big Data (R25) RFA-LM-15-002
NIH Big Data to Knowledge (BD2K) Initiative Research Education: Massive Open Online Course (MOOC) on Data Management for Biomedical Big Data (R25) RFA-LM-15-001

4D Nucleome Imaging Tools (U01) RFA-RM-14-009

Study of Nuclear Bodies and Compartments (U01) RFA-RM-14-008

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

NIH Pathway to Independence Award (Parent K99/R00) PA-15-083

Predictive Multiscale Models for Biomedical, Biological, Behavioral, Environmental and Clinical Research (U01) PAR-15-085

Building on High Impact Basic Neurobiology Through Assay Development: Advancing Tools for Therapeutic Discovery (R01) PAR-15-066

Promoting Research in Basic Neuroscience (R01) PAS-15-029

Mechanistic Studies of Pain and Alcohol Dependence (R01) PA-15-026

Global Brain and Nervous System Disorders Research Across the Lifespan (R01) PAR-14-332

Global Brain and Nervous System Disorders Research Across the Lifespan (R21) PAR-14-331

Advancing Interventions to Improve Medication Adherence (R01) PA-14-334

Developing Interventions for Health-Enhancing Physical Activity (R21/R33) PAR-14-321

Testing Interventions for Health-Enhancing Physical Activity (R01) PAR-14-315

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

On November 20, 2014, NIDA, in collaboration with numerous other NIH components and with the FDA Center for Tobacco Products issued **Administrative Supplements for Tobacco Regulatory Research on the Public Display of Harmful and Potentially Harmful Constituents (HPHC) Information (Admin Supp)** PA-15-046. The purpose of this FOA is to generate data to support the implementation of public displays of HPHC information. The NIH and the FDA have formed an interagency partnership to foster research relevant to FDA's tobacco regulatory authorities. The award under this FOA will be administered by NIH using designated funds from the FDA CTP for tobacco regulatory science mandated by the Family Smoking Prevention and Tobacco Control Act (FSPTCA), Public Law 111-31. Open date: December 12, 2014. Application due date(s): January 12, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

Other Program Activities

CTN Update

A total of 56 protocols have been initiated since 2001, including multi-site clinical trials (40), multi-site surveys (3), studies in special populations (8), and secondary analyses of data across various

trials (5). In addition, 28 ancillary studies have been supported by CTN and non-CTN funds. Nearly 17,000 participants have been enrolled in CTN studies. Information on protocols can be found at: http://www.drugabuse.gov/about-nida/organization/cctn/ctn/research-studies

NIDA's Blending Initiative

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

In October 2014 the Blending Initiative launched a new educational effort − *Talking to Patients about Health Risk Behaviors*. The two programs comprising this unique educational opportunity provide a unique forum where the CME course and the Patient Simulation jointly provide practical guidance for physicians and other clinicians in effective Motivational Interviewing techniques that will facilitate conversations with patients to address Health Risk Behaviors. The CME Course guides physicians and other clinicians through practical skills building and technique development using videos to model effective communication, while the Patient Simulation allows for real time testing and reinforcement of these skills in the clinical setting. Links to the education are found at http://www.drugabuse.gov/blending-initiative/cme-ce-simulation.

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

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

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

- Addiction Health Services Research (AHSR) Boston, MA October 15-17, 2014
- American Academy of Family Physicians (AAFP) Washington, DC October 21-15, 2014

NIDA Language Access Implementation Plan

In accordance with Executive Order 13166 (PDF, 256kb), *Improving Access to Services for Persons with Limited English Proficiency*, the NIH Language Access Plan provides a blueprint for ensuring that individuals with Limited English Proficiency (LEP) have meaningful access to all of NIH's programs and activities. The **NIDA Language Access Implementation Plan**, lays out how NIDA intends to implement this plan. NIDA welcomes feedback on how to best serve the needs of its stakeholders and the LEP community. Please visit http://www.drugabuse.gov/accessibility/language-access-implementation-plan) for more information.

Office of the Scientific Director, Office of Education and Career Development
From June to August 2014, the IRP hosted 53 summer interns from the NIH Summer Internship Program and the Research Training for Under-represented Populations Program. Activities included Science Skills Boot Camp; seminars by IRP scientists on their research and the major neurotransmitter systems; workshops on creating and presenting a poster; giving a scientific talk, and applying to graduate and medical school; and two Poster Days, one at the IRP and one at NIH.

On December 1, 2014, the NIDA and NIA intramural programs held the 6th annual Fellows Symposium. The day-long event honored Fellows who were 2015 FARE (Fellows Award for Research Excellence) winners. Events included Skill Blitzes, oral presentations by the FARE winners, and a poster session. The keynote address was given by Dr. Alan Leshner, CEO of the American Association for the Advancement of Science and former NIDA Director. The title of his presentation was "The Current Climate for Careers in Science."

From July to November 2014, the NIDA IRP Office of Education and Career Development, together with the NIH Office of Intramural Training and Education and NIH Library, have offered the following workshops or seminars: Interviewing for Professional School, Interviewing for Industry Jobs, Introduction to Data Management, EndNote Training, Impact Assessment for Authors, Graduate School Planning and Applying, Scientists Teaching Science (9-week online course), Negotiating an Industry Position, Eat That Frog: Time Management, Finding and Reusing Scientific Data, Improving Spoken English, Assertiveness Workshop, and Protein Structural Analysis Training.

Dr. Yu (Woody) Lin, DCNBR, joined NIDA R25 FOA Workgroup, a task force on FOA reissuance of NIDA Research Education Program for Clinical Researchers and Clinicians (R25)
Dr. Steven Grant, DCNBR, joined Team B (Invasive Studies of the Human Brain) of the BRAIN Initiative in addition to continuing to represent NIDA on Team C (Non-Invasive Studies of the Human Brain).

Dr. Steven Grant serves as the alternate NIDA representative on the Big Data to Knowledge Excecutive Committee, as well as representing NIDA on several project workgroups (Data Discovery Index Project Team, Sustainability Workgroup).

COMMUNICATIONS

PUBLICATIONS/VIDEOS

NIDA Publications and Online Resources

- Drugs, Brains, and Behavior: The Science of Addiction (Revised July 2014)
- Mind Over Matter: The Brain's Response to Marijuana (Revised August 2014)
- Mind Over Matter: The Brain's Response to Opioids (Revised September 2014)
- Electronic Cigarettes (DrugFacts) (Revised September 2014)
- Media Guide (Revised September 2014)
- Heroin (DrugFacts) (Revised October 2014)
- Prescription Drug Abuse Research Report (Revised November 2014)
- Heroin Research Report (Revised November 2014)
- Marijuana Research Report (Revised December 2014
- Drugged Driving (DrugFacts) (Revised December 2014)
- High School and Youth Trends (DrugFacts) (Revised December 2014)
- Hallucinogens - LSD, Peyote, Psilocybin, and PCP (DrugFacts) (Revised December 2014)
- Is Marijuana Medicine? (DrugFacts) (Revised December 2014)
- Prescription and Over-the-Counter Medications (DrugFacts) (Revised December 2014)
- Cigarettes and Other Tobacco Products (DrugFacts) (Revised December 2014)
- Club Drugs (GHB, Ketamine, and Rohypnol) (DrugFacts) (Revised December 2014)

En Espanol:

- Drogas: Derribemos los mitos (Drugs: Shatter the Myths) (Published in Spanish November 2014)
- La marihuana: Informacion para los adolescents (Marijuana: Facts for Teens) (Revised November 2014)
- Marihuana: datos que los padres deben saber (Marijuana: Facts Parents Need to Know) (Revised November 2014)
- Las drogas, el cerebro y el comportamiento: La ciencia de la adiccion (Drugs, Brains and Behavior: The Science of Addiction) (Revised November 2014)
- La marihuana es un medicamento? (Is Marijuana Medicine? Drug Facts) (Revised November 2014)
- Marihuana (Marijuana Drug Facts) (Revised November 2014)

Websites and Online Resources:

- **Step-by-Step Guides for seeking drug abuse treatment:** http://www.drugabuse.gov/related-topics/treatment (Launched September 2014)
- **Landing page on drug testing:** http://www.drugabuse.gov/related-topics/drug-testing (Launched September 2014)
- **Landing page on mental health:** http://www.drugabuse.gov/related-topics/mental-health (Launched September 2014)

- **Landing page on pain:** http://www.drugabuse.gov/related-topics/pain (Launched October 2014)
- **Drugs + HIV > learn the link:** http://hiv.drugabuse.gov/ (Updated in English and Spanish October 2014)

NIDA Notes (now online only)

Highlights:

Animation: The Rise and Fall of the Cocaine High (http://www.drugabuse.gov/news-events/nida-notes/2014/11/animation-rise-fall-cocaine-high)
Narrative of Discovery: In Search of a Medication to Treat Methamphetamine Addiction: This is the first in a new series of articles that bring readers fully into the life and adventure of research, by following a researcher (Linda Dwoskin) from the start of a project to its culmination. Additional selected articles report that varenicline is effective as a nicotine cessation treatment for mentally ill individuals; smoking cessation does not interfere with recovery from drug abuse; THC exposure in adolescence may cause epigenetic changes that are transmitted to the next generation; a new approach uses immune cells to deliver anti-HIV medications. ***NIDA Notes*** receives 35,000 visits monthly and is shared via, and are promoted on Twitter, Linked-In, and Facebook, and (videos) YouTube. As of February 2015, through an agreement with the Institute for Research, Education, and Training in Addictions, social workers and substance abuse clinicians will be able to receive CEU credits by reading and responding to a quiz about *NIDA Notes* articles.

Videos

- **CEWG Region Report**
  http://youtu.be/PCEQd1H6nXY
- **Addiction Science Fair Winners 2014: Aakash Jain**
  http://youtu.be/Y0ZHvdWonC4
- **Addiction Science Fair Winners 2014: Lily Wei Lee**
  http://youtu.be/Dbupp1-5aBU
- **Addiction Science Fair Winners 2014: Alexandra Ulmer and Sarayu Caulfield**
http://youtu.be/1E58FanCrmw
- **What's New at NIDA: Office of Science Policy and Communication Director's Notes for August**
  http://youtu.be/NEv-5PVGrq8
- **The Swiss Cheese Model of Drug Addiction**
  http://youtu.be/SufLpGPauII
- **SPB Brain Animation**
  http://youtu.be/DMcmrP-BWGk
- **Pain Awareness Month: Dr. Nora Volkow on Pain Research and Opioids**
  http://youtu.be/4xaEwa5XULA
- **Pain Awareness Month: Dr. Story Landis on The Pain Consortium**
http://youtu.be/o2M4mkeaQOA
- **National Drug Facts Week Promo**
  http://youtu.be/lZ1qayWXnz0

- **NCCAM-Pain Video**
  http://youtu.be/XUHifNHlzjU
- **NINR-Pain Video**
  http://youtu.be/qYbi6wdsOME
- **The Party: Drugs and HIV, "D'cisions" series (5) Videos**
  http://youtu.be/rKCfagQ-4cA
  http://youtu.be/1rhb_1OOtUg
  http://youtu.be/EBEk5NbxbBA
  http://youtu.be/UvDtLfOhth8
  http://youtu.be/xIU2lGp9bNk
- **NAC for Treating Marijuana Addiction: Dr. Kevin M. Gray**
  http://youtu.be/md4lRQsLlnE
- **What's New at NIDA: Office of Science Policy and Communication Director's Notes for October**

http://youtu.be/5ZUYvTzx_YA

- **NIDA Encourages Community Based Marijuana Research: Dr. Wilson Compton**
  http://youtu.be/7127QLM2YWA
- **NIH CFC 2014 Director's Challenge – NIDA**
  http://youtu.be/GbkD60GhWQk
- **Dr. Wilson Compton Discuss MTF 2014 Results**
  http://youtu.be/aTB6iPz3H5E
- **Dr. Nora Volkow Discuss MTF 2014 Results**
  http://youtu.be/GnraNucCHH8
- **Teen Drug Use: 2014 Monitoring the Future Survey Results**
  http://youtu.be/8KaYHlCfAGA
- **What's New at NIDA: Office of Science Policy and Communication Director's Notes for January**
  http://youtu.be/C8u6RTZsIoU

CTN-Related Publications

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

Data from 34 CTN studies are now available on the NIDA Data Share website http://datashare.nida.nih.gov/. Over 3,200 data sets have been downloaded by researchers from 69 countries. These data sets are in compliance with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap. The NIDA Data Share is also part of the Neuroscience Information Framework (NIF), which is a dynamic inventory of Web-based neuroscience resources: data, materials, and tools accessible via any computer connected to the Internet.

Other Publications

Aklin WM, Wong CJ, Svikis D, Stitzer ML, Bigelow GE, Hampton J, Silverman K. A reinforcement-based therapeutic workplace for the long-term treatment of substance dependence in Methadone Maintained Patients: Eight year abstinence and employment outcomes. Journal of Substance Abuse Treatment 2014; 47: 329-338.

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Bogenschutz MP, Donovan DM, Mandler RN, Perl HI, Forcehimes AA, Crandall C, Lindblad R, Oden NL, Sharma G, Metsch L, Lyons MS, McCormack R, Konstantopoulos WM, Douaihy A. Uptake of HIV testing in substance use disorder treatment programs that offer on-site testing. Kyle TL, Horigian VE, Tross S, Gruber VA, Pereyra M, Mandler RN, Feaster DJ, Metsch LR. AIDS Behav. 2014 Jul 30. [Epub ahead of print].

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Onken L, Shoham V. Technology and the Stage Model of behavioral intervention development. In L. Marsch, S. Lord, & J. Dallery (Eds), Behavioral Healthcare and Technology: Using Science-Based Innovations to Transform Practice. Oxford, England: Oxford University Press, 2014.

Satterlee J, Pollock J et al., Novel RNA modifications in the nervous system: form and function. Satterlee JS, Basanta-Sanchez M, Blanco S, Li JB, Meyer K, Pollock J, Sadri-Vakili G, Rybak-Wolf A. J Neurosci. 2014 Nov 12;34(46):15170-15177.

Satterlee J, Rutter J, Procaccini Community Resources and Technologies Developed Through the NIH Roadmap Epigenomics Program. Satterlee JS, Beckel-Mitchener A, McAllister K, Procaccini DC, Rutter JL, Tyson FL, Chadwick LH. Methods Mol Biol. 2015;1238:27-49.

Visher CA, Hiller M, Belenko S, Pankow J, Dembo R, Frisman LK, Pearson FS, Swan H, Wiley TR. The effect of a local change team intervention on staff attitudes towards HIV service delivery in correctional settings: a randomized trial. AIDS Educ Prev. 2014 Oct;26(5):411-28.

Walton KM, Abrams DB, Bailey WC, Clark D, Connolly GN, Djordjevic MV, Eissenberg TE, Fiore MC, Goniewicz ML, Haverkos L, Hecht SS, Henningfield JE, Hughes JR, Oncken CA, Postow L, Rose JE, Wanke KL, Yang L, Hatsukami DK. Nicotine Tob Res. 2014 Oct 21. pii: ntu214. [Epub ahead of print].

COMMUNITY AND PRESS EVENTS

Dr. Volkow Featured Speaker at TEDMED

On September 11, Dr. Volkow was a featured speaker at the TEDMED 2014 conference held at the John F. Kennedy Center for the Performing Arts in Washington, DC. TEDMED is an annual multi-disciplinary gathering where leaders from all sectors of society come together to explore the promise of technology and potential of human achievement in health and medicine. This year's TEDMED theme was "Unlocking Imagination in Service of Health and Medicine." Dr. Volkow appeared as one of 11 featured experts in Session 4: "Stealing Smart," where speakers shared inspiring stories and ideas about how to adapt solutions from other industries and fields to solve the most intractable problems in health and medicine. Dr. Volkow addressed the neuroscience of obesity and the parallels between compulsive overeating and drug addiction. The NIDA press team issued a media availability, provided social media support for the event and facilitated interviews with *The Atlantic*, *Fox Business Network* and *WebMD.*

Pathways to Prevention: The Role of Opioids in the Treatment of Chronic Pain

In support of a conference on the use of opioids for chronic pain – held September 29-30 by the NIH Office of Disease Prevention and the NIH Pain Consortium – the NIDA press team facilitated three interviews: two with Dr. Wilson Compton (an independent documentary and *Frontline Medical Communications)* and one with Dr. David Thomas (*MedPage*). The NIDA communication staff also developed a plan to place rotators on the NIDA website, distribute a NIDA-wide promotion email, and publicize the meeting through Twitter, Facebook, and Linked-In posts.

NIDA Hosts Mini-Convention at Society for Neuroscience Annual Meeting, Presents Jacob P. Waletzky Award and Participates in NIH Press Conference

On November 14th, in the Natcher Auditorium on the NIH Campus, NIDA hosted its annual one-day mini-convention, *Frontiers in Addiction Research*, a satellite event of the Society for Neuroscience annual meeting. NIDA-funded scientists from around the world presented recent findings and discussed future directions in neuroscience and addiction research. NIDA Director Dr. Nora Volkow gave the welcoming remarks and introduced the winners of the Jacob P. Waletzky Award. The NIDA press team issued a media advisory about the conference, took photos for the NIH Record, and promoted the event through NIDA's social media channels. On November 16th, Dr. Volkow was one of seven NIH directors to participate in a Washington, D.C. press conference highlighting the status of NIDA's research being presented at the SfN meeting. The press team coordinated with NIMH to determine press briefing logistics and provided social media outreach.

NIDA Hosts National Teleconference and Twitter Chat to Discuss 2014 Monitoring the Future Results

NIDA hosted a press teleconference and twitter chat on December 16, 2014, to discuss the findings of the 2014 Monitoring the Future (MTF) survey. The annual survey, funded by NIDA and conducted by researchers at the University of Michigan at Ann Arbor, measures drug use and attitudes among eighth, 10th, and twelfth graders nationwide. The NIDA press team issued a media advisory for the teleconference and a press release about the survey results; coordinated the logistics of the teleconference and twitter chat; and facilitated interviews, resulting in hundreds of placements in media outlets and social media platforms nationwide.

2015 Chat Day and National Drug Facts Week (NDFW)
NIDA conducted its annual Chat Day (January 30) and NDFW (January 26 - February 1), which included approximately 1500 events in all 50 states and several countries. Over 130 high schools registered for Chat Day and hundreds of questions were answered by NIDA scientists. NIDA developed and distributed press and promotional materials, cultivated radio and organizational partnerships, pitched to select media, coordinated two Radio Media Tours for English and Spanish speaking audiences, and promoted the week via traditional and social media outreach. Visit http://teens.drugabuse.gov/national-drug-facts-week for more information.

PRESS RELEASES

September 9, 2014 - National Drug Facts Week 2015 to begin January 26
NIH observance links teens with scientific experts

National Drug Facts Week, which brings together teens and scientific experts to shatter persistent myths about drug use and addiction, will be held Jan. 26 through Feb. 1, 2015. Ideas for community-based events, as well as success stories from previous years, are highlighted on the National Drug Facts Week Web portal. Last year, more than 1,000 events were held with teens throughout all states, and several internationally. The fifth National Drug Facts Week is sponsored by the National Institute on Drug Abuse, which is part of the National Institutes of Health.

"National Drug Facts Week has been growing every year, from 92 events at its inception almost five years ago," said NIDA Director Dr. Nora D. Volkow. "This tells us how much teens - who are bombarded daily with misinformation about drugs - want science-based facts about drug use."

National Drug Facts Week was launched in 2010 to counteract the myths that teens often hear from the Internet, TV, movies, music, or friends. One popular myth is that marijuana is harmless, although science tells us that marijuana use by teens may negatively affect brain development and impair school and athletic performance. Teen use of marijuana is up compared to five years ago, perhaps because fewer teens consider marijuana to be a harmful drug.

To help shatter the myths surrounding marijuana and other addictive substances, National Drug Facts Week encourages events that allow teens to ask questions of addiction scientists or health experts about drug use and addiction. Events can be sponsored by a variety of organizations, including schools, community groups, sports clubs, and hospitals. Topics for discussion can include not only what science tells us about marijuana, but also about prescription drug abuse, and the use of tobacco and alcohol.

NIDA provides an online toolkit that advises teens and their adult advisors how to create an event, publicize it, find an expert, and obtain scientific information on drugs. This year, NIDA has merged its National Drug Facts Week website with its popular NIDA for Teens site, http://teens.drugabuse.gov/national-drug-facts-week. This will enable easier browsing between event planning tools and NIDA's drug information fact sheets, which are designed with teen-friendly language and graphics. Event holders who register online will receive free booklets with science-based facts about drugs, including one of NIDA's most in-demand teen publications, Drugs: Shatter the Myths. Also this year, NIDA offers three interactive tools that can be projected on large screens at events or used with mobile devices:

- The online 2015 National Drug IQ Challenge is a 12-question multiple choice quiz that teens and adults can take to test their knowledge about drugs. Past-year challenges can be found here: http://teens.drugabuse.gov/quiz/national-drug-facts-week/take-iq-challenge/2014. The 2015 challenge will be posted when it is available.
- Choose Your Path interactive videos encourage students to make decisions about the abuse of prescription drugs using scenarios from their everyday lives: http://teens.drugabuse.gov/peerx/choose-your-path.
- The interactive version of the popular poster Drugs + Your Body: It Isn't Pretty highlights the effects drugs have on the teen body. It was created in partnership with Scholastic: http://www.scholastic.com/drugs-and-your-body/.

National Drug Facts Week is again supported by many federal agencies, including the White House Office of National Drug Control Policy (ONDCP); the National Institute on Alcohol Abuse and Alcoholism at NIH; the Office of Safe and Healthy Students in the U.S. Department of Education; the Substance Abuse and Mental Health Services Administration in the Department of Health and Human Services; the Drug Enforcement Administration (DEA) in the U.S. Department of Justice; and the U.S. Department of Housing and Urban Development. (HUD). Each agency will post National Drug Facts Week information on its website and encourage the development of special events linking experts to teens.

"President Obama's vision is for all of America's children to grow up in healthy and safe communities," said ONDCP Acting Director Michael Botticelli. "This administration's drug policy is based on neuroscience, and we are committed to informing young people and health care professionals about the negative consequences drug and alcohol use can have on their futures."

The Office of Safe and Healthy Students will help promote National Drug Facts Week and encourage schools to participate. "National Drug Facts Week allows NIDA staff to connect directly with youth and to share facts on drug use in a direct, evidence-based, and non-judgmental fashion," said David Esquith, director of the Office of Safe and Healthy Students. "Once again, our office is pleased to help promote this week's activities and to encourage schools to participate."

DEA will again share in efforts to encourage community-based events. "National Drug Facts Week provides a unique opportunity to discuss drug abuse, relevant science, and the dangers of addiction. DEA is proud to encourage community-based events that engage teens in a dialogue about drugs," said DEA Administrator Michele M. Leonhart. "Having an honest and open discussion about the dangers of drug abuse is a significant first step in drug prevention. We are pleased to support NIDA's efforts to help youth make informed choices."

HUD, which reaches approximately 1.5 million families globally, is participating by encouraging executive and field office public housing directors to hold National Drug Facts Week events and by promoting the week-long observance through Facebook.

Also during National Drug Facts Week, NIDA scientists will hold their annual Web chat with teens around the country. Drug Facts Chat Day will be held Jan. 30 from 8 a.m. to 6 p.m. Eastern time. Further details on the popular annual chat, including registration information and transcripts from previous years, can be found at http://teens.drugabuse.gov/national-drug-facts-week/chat-with-scientists.

Organizations with questions about National Drug Facts Week can e-mail NIDA at drugfacts@nida.nih.gov. Event organizers can register events starting today at http://teens.drugabuse.gov/national-drug-facts-week/register.

http://www.drugabuse.gov/news-events/news-releases/2014/09/national-drug-facts-week-2015-to-begin-january-26

October 16, 2014 - Using social media to better understand, prevent, and treat substance use
NIH announces 11 awards funded across three Institutes
More than $11 million over three years will be used to support research exploring the use of social media to advance the scientific understanding, prevention, and treatment of substance use and addiction. The awards are funded through the Collaborative Research on Addiction at NIH (CRAN), an NIH consortium involving the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), and the National Cancer Institute (NCI). The consortium was established to integrate resources and expertise to advance research and improve public health outcomes related to the use of alcohol, tobacco, and other addictive substances. NIAAA, NIDA, and NCI are components of the National Institutes of Health.

"These awards are the result of an active collaboration among the three institutes to develop innovative approaches that advance the science of substance use and addiction," said NIDA Director Dr. Nora D. Volkow. "We hope to learn more about how changing technologies affect interpersonal communications and factual knowledge about tobacco, alcohol, and illicit drugs, including the nonmedical use of prescription drugs."

Interactive platforms such as Facebook and Twitter have become important sources of public information, and are powerful tools to help scientists identify prevailing attitudes and myths and convey accurate information to the public about alcohol, tobacco, and other addictive substances. Researchers can analyze social media interactions to gain insights into patterns of use, risk factors, and behaviors associated with substance use. By providing a platform for communicating science-based, health-related messages, social media may also enhance screening, prevention, and treatment of substance use and addiction. To help address these needs, CRAN issued two funding opportunities to support research that leverages social media platforms to advance the scientific understanding of substance use or improve the treatment and prevention of behaviors related to substance use.

"The ubiquity and widespread use of social media underscores the need to address numerous questions regarding the intersection of social media with substance use and abuse, as well as its potential as a tool for preventing and treating substance abuse problems," said NIAAA Director Dr. George Koob. "With these awards the CRAN collaboration is making an important investment that could impact the diverse health problems associated with the abuse of alcohol, tobacco, and other addictive substances."

"Social media has the potential to fill important gaps in our current understanding of tobacco, alcohol and drug use and to improve the efficacy of substance abuse interventions. For example, user-generated social media interactions can reveal important insights into substance use patterns and various social factors," said Dr. Wen-ying (Sylvia) Chou, program director in NCI's Health Communications and Informatics Research Branch and NCI's program contact for the funding

opportunities. “Social media platforms also have the potential to increase the effectiveness of substance use prevention and treatment efforts by providing technologically mediated solutions.”

Awardees are:

- Warren Bickel, Ph.D., Virginia Tech, Blacksburg

Social [networks] of recovery: Social media as therapy development (NIDA grant DA039456)

- Patricia Cavazos-Rehg, Ph.D., Washington University, St. Louis

Implications of social media content and engagement for alcohol and marijuana use (NIDA grant DA039455)

- Brenda Curtis, Ph.D., Treatment Research Institute, Philadelphia

Predicting [alcohol and other drug] relapse and treatment completion from social media use (NIDA grant DA039457)

- Raminta Daniulaityte, Ph.D., Wright State University, Dayton, Ohio

Trending: Social media analysis to monitor cannabis and synthetic cannabinoid use (NIDA grant DA039454)

- Yong Ge, Ph.D., University Of North Carolina at Charlotte

Mining patterns of substance use by young adults with social media data (NIAAA grant AA023975)

- *Amanda Graham*, Ph.D., American Legacy Foundation, Washington

Social dynamics of substance use in online social networks for smoking cessation (NCI grant CA192345)

- Annice Kim, Ph.D., Research Triangle Institute, Research Triangle Park, North Carolina

Using social media data for e-cigarette surveillance and policy research (NCI grant CA192240)

- Sabrina Oesterle, Ph.D., University of Washington, Seattle

Using Facebook to recruit parents to a parenting program to prevent teen drug use (NIDA grant DA039466)

- Marya Schulte, Ph.D., University of California, Los Angeles

PURPOSE: A social media intervention for parent support (NIDA grant DA039459)

- Scott Ian Vrieze, Ph.D., University of Colorado, Boulder

Social media, online measures, and substance use development in adolescent twins (NIAAA grant AA023974)

- Sean Young, Ph.D., University of California, Los Angeles

Adapting the HOPE social media intervention to reduce prescription drug abuse (NIDA grant DA039458)

For descriptions of each project, go to http://projectreporter.nih.gov/Reporter_Viewsh.cfm?sl=13E8C00F478AC1D67598B8961CAA4A01A2FFCEB861BF. For more information on CRAN, go to http://addictionresearch.nih.gov/about-us.

http://www.drugabuse.gov/news-events/news-releases/2014/10/using-social-media-to-better-understand-prevent-treat-substance-use

November 12, 2014 - NIDA researchers confirm important brain reward pathway
NIH study in rodents identifies a pathway that starts with glutamate and ends with activation of dopamine reward system

Details of the role of glutamate, the brain's excitatory chemical, in a drug reward pathway have been identified for the first time.

This discovery in rodents - published today in Nature Communications - shows that stimulation of glutamate neurons in a specific brain region (the dorsal raphe nucleus) leads to activation of dopamine-containing neurons in the brain's reward circuit (dopamine reward system).

Dopamine is a neurotransmitter present in regions of the brain that regulate movement, emotion, motivation, and feelings of pleasure. Glutamate is a neurotransmitter whose receptors are important for neural communication, memory formation, and learning. The research was conducted at the Intramural Research Program (IRP) of the National Institute on Drug Abuse (NIDA), which is part of the National Institutes of Health.

The research focused on the dorsal raphe nucleus, which has long been a brain region of interest to drug abuse researchers, since nerve cells in this area connect to part of the dopamine reward system. Many of the pathways are rich in serotonin, a neurotransmitter linked to mood regulation. Even though electrical stimulation of the dorsal raphe nucleus promotes reward-related behaviors, drugs that increase serotonin have low abuse potential. As a result, this region of the brain has always presented a seeming contradiction, since it is involved in drug reward but is also abundant in serotonin - a chemical not known for a role in drug reinforcement. This has led researchers to theorize that another neurotransmitter may be responsible for the role that the dorsal raphe nucleus plays in reward.

"We now have strong evidence of a reward pathway that starts with stimulation of glutamate neurons in the dorsal raphe nucleus and ends in activation of the dopamine reward system," said NIDA Director Dr. Nora D. Volkow. "These findings help us better understand the brain's reward circuitry and opens up new avenues of research into the neurobiology of drug addiction."

In these rodent models, researchers used special tracers and labelling compounds to confirm that this circuit in the reward pathway begins with glutamate cells in the dorsal raphe nucleus that connect to dopamine cells in the ventral tegmental area, which in turn travel to the nucleus accumbens, a brain structure linked to motivation, pleasure, and reward. After verifying the pathway, investigators used optogenetic techniques (using light to control activity of modified cells) and chemical blockers to confirm that glutamate, not serotonin, is responsible for activating this reward circuitry.

"This glutamatergic pathway is the first fully characterized link between electrically stimulated reward circuitry and the dopamine system on which it depends," said Dr. Marisela Morales, NIDA IRP scientist and senior author on the paper. "The discovery of this specific brain pathway opens new avenues to examine its participation in a variety of disorders related to motivation."
The paper by Qi et al. can be found at www.nature.com/ncomms/index.html. For similar research currently being conducted by NIDA IRP in this area, go to:
http://irp.drugabuse.gov/cnrb.php#Anchor-Anatomy-48213.

http://www.drugabuse.gov/news-events/news-releases/2014/11/nida-researchers-confirm-important-brain-reward-pathway

December 16, 2014 - Teen prescription opioid abuse, cigarette, and alcohol use trends down
However, NIH's 2014 Monitoring the Future survey shows high rates of e-cigarette use and fewer concerns about marijuana's risks

Use of cigarettes, alcohol, and abuse of prescription pain relievers among teens has declined since 2013 while marijuana use rates were stable, according to the 2014 Monitoring the Future (MTF) survey, released today by the National Institute on Drug Abuse (NIDA). However, use of e-cigarettes, measured in the report for the first time, is high.

These 2014 results are part of an overall two-decade trend among the nation's youth. The MTF survey measures drug use and attitudes among eighth, 10th, and 12th graders, is funded by NIDA, and is conducted by researchers at the University of Michigan at Ann Arbor. NIDA is part of the National Institutes of Health.

"With the rates of many drugs decreasing, and the rates of marijuana use appearing to level off, it is possible that prevention efforts are having an effect," said NIDA Director Nora D. Volkow, M.D. "It is now more important than ever for the public health community to continue to educate teens, parents, teachers, community leaders, the media and health care providers about the specific harms of drug use among teens, whose brains are still developing."

"This year's Monitoring the Future data show promising signs on the declining rates of adolescent substance use, and reinforce the need to continue efforts on prevention, treatment, and recovery," said National Drug Control Policy Acting Director Michael Botticelli. "The Obama administration remains steadfast in its commitment to reduce drug use and its consequences—and we know that the best way to reduce drug use is to prevent it from ever starting. I encourage parents, teachers, coaches, and mentors to have a conversation with a young person in their lives about making the healthy decisions that will keep them on a path toward a successful future."

The 2014 survey showed that past month use of smoked marijuana remained steady among eighth graders at 6.5 percent, 10th graders at 16.6 percent and 12th graders at 21.2 percent. Close to 6 percent of 12th graders report daily use of marijuana. This survey also revealed that, in 2014, in states with medical marijuana laws, 40 percent of 12th graders who reported using marijuana in the past year said they had consumed marijuana in food products (edibles) versus 26 percent in non-medical marijuana states.

However, the majority of high school seniors do not think occasional marijuana smoking is harmful, with only 16.4 percent saying occasional use puts the user at great risk, compared to 27.4 percent five years ago. By contrast, 56.7 percent of seniors say they disapprove of occasional marijuana smoking. Among eighth graders, there was a drop in perceived availability, with 36.9 percent saying it is easy to get marijuana, compared to last year's 39.1 percent. Eighty-one percent of seniors say it is easy to get marijuana.

The findings related to prescription and over-the-counter drug abuse continued positive downward trends in 2014. Past year use of narcotics other than heroin (which includes all opioid pain relievers) was reported by 6.1 percent of high school seniors, compared with 7.1 percent a year ago and markedly lower than the 2004 peak of 9.5 percent. Past year use of the opioid pain reliever Vicodin showed a significant five-year drop, with 4.8 percent of 12th graders using Vicodin for non-medical reasons, half of what it was just five years ago, at 9.7 percent.

There was also a drop in the past year use of cough/cold medicines containing dextromethorphan (DXM) among eighth graders, with only 2 percent using them for non-medical reasons, down from 3.8 percent five years ago. By contrast, past year non-medical use of the stimulant Adderall (often prescribed for ADHD) remained relatively steady, at 6.8 percent for high school seniors. The survey continues to show that most teens get these medicines from friends or relatives and to a lesser degree from their own prescriptions.

Measured for the first time in the MTF survey this year, the use of electronic cigarettes (e-cigarettes) is high among teens. Past-month use by eighth graders is 8.7 percent, for 10th graders is 16.2 percent, and for 12th graders is 17.1 percent. NIDA is conducting research into use patterns and health effects of e-cigarettes.
Daily cigarette smoking has decreased markedly over the past five years (almost 50 percent) across all grades. For eighth graders, it dropped to 1.4 percent compared to 2.7 percent five years ago. Among 10th graders, it dropped to 3.2 percent compared to 6.3 percent five years ago. Among high school seniors, it dropped to 6.7 percent, down from 8.5 percent last year and 11.2 percent five years ago.

"Despite the positive developments this year, we are concerned about the levels of e-cigarette use among teens that we are seeing," said Lloyd D. Johnston, Ph.D., principal investigator, Institute for Social Research, University of Michigan. "It would be a tragedy if this product undid some of the great progress made to date in reducing cigarette smoking by teens."

The survey also looks at a variety of illicit drugs in addition to marijuana. Past year use of MDMA (also known as ecstasy or Molly) saw a decline among 10th graders to 2.3 percent, from 3.6 percent in 2013, now just about one third of the 2001 peak level of 6.2 percent. The news is also good related to the use of inhalants. With rates traditionally highest among eighth graders (unlike most other drugs), past year use among that age group is at 5.3 percent, down from 8.1 percent five years ago and from 12.8 percent at its most recent peak rate in 1995.

Rates of some of the newer drug trends have also dropped. There has been a considerable decline in past year use of K2/Spice (sometimes called synthetic marijuana) in the two years the survey has been tracking its use in all three grades. For 12th graders, 5.8 percent reported its use this year, which is significantly lower than 7.9 percent last year and 11.3 percent in 2012. Use of the hallucinogen salvia among 12th graders in the past year also dropped significantly to 1.8 percent, from 3.4 percent in 2013. Past year use of the amphetamine-like stimulants known as bath salts remained at low rates, and actually dropped considerably among eighth graders, to 0.5 percent compared to 1 percent last year.

Alcohol use continues its gradual decline in all grades. Eighth, 10th and 12th graders reported past month use of 9.0, 23.5 and 37.4 percent respectively, compared to 10.2, 25.7, and 39.2 percent last year. This represents a significant drop in the past five years, with rates at 14.9 percent, 30.4 percent

and 43.5 percent in 2009. There was a significant drop in binge drinking (five or more drinks in a row in the last two weeks) in 2014 among high school seniors, which is now under 20 percent. The most recent peak rate of binge drinking for seniors was in 1998 at 31.5 percent.

"We are encouraged to see a continued decrease in binge drinking among young people," said George F. Koob, Ph.D., director of the National Institute on Alcohol Abuse and Alcoholism. "Still, nearly 1 in 5 high school seniors report binge drinking within the past two weeks, which is unacceptably high and underscores the need for underage drinking research to remain a priority."

Overall, 41,551 students from 377 public and private schools participated in this year's MTF survey. Since 1975, the survey has measured drug, alcohol, and cigarette use and related attitudes in 12th graders nationwide. Eighth and 10th graders were added to the survey in 1991. Survey participants generally report their drug use behaviors across three time periods: lifetime, past year, and past month. Questions are also asked about daily cigarette and marijuana use. NIDA has provided funding for the survey since its inception by a team of investigators at the University of Michigan at Ann Arbor, led by Drs. Lloyd Johnston and Richard Miech. MTF is funded under grant number DA001411. Additional information on the MTF Survey, as well as comments from Dr. Volkow, can be found at www.drugabuse.gov/drugpages/MTF.html. The University of Michigan press release can be found at http://monitoringthefuture.org/embargoed.

MTF is one of three major surveys sponsored by the U.S. Department of Health and Human Services that provide data on substance use among youth. The others are the National Survey on Drug Use and Health and the Youth Risk Behavior Survey. The MTF website is: www.monitoringthefuture.org. Follow Monitoring the Future 2014 news on Twitter at @NIDANews, or join the conversation by using: #MTF2014. Additional survey results can be found at www.hhs.gov/news or www.whitehouse.gov/ondcp. Information on all of the surveyed drugs can be found on NIDA's Web site: www.drugabuse.gov.

The National Survey on Drug Use and Health, sponsored by the Substance Abuse and Mental Health Services Administration, is the primary source of statistical information on substance use in the U.S. population 12 years of age and older. More information is available at: http://www.samhsa.gov/data/population-data-nsduh.

The Youth Risk Behavior Survey, part of HHS' Centers for Disease Control and Prevention's (CDC) Youth Risk Behavior Surveillance System, is a school–based survey that collects data from students in grades nine–12. The survey includes questions on a wide variety of health–related risk behaviors, including substance abuse. More information is available at www.cdc.gov/HealthyYouth/yrbs/index.htm. Additionally, the National Youth Tobacco Survey, a school-based survey of U.S. students in grades six-12 conducted by the CDC in collaboration with the Food and Drug Administration, collects data on the use of multiple tobacco products, including e-cigarettes. More information is available at www.cdc.gov/tobacco/data_statistics/surveys/NYTS/.

http://www.drugabuse.gov/news-events/news-releases/2014/12/teen-prescription-opioid-abuse-cigarette-alcohol-use-trends-down

SCIENCE SPOTLIGHTS AND ANNOUNCEMENTS

September 2, 2014: ***NIDA Director Dr. Nora Volkow to speak at TEDMED 2014***. Dr. Nora Volkow, Director of NIDA, was a featured speaker at the TEDMED 2014 conference held in Washington, DC. A world-renowned neuroscientist and leading expert on addiction as a brain disease, Dr. Volkow addressed the obesity epidemic and the parallels between compulsive overeating and drug addiction. Dr. Volkow was one of 80 speakers selected to speak at TEDMED, the annual multi-disciplinary gathering where leaders from all sectors of society come together to explore the promise of technology and potential of human achievement in health and medicine. http://www.drugabuse.gov/news-events/news-releases/2014/09/nida-director-dr-nora-volkow-to-speak-tedmed-2014

September 2, 2014: ***Commentary: More research needed into marijuana's effects on brain development and function.*** A journal commentary by Harvard researcher and NIDA grantee Bertha K. Madras stressed the importance of a large scale longitudinal study to better assess the effects of marijuana use on human brain development and function. Dr. Madras noted research that suggests regular marijuana use that begins in youth "blunts" the brain's normal responses; results in increased anxiety and restlessness; and contributes to a high degree of negative emotionality. http://www.drugabuse.gov/news-events/news-releases/2014/09/commentary-more-research-needed-marijuanas-effects-brain-development-function

September 10, 2014: *Short video increases HIV testing in emergency department patients who initially declined.* A NIDA-funded study showed that one-third of emergency department patients who initially declined to be tested for HIV changed their minds after watching a 16-minute video. This video described the importance of testing as well as demonstrated how an HIV test can be conducted without drawing blood (i.e., orally) and provide results in approximately 20 minutes. http://www.drugabuse.gov/news-events/news-releases/2014/09/short-video-increases-hiv-testing-in-emergency-department-patients-who-initially-declined

September 17, 2014: *Review summarizes research on health effects of K2/Spice.*
An article, authored by scientists from NIDA and the University of Maryland, provided an overview of preclinical and clinical research on synthetic cannabinoids, often sold under brand names such as K2 or Spice. Areas covered by this review included who is using and why; research on brain receptor binding and intensity of drug effects; symptoms reported during emergency room visits; psychiatric effects; withdrawal; effects on driving; and deaths associated with synthetic cannabinoid use. http://www.drugabuse.gov/news-events/news-releases/2014/09/review-summarizes-research-health-effects-k2spice

September 22, 2014: *Unique interaction discovered between brain regions involved in addiction, depression.*
NIDA IRP researchers discovered a unique interaction between a nerve cell in the brain's ventral tegmental area and the lateral habenula - a pathway implicated in mental health disorders such as addiction and depression. This nerve cell releases both excitatory (glutamate) and inhibitory (GABA) chemicals, contrary to long-established theories assuming release of a single chemical (either glutamate or GABA). This previously undiscovered form of chemical communication allows for either increases or decreases in lateral habenula activity, which provides much more flexibility in modulating brain function compared to the single transmitter model.

http://www.drugabuse.gov/news-events/news-releases/2014/09/unique-interaction-discovered-between-brain-regions-involved-in-addiction-depression

October 27, 2014: *New CME/CE course addresses substance use.*
A continuing medical education/continuing education course (CME/CE), *Talking to Patients About Health Risk Behaviors*, added to a growing body of tools available through the National Institute on Drug Abuse (NIDA) to help healthcare professionals care for patients at risk for substance use disorders. The course -- a joint program between NIDA, Medscape Education and SIMmersion -- was developed by experts from the fields of internal, family and emergency medicines. It was created with the support of NIDA's Blending initiative, a program that helps translate the latest research findings into useful clinical tools.
http://www.drugabuse.gov/news-events/news-releases/2014/10/new-cmece-course-addresses-substance-use

November 6, 2014: *NIDA Mini-Convention: Frontiers in Addiction Research.*
NIDA hosted its annual one-day mini-convention, a satellite event of the Society for Neuroscience annual meeting on November 14, 2014 in the Natcher Auditorium on NIH Campus. NIDA-supported scientists presented recent findings and discuss future directions in neuroscience and addiction research.
http://www.drugabuse.gov/news-events/news-releases/2014/11/nida-mini-convention-frontiers-in-addiction-research

November 19, 2014: *Evidence grows that heavy marijuana use may harm the brain.*
NIDA-funded research showed that heavy marijuana use (at least four times per week over the past six months) is linked to adverse changes in the function and structure of brain areas associated with reward, decision making, and motivation. Heavy marijuana use can also enhance some brain circuits – possibly to compensate for reduced function in specific brain regions. This effect was more pronounced in those who started using at a young age, indicating that developing brains are particularly vulnerable to marijuana's effects.
http://www.drugabuse.gov/news-events/news-releases/2014/11/evidence-grows-heavy-marijuana-use-may-harm-brain

November 20, 2014: *Buprenorphine tapering less effective than ongoing maintenance for prescription opioid abuse.*
A NIDA-funded study concluded that maintenance buprenorphine therapy is more effective than tapering and discontinuation of the medication in treating prescription opioid-dependent patients in primary care settings. The results suggested that buprenorphine taper should be used only when it is clinically indicated in the treatment of patients dependent on prescription opioids.
Additional research is needed to help identify factors associated with successful tapering and maintenance therapy.
http://www.drugabuse.gov/news-events/news-releases/2014/11/buprenorphine-tapering-less-effective-than-ongoing-maintenance-prescription-opioid-abuse

December 2, 2014: *Regulating a single gene may alter addiction and stress responses.*
Researchers have now used genetically engineered DNA binding proteins to target specific processes within a gene - located within a brain reward center in the mouse. By regulating the activity of this specific gene, the scientists found they were able to alter gene expression and

behaviors related to addiction and stress. This technique may lead to new treatments for substance use and other mental health disorders.
http://www.drugabuse.gov/news-events/news-releases/2014/12/regulating-single-gene-may-alter-addiction-stress-responses

December 9, 2014: *National Institute on Drug Abuse to discuss results of 2014 Monitoring the Future Survey.*
NIDA held a teleconference on Tuesday, December 16, to discuss the results of the 2014 Monitoring the Future (MTF) survey. The survey, conducted earlier this year by scientists at the University of Michigan, tracked annual drug use and attitudes among eighth, 10th, and 12th-grade students. For the first time, this year's MTF survey included data on the use of e-cigarettes, as well as the attitudes about, and prevalence of, marijuana use, prescription medications, alcohol, and tobacco.
http://www.drugabuse.gov/news-events/news-releases/2014/12/national-institute-drug-abuse-to-discuss-results-2014-monitoring-future-survey

December 19, 2014: *Methamphetamine or amphetamine abuse linked to higher risk of Parkinson's disease.*
People who abuse amphetamine-type drugs such as methamphetamine may be at increased risk for developing dopamine-related disorders such as Parkinson's disease, according to research funded by NIDA and NCI. This is consistent with prior studies in animals showing that abuse of these drugs can damage dopamine neurons.
http://www.drugabuse.gov/news-events/news-releases/2014/12/methamphetamine-or-amphetamine-abuse-linked-to-higher-risk-parkinsons-disease

December 29, 2014: *Prescriptions for anti-anxiety medications put teens at risk.*
Teens prescribed anxiety or sleep medications are more likely to abuse them later (compared to those who had never had a prescription). Teens reported they used these medications to self-treat insomnia or anxiety or to get "high." This research, the first longitudinal study to examine nonmedical use and medical misuse of anxiety and sleep medications among adolescents, was conducted by scientists at the University of Michigan and funded by NIDA and NCATS.
http://www.drugabuse.gov/news-events/news-releases/2014/12/prescriptions-anti-anxiety-medications-put-teens-risk

December 30, 2014: *Registration open for Drug Facts Chat Day; 2015 Drug IQ Challenge preview available.*
Schools can now register for Drug Facts Chat Day, NIDA's annual Web chat that connects NIH scientists with teens around the country, at http://drugfactsweek.drugabuse.gov/chat/index.php. Drug Facts Chat Day occurs on January 30 during National Drug Facts Week, which runs from January 26 – February 1, 2015.
http://www.drugabuse.gov/news-events/news-releases/2014/12/registration-open-drug-facts-chat-day-2015-drug-iq-challenge-preview-available

December 31, 2014: *Women who receive gender-specific substance abuse treatment have greater chance of employment.*
Women who receive treatment in gender-sensitive programs are more likely to be employed 12 months after treatment admission than women in more traditional treatment programs, according to research funded by NIDA.

http://www.drugabuse.gov/news-events/news-releases/2014/12/women-who-receive-gender-specific-substance-abuse-treatment-have-greater-chance-employment

January 8, 2015: *Effects of cigarette smoking on brain differ between men and women.* Researchers from Yale University discovered that brain activation during smoking occurs differently in men than in women. The research used a new method of brain imaging scan analysis, and was funded by NIDA and the NIH Office of Research on Women's Health. http://www.drugabuse.gov/news-events/news-releases/2015/01/effects-cigarette-smoking-brain-differ-between-men-women

January 12, 2015: *Nicotine metabolism rates may impact success of smoking cessation treatments.* A randomized clinical trial of smokers trying to quit found that the effectiveness of particular smoking cessation therapies might relate to how quickly their body metabolizes nicotine. The NIH-funded study compared success rates of the nicotine patch versus the prescription medication varenicline.
http://www.drugabuse.gov/news-events/news-releases/2015/01/nicotine-metabolism-rates-may-impact-success-smoking-cessation-treatments

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INTERVIEW HIGHLIGHTS: August 2014 – December 2014

Al Jazeera – Dr. Nora Volkow was interviewed about Monitoring the Future.
Bloomberg – Dr. Susan Weiss was interviewed about marijuana.
CBS Radio Network – Dr. Wilson Compton was interviewed about Monitoring the Future.
CNN – Dr. Nora Volkow was interviewed about Monitoring the Future.
CNN – Dr. Susan Weiss was interviewed about a NIDA research study about marijuana.
CNN Special Projects – Dr. Marilyn Huestis was interviewed about K2/Spice.
Consumers Digest – Dr. Wilson Compton was interviewed about pain/opioids.
ESPN – Dr. Marilyn Huestis was interviewed about drug testing.
Fox Business Network – Dr. Nora Volkow was interviewed about her TEDMED presentation.
HBO Real Sports with Bryant Gumbel – Dr. Wilson Compton was interviewed about heroin.
Men's Journal – Dr. Wilson Compton was interviewed about marijuana.
NBC News Network – Dr. Wilson Compton was interviewed about Monitoring the Future.
Newsweek – Dr. Ruben Baler was interviewed about marijuana.
Philadelphia Inquirer – Dr. Joe Frascella was interviewed about nicotine.
Sunday Times London - Dr. Nora Volkow was interviewed about ISEF Science Fair Winners.
The Atlantic – Dr. Wilson Compton was interviewed about Monitoring the Future.
The Boston Globe – Dr. Wilson Compton was interviewed about marijuana.
The New York Times – Dr. Nora Volkow was interviewed about marijuana.
The Wall Street Journal – Dr. Nora Volkow was interviewed about ISEF Science Fair Winners.
The Wall Street Journal (2) – Dr. Wilson Compton was interviewed about naloxone and elderly drug abuse.
Time (2) – Dr. Nora Volkow was interviewed about Monitoring the Future and marijuana.
Time – Dr. Marilyn Huestis was interviewed about drugged driving.
Time Online – Dr. David Thomas was interviewed about pain/opioids.
Tom Joyner Morning Show – Dr. Wilson Compton was interviewed about Monitoring the Future.

Total News Source - Dr. Nora Volkow was interviewed about Monitoring the Future.
U.S. News & World Report – Dr. Wilson Compton was interviewed about Monitoring the Future.
USA Today – Dr. Nora Volkow was interviewed about Monitoring the Future.
Washington Times - Dr. Wilson Compton was interviewed about Monitoring the Future.

Dr. Loreno Leggio, IRP, was recently interviewed by Hannah Thomas-Peter from Sky NEWS ("Call to ban intravenous drips as hangover cure"), which was also featured in several national and international websites and TV channels.
In December 2014, *Chemical and Engineering News* published an article about Dr. Amina Woods', IRP, work on alterations in brain lipids due to chronic ethanol consumption.

MEETINGS/CONFERENCES

On November 14, 2014 NIDA held the annual **Frontiers in Addiction Research Mini-convention**, a satellite meeting of the Society for Neuroscience Meeting. The 2014 mini-convention included presentations on: Emerging and Novel Aspects of Neuronal Transmission; Extracellular RNAs in Neuroscience: Biology, Biomarkers, and Therapeutics; Advances in High Resolution and Large Scale Imaging of Brain Networks and Circuits; and The Effects of Drug-, Stress-, and Pain-induced Neuroinflammation on Glymphatics and Sleep. It also featured key note presentations by the 2013 and 2014 winners of the SfN Jacob P. Waletzky Award, which recognizes excellence in research in the area of substance abuse and the brain and nervous system, and a poster session showcasing the work of early career investigators. The winner of the 2014 Jacob P. Waletzky Award was Dr. Paul Phillips from the University of Washington and the 2013 winner was Dr. Rita Goldstein from the Friedman Brain Institute at the Icahn School of Medicine at Mount Sinai.

On September 24, 2014, the Trans-NIH (NIAAA, NICHD, NIDA, NIMH, NINDS) **Addressing Health Disparities through Neuroscience: Views by Two** committee held a seminar on "Cultural Neuroscience," an emerging interdisciplinary field that focuses on the influence of personally held opinions, attitudes, beliefs, mores, and laws on brain, mind and behavior. Coordinated by Flair Lindsey of the Office of Diversity and Health Disparities (NIDA representative), the seminar featured Drs. George Northoff (University of Ottawa) and Denise C. Park (University of Texas), who's presentations provided further insight into cultural neuroscience, discussed interdisciplinary approaches to adopting cultural neuroscience research methods to reduce health disparities and empirically-based advances in cultural neuroscience for further investigation. Launched in 2011, the goal of the *Addressing Health Disparities through Neuroscience* seminar series is to increase awareness of health disparities relating to neuroscience through a collegial discussion between 2 renowned scientists on a shared topic.

On September 19, 2014, NIDA's Office of Diversity and Health Disparities convened a meeting of scientific and research training experts from **NIDA Diversity Networks** to discuss the mentoring, training and grant-writing needs of underrepresented scholars. The meeting focused on programmatic strategies NIDA should take to increase the success of underrepresented early-stage independent investigators in the NIH grant submission process. The invited participants discussed feasible strategies and pitfalls to avoid when developing a sustainable grant-writing program for early-stage independent investigators. NIDA ODHD intends to use recommendations and suggestions provided during this meeting to develop a long-term grant writing program.

On September 22, 2014, NIDA's Office of Diversity and Health Disparities convened a meeting of eight students selected from the 2014 NIDA Summer Research Internship program to present their research project at NIDA Headquarters, and learn about NIDA's research priorities and career development opportunities. Students were from different racial and ethnic backgrounds and scientific areas. The NIDA Summer Research Program provides research internships for high school and undergraduate students, with a goal of recruiting underrepresented racial/ethnic populations into research. Internships include a paid 8 week intensive, hands-on drug abuse and addiction research experience that provides students with the opportunity to gain an understanding of the research process. Internships are conducted with NIDA-funded investigators across the country. This meeting was an excellent opportunity for these budding scientists to learn about NIDA, meet NIDA staff, and learn how to pursue a career in substance abuse and addiction research.

Dr. Albert Avila, Director, Office of Diversity and Health Disparities, presented at the National Hispanic Science Network annual research conference in El Paso, Texas on September 4-6, 2014. Dr. Avila presented on NIDA's research priorities, diversity enhancing programs, and research funding opportunities available to early career investigators. In addition, he co-chaired two sessions, "Mixed Heritage across Racial/Ethnic Populations" and "NIDA-NHSN R25 Fellowship: Embracing Professional Development in NIDA-Oriented Careers through Mentoring, Resource Sharing, and Networking." He met individually with perspective grantees in regards to research proposals, funding opportunities, and application review.

Dr. Albert Avila presented at the "9th Drug Abuse Research Symposium at Charles Drew University" on September 12, 2014. Presentation themes spanned NIDA's research priorities, diversity enhancing programs, and research funding opportunities available to early career investigators. The conference was streamed to four other NIDA DIDARP institutions to reach a broad audience.

Dr. Albert Avila presented a seminar "NIDA Priorities and Research Training Opportunities 101" at the University of South Carolina on October 9, 2014. He met with faculty on the development of institutional and diversity training programs and met with students regarding research careers and professional development topics.

Dr. Albert Avila co-moderated and presented at the "4th Annual NIH Blueprint Enhancing Diversity through Undergraduate Research Education Experiences (ENDURE)" meeting held prior to SfN in Washington, D.C. on November 15, 2014. Highlights of the meeting included a presentation on NIH funding opportunities followed by round table discussion of various research and professional development topics targeted toward graduate students, postdoctoral and early career investigators.

On August 9, 2014, Pamela Goodlow, Public Health Analyst, Office of Diversity and Health Disparities, represented NIDA in an NIH-sponsored forum "Funding and Training Opportunities" at the annual American Psychological Association (APA) Convention, held in Washington, D.C. She presented information on the various research training and independent funding and related funding opportunities available to APA attendees, and was one of eight NIH representatives present.

Pamela Goodlow of the Office of Diversity and Health Disparities presented and met individually with over 50 students at the semi-annual "NIH Funding Opportunities for Students" session at Howard University in Washington, D.C. on October 21, 2014. Undergraduate and graduate

students from Howard University Departments of Biological Sciences and other health sciences departments attended the session, seeking part-time and summer research opportunities.

Pamela Goodlow of the Office of Diversity and Health Disparities hosted a two-day grant writing workshop: Addiction Research Training Institute "*Booster Session*," held at NIDA Headquarters (NSC) in Bethesda, Maryland on August 21-22, 2014. The two-day workshop, sponsored with NIDA's *African American Researchers and Scholars Advisory Workgroup*, paired early-career investigators seeking funding through the NIH with currently-funded NIDA investigators in intensive one-on-one grant-writing and mentoring sessions. Attendees are expected to submit grant applications to the NIH within six months of participation in the *Booster Session* workshop.

Flair Lindsey, Program Analyst, Office of Diversity and Health Disparities, coordinated the seminar "Discrimination and Bias in the Grant Review Process: Problems and Challenge," which featured guest speaker Dr. Frederick T.L. Leong of Michigan State University. Held on October 7, 2014 at NIDA Headquarters (NSC) in Bethesda, Maryland as a part of the ongoing *NIDA ODHD Translational Research Seminar Series: Promoting Diversity and Moving toward Health Equity,* the at-capacity seminar attracted a diverse audience of NIH professionals. The seminar was also made available to the NIH community via Webex internet conferencing. Dr. Leong's timely presentation used the Ginther et al (2011) report as a starting point, further deconstructing the problem of discrimination and bias in the grant review process and identifying the associated problems and challenges.

Dr. Jack Stein, Director, OSPC, participated on a panel presentation, "Federal and State Update on Implications for the Addiction Workforce" at the 2014 Annual Conference of the Association of Addiction Professionals, in Seattle, WA, on September 1, 2014.

Dr. Ruben Baler**,** OSPC, gave a lecture on "Addiction as a Brain Disease: What Science Tells Us" at the 2014 Drug-Free Communities (DFC) Support Program for New Grantees at the Renaissance Hotel, Washington D.C., on December 9, 2014.

Dr. Ruben Baler presented on "Substance Abuse and Brain Development" at the 4-H Health Rocks Youth Ambassador Summit, Wicomico County, MD, on October 23, 2014.

Dr. John Satterlee, DBNBR, attended the RNA Editing, Epitranscriptomics, and Processing in Cancer Progression meeting, September 10, 2014, Rockville, MD

Dr. John Satterlee attended the CSHL Conference on Regulatory and ncRNAs. August 26-30, 2014.

Dr. John Satterlee gave a presentation entitled "Neuroepigenomics: Resources, Obstacles, and Opportunities" on November 16, 2014 at the Society for Neuroscience satellite NeuroEpigenetics Symposium: Research Questions, Technological Advances and Analytical Challenges.

Drs. John Satterlee and Jonathan D. Pollock, DBNBR, chaired the Society for Neuroscience Minisymposium, entitled, "Novel RNA modifications in the Nervous System: Form and Function, November 18, 2014, Washington, D.C.

Dr. Jonathan D. Pollock attended the BRAIN Initiative Investigators Kick-off Meeting, November 20-21, 2014 at the North Bethesda Marriott, Rockville, MD, Nov 20, 2014.

Dr. Da-Yu Wu, DBNBR, attended the International Society for Developmental Neuroscience, Montreal, Canada, July 19 to July 24, 2014,

Dr. Da-Yu, Wu served as a reviewer for the NIH US-Japan Brain Research Cooperative Program, Bethesda, MD, October 22, 2014.

Dr. Nancy Pilotte, DBNBR, chaired the Early Career Workshop at the Society for Neuroscience Annual Meeting. Roger Sorensen, Hal Gordon (DCNBR), Pilotte, and Anto Bonci (IRP) were presenters.

Drs. Roger Sorensen and Nancy Pilotte, DBNBR, co-chaired a symposium at NIDA mini-convention entitled, "Emerging and Novel Aspects of Neuronal Transmission"

Dr. Minda Lynch, DBNBR, co-organized and chaired the symposium "Regulation of Feeding: A Metabolic Pathway to Addiction?" at the 48th Winter Conference on Brain Research, Big Sky, Montana, January 2015.

Dr. Susan Volman, DBNBR, helped plan and facilitate a session on "The BRAIN Initiative and its links to Multiscale Modeling" at the 2014 Multiscale Modeling Consortium Meeting, September 3-4, 2014 in Bethesda, MD.

Dr. Susan Volman organized the New Investigator Poster Session for the NIDA Frontiers in Addiction Mini-Convention satellite meeting of the Annual Society for Neuroscience Meeting, November 14, 2014 in Bethesda, MD.

On November 4, 2014, Dr. Rao S. Rapaka DBNBR, presented "A Historical Introduction to the Chemistry of Cannabinoids, Endocannabinoids, and Marijuana." Dr. Rapaka focused on the history and development of the cannabinoids program at NIDA.

On September 8-9, 2014, DPMCDA convened a meeting entitled "Emerging Targets for Stimulant Use Disorders". A total of ten new targets/pathways were presented by advocates or experts in their respective fields. A panel of industry experts were also invited and asked to provide specific feedback on each target/pathway, focusing on issues related to drug development and druggability. Papers written by presenters in support of each target, as well at the general feedback received from the industry participants, are to be published in CNS & Neurological Disorders-Drug Targets in early 2015.

On November 6-8, 2014, Dr. Harold Perl gave a Plenary talk at the 38th Annual National Conference of the Association for Medical Education and Research in Substance Abuse on in San Francisco, CA. Title of the Plenary was: Addressing Substance Use in Medical Settings: Expanding Our Reach. He also served as Chair of the Skills Workshop Committee for the conference.

On October 15-17, 2014, Dr. Dionne Jones, DESPR, Services Research Branch organized and chaired a panel, "Linking Vulnerable Populations to Treatment and Care" at the Addictions Health Services Research Conference, Boston, MA.

On September 16-18, 2014, Dr. Harold Perl gave two panel presentations and served as Discussant for a third panel at the 27th Annual Prevention Research Conference of the National Prevention Network, in Hartford, CT. Titles of the presentations were: Drugged Driving Research and Prevention Resources: NIDA's Interest and Perspective and Outcomes from the SAMHSA SPF SIG Cross-Site Evaluation for Cohorts I and II: NIDA's Collaborative Investment. The third panel was titled: Media Literacy Education and Substance Abuse Prevention.

On September 22, 2014, Dr. Dionne Jones presented on "Research Initiatives and Activities in DESPR/NIDA" at NIDA's Office of Diversity and Health Disparities 2014 Summer Research Internship Meeting, Bethesda, MD.

On October 15-17, 2014, Dr. Dionne Jones presented a "Pre-Conference Workshop for Early Career Investigators", with NIAAA staff at the Addictions Health Services Research Conference, Boston, MA.

On October 22, 2014, Dr. Dionne Jones presented on "Grantsmanship at NIH" at The George Washington University, Washington, DC.

On September 22, 2014, Dr. Eve Reider, DESPR, Prevention Research Branch participated in the first yearly meeting of the joint NIH-DOD FY2013 Funding Opportunity Announcement (FOA) (DA13-012/013) on substance abuse prevention in U.S. military personnel, veterans and their families near Fort Detrick, MD. Twelve grants were funded from this FOA, including 7 NIH grants (3 NIDA, 2 NIAAA, 2 NCCAM) and 5 DoD grants. The meeting was conducted within the structure of the Military Operational Medicine Research Program (MOMR) Substance Abuse In Progress Review structure, and included a substance abuse panel of subject matter experts that included representation from each of the military branches and NIH staff involved in the development of the FOA (Dr. Eve Reider, NIDA, Dr. Aaron White, NIAAA, and Dr. Kristen Huntley, NCCAM).

Dr. Eve Reider was invited to participate in a Joint Program Review Panel, 2014-2015, Psychological Health, through the Military Operational Medicine Research Program, Department of the Army, U.S. Army Medical Research and Materiel Command.

Dr. Eve Reider was invited by the Military Operational Medicine Research Program (MOMRP)/Joint Program Committee for Military Operational Medicine (JPC5) to serve as a subject matter expert for In-Progress Reviews (IPR) of Defense Health Program funded research, held at Fort Detrick, Frederick, Maryland. She participated as a panelist in the following In Progress Reviews at MOMRP: PTSD Services Research and Exposure Therapy, August 5-6, 2014; Resilience Research, August 26-27, 2014; and Substance Abuse, September 22-24, 2014.

On June 19, 2014, Dr. Eve Reider participated in the planning and coordination of presentations on NIDA's substance abuse treatment portfolios that took place for the Office of Research and Development at the Veterans Administration in Washington, D.C. Drs. Jamie Biswas, Medications Research Grants Branch, and Lisa Onken, Behavioral and Integrative Treatment Branch, presented on treatments for substance abuse and co-occurring disorders. Dr. Terri Gleason, VA ORD, presented on the VA substance abuse portfolio.

On November 5-6, 2014, Drs. Eve Reider and Belinda Sims, DESPR, Prevention Research Branch, participated in the planning of the third Institute of Medicine-National Research Council Forum meeting on Promoting Children's Cognitive, Affective, and Behavioral Health. The meeting was titled "Innovations in Design and Utilization of Measurement Systems to Promote Children's Cognitive, Affective, and Behavioral Health." Drs. Reider and Sims participated in the planning of a panel "Toward Efficient and Sustainable Delivery of Interventions." Speakers on this panel included**:** Richard Catalano, Ph.D., University of Washington; Lisa Saldana, Ph.D., Oregon Social Learning Center; Marion Forgatch, Ph.D., Oregon Social Learning Center; and Carlos Gallo, Ph.D., Northwestern University. The meeting took place at the National Academy of Science Building, Washington, D.C.

On October 15-17, 2014, Dr. Tisha Wiley, DESPR, Services Research Branch, co-chaired a panel, "Juvenile Justice-Translating Research Interventions for Adolescents in the Legal System (JJ-TRIALS): A Multi-site, Cooperative Implementation Science Initiative" at the Addictions Health Services Research Conference, Boston, MA, October 15-17, 2014. This panel described the theoretical framework, measurement framework, focal evidence-based interventions, and community partner involvement in NIDA's JJ-TRIALS initiative. As NIDA's JJ-TRIALS science officer, Dr. Wiley co-authored all of the presentations in the panel.

On November 8, 2014, Dr. Eve Reider was involved in a presentation at the 30th Annual International Society for Traumatic Stress Studies (ISTSS) 30th Annual Meeting, in Miami, FL. The presentation was titled "Federal Agencies Supporting PTSD Research: Priorities and National Research Action Plan." Presenters included Terri Gleason, VA, Farris Tuma and Susan Borja, NIMH, Ronald Hoover, Katherine Nassauer, and Dennis McGurk, DoD, and Patricia Powell, NIAAA.

On October 27, 2014, Dr. Eve Reider was invited to present at a Marine Corps Commander's Prevention Brief, at Quantico, VA. Dr. Reider presented on "Substance Abuse in the Military: An Opportunity for Prevention."

On October 15-17, 2014, Dr. Tisha Wiley co-chaired a panel, "Implementation Science on Addiction Service Integration: A Panel Discussion" at the Addictions Health Services Research Conference, Boston, MA, October 15-17, 2014.

On August 14th, 2014, Dr. Cheryl Anne Boyce, DCNBR, led a webinar workshop entitled Building a Competitive Research Program: What They Never Told You - But Really Need to Know (Part B) with participants Drs. Karen Y. Sirocco (NIDA), LeShawndra Price (NIMH), Karen Gavin-Evans (NIMH) and Kellina Craig-Henderson (NSF). Federal funding opportunities from the National Institutes of Health (NIH) were highlighted as well as the review, resubmission and budget issues regarding grant applications. The workshop was sponsored by the Robert Wood Johnson Foundation (RWJF) New Connections: Increasing Diversity of RWJF Programming.

Dr. Cheryl Anne Boyce served as the invited speaker for The Meharry-Vanderbilt Alliance 15-Year Anniversary Lecture Series on Health Disparities and Population Health and presented the talk "Building the Scientific Workforce and Innovation for Clinical Translational Research: Culture Counts and Collaborations Matter" at Meharry Medical College in Nashville, TN and via webcast on September 23, 2014.

On September 24, 2014, Dr. Cheryl Anne Boyce presented a Grants Workshop for New Investigators at Meharry Medical College for the Meharry-Vanderbilt Alliance in Nashville, TN.

On September 30, 2014, Dr. Cheryl Anne Boyce and Valerie Maholmes (NICHD) hosted the President's Commission to Eliminate Child Abuse and Neglect Fatalities Joint Meeting with NIH Child Abuse and Neglect Working Group (NIH CANWG) in Bethesda, MD. Dr. Boyce presented on "NIH CANWG Background and History."

Dr. Cheryl Anne Boyce and Dr. Kathy Etz (DESPR) co-hosted a webinar on the National Addiction and HIV Data Archive Program (NAHDAP) with a presentation Dr. Amy Pienta, NAHDAP Director, University of Michigan, on October 14, 2014 for DCNBR.

At the American Academy of Child and Adolescent Psychiatry's 61st Annual Meeting in San Diego, CA, several sessions were sponsored by NIDA. Dr. Cheryl Anne Boyce participated in the AACAP K12 Information Session on the research training program on October 22, 2014. Another training themed session entitled, "Research Career Development and Priorities in Addiction and Mental Health" on October 23, 2014 included presentations by Dr. Boyce with NIH colleagues Dr. Geetha Subramaniam (NIDA CTN) and Dr. Shelli Avenevoli (NIMH). NIH Grantees Dr. Neal Ryan (University of Pittsburgh), Dr. Melissa DelBello (University of Cincinnati), and Dr. Bradley Peterson (Children's Hospital Los Angeles) served on a panel to discuss their research career trajectories. Dr. Boyce also co-chaired a scientific symposium organized with Dr. James Bjork (formerly of NIDA DCNBR, currently at VCU) featuring the results of the NIDA funded multi-site data initiative Pediatric Imaging, Neurocognition, and Genetics (PING): Innovations to Explore Brain Connectivity Across Development. This symposium included presentations by NIDA research investigators Dr. Terry Jernigan (UCSD); Dr. Anders Dale (UCSD); Dr. Elizabeth Sowell (Children's Hospital Los Angeles), and Dr. Linda Chang (University of Hawaii). Dr. BJ Casey (Cornell University) served as the discussant for the session.

Dr. Karen Sirocco, DCNBR, attended The Prescription Drug Abuse Interagency Meeting on October 22, 2014, hosted by the Office of National Drug Control Policy which was held in Washington, DC. The purpose of the meeting was to bring together Federal government representatives to provide an update on implementation of the prescription drug abuse prevention plan and agency activities concerning consequences e.g., Neonatal Abstinence Syndrome (NAS), overdose prevention and overdose education/naloxone, infections and IDU, and transition to heroin.

Dr. Karen Sirocco participated in the Capsule Team to discuss a paper that will be submitted to the Pediatric HIV/AIDS Cohort Study (PHACS) Scientific Leadership Group for consideration of funding entitled "Substance Use and Neurocognition among Youth with Perinatally Acquired HIV Infection and Perinatal HIV Exposure but Uninfected" at the PHACS Fall 2014 Network Meeting which took place in Bethesda, Maryland on October 22-23, 2014.

Dr. Cheryl Anne Boyce attended the National consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) Director's Meeting on October 29-30, 2014 in Bethesda, MD. NIDA staff Drs. Joseph Frascella, Steven Grant and Kevin Conway also attended the grantees' meeting with fellow NIAAA colleagues Dr. Ellen Witt, John Matochik, and Antonio Noronha and NIMH colleagues Drs. Shelli Avenevoli and Stacia Friedman. Dr. George Koob, Director NIAAA, also attended a portion of the meeting and addressed the research investigators and meeting participants.

Dr. Cheryl Anne Boyce attended An NIMH Workshop for Early Stage Research Investigators on November 4-5, 2014 in Bethesda, MD.

Dr. Cheryl Anne Boyce served as a speed mentor for the Annual Building Interdisciplinary Research Careers in Women's Health (BIRCWH, K12) Scholars Meeting on Wednesday, November 5, 2014 at the NIH Porter Neuroscience Center, in Bethesda, MD along with DCNBR colleagues Drs. Cora Lee Wetherington and Samia Noursi.

Dr. Cheryl Anne Boyce served as faculty for the Robert Wood Johnson Foundation (RWJF) New Connections Eighth Annual Research and Coaching Clinic in, New Orleans, LA held November 14-16, 2014.

Dr. Cheryl Anne Boyce attended the 2014 Minority Health and Health Disparities Grantees' Conference sponsored by NIMHD held December 1-3, 2014 in National Harbor, MD.

On December 2, 2014, Dr. Cheryl Anne Boyce served as the discussant for the webinar "The Biological Embedding of Child Abuse and Implications for Policy and Practice" based on the recent Society for Research in Child Development (SRCD) Policy Report. The session featured NIH grantees Dr. Seth Pollak (University of Wisconsin-Madison) and Dr. Sara Jaffee (University of Pennsylvania) as presenters and Dr. Valerie Maholmes (NICHD) as the chair.

On December 11, 2014, Dr. Karen Sirocco served as the NIDA representative and attended the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD) Executive Committee Membership meeting in Rockville, MD. The purpose of this annual meeting was to facilitate agency representatives in sharing information on past fiscal year activities and to encourage development of collaborations and communications. Dr. Cheryl Anne Boyce attended via teleconference

Dr. Harold Gordon, DCNBR, chaired a symposium entitled, The Effect of Drug-, Stress-, Pain-induced Neuroinflammation on Glymphatics and Sleep Quality, at the Frontiers in Addiction Research NIDA Mini-Convention held on the NIH campus in Bethesda, MD on November 14, 2014, prior to the Annual Meeting of the Society for Neuroscience.

Dr. Harold Gordon together with Drs. Nancy Pilotte and Roger Sorenson of DBNBR and Dr. Antonello Bonci of NIDA's IRP presented a workshop for young investigators at the Annual Meeting of the Society for Neuroscience, in Washington, DC. on November 16, 2014.

Drs. Steve Grant and James Bjork, DCNBR, co-chaired a symposium entitled: "Legal Damages: New Insights into Chronic Marijuana Effects on Human Brain Structure and Function" held on December 11, 2013, at the 52nd Annual Meeting of the American College of Neuropsychopharmacology in Hollywood, FL.

Dr. Steven Grant gave a talk entitled "A National Longitudinal Study of Neurodevelopmental Consequences of Substance Use: Progress and Prospects" at the FLUX Developmental Cognitive Neuroscience Conference held in Los Angeles, CA on September 11–13, 2014.

Dr. Steven Grant represented NIDA at the MacArthur Foundation Research Network on Law and Neuroscience meeting in held in Santa Monica, CA on October 17–19, 2014.

Drs. Steven Grant and James Bjork (now at Virginia Commonwealth University) co-chaired a session entitled "Advances in High Resolution and Large Scale Imaging of Brain Networks and Circuits"at the Frontiers in Addiction Research NIDA Mini-Convention held on the NIH campus in Bethesda, MD prior to the Annual Meeting of the Society for Neuroscience held in Washington, DC on November 14, 2014.

Drs. Steven Grant, Mary Kautz, Yu (Woody) Lin, and Harold Gordon, DCNBR, represented NIDA at the Annual Meeting of the Society for Neuroscience held in Washington, DC, November 15–19, 2014.

Dr. Steven Grant served as the NIDA representative on the Federal Liaison group at the Principle Investigator meeting for the Intelligence Advanced Research Project Agency SHARP (Strengthening Human Adaptive Reasoning and Problem Solving Program) meeting held in Crystal City, VA on November 20–21, 2014.

Dr. Steven Grant chaired a panel entitled "Translating Clinical Neuroscience into Clinical Practice: Promise and Peril" at the American College of Neuropscychopharmacology Annual Meeting held in Phoenix, AZ on December 10, 2014.

Dr. Samia Noursi, DCNBR, gave a presentation at the Vermont Center on Behavior and Health 2nd Annual Conference on Behavior Change, Health and Health Disparities, Oct 2-3, 2014, Burlington Vermont. Her presentation focused on funding opportunities on drug abuse for junior investigators.

Dr. Cora Lee Wetherington, DCNBR, was a session moderator at the workshop sponsored by the NIH Office of Research on Women's Health, Methods and Techniques for Integrating Biological Variable 'Sex' in Preclinical Research, on October 20, 2014. She moderated Session III. "Practical methods to integrate the biological variable sex into research projects."

Dr. Cora Lee Wetherington was moderator for an oral presentation session at the annual Interdisciplinary Women's Health Research Symposium held by the NIH Office of Research on Women's Health, November 6, 2014, in Masur Auditorium, NIH Main Campus.

Dr. Kevin Walton, DPMCDA, was invited to speak at the Duke Nicotine Research Conference, "E-Cigarettes and their role in Smoking Cessation and Harm Reduction", October 15, 2014.

The American Academy of Child & Adolescent Psychiatry (AACAP) 61st Annual Meeting was held October 20-26, 2014 in San Diego, CA. Dr. Geetha Subramaniam chaired the symposium titled "Prescription Stimulant Use and Misuse in Youth: Clinical Practice Implications."

Dr. Geetha Subramaniam, CCTN, co-chaired a session to address the important differences in treating adolescents with substance use disorders (SUD) at the 2014 Addiction Health Services Research (AHSR) Conference, held October 15-17 in Boston, MA. She led a discussion on recent approaches to screening adolescents.

Dr. Udi Ghitza, CCTN, chaired the session titled "Chronic Care Management (CCM) in Substance use Disorders (SUD): Role of the Electronic Health Record in SUD Research and Care" at the 2014 Addiction Health Services Research (AHSR) Conference, held October 15-17 in Boston, MA.

Dr. Amy Newman, IRP, gave an invited lecture at the Wake Forest School of Medicine this fall.

Dr. Michael Baumann, IRP, was invited to give an oral presentation entitled "Pharmacology of 'next generation' cathinone analogs" for the medicinal chemistry department at Virginia Commonwealth University in Richmond, VA, on October 10, 2014.
Dr. Michael Baumann chaired and presented research data at a mini-symposium held at the annual meeting of the Society for Neuroscience in Washington DC on November 18, 2014. The mini-symposium was entitled "Bath salts, spice, and related designer drugs: The science behind the headlines."

Dr. Lorenzo Leggio, IRP, together with Dr. George Koob, NIAAA chaired a panel entitled "Alcohol craving: The gut and liver in the brain" at the 53th ACNP meeting in Phoenix, AZ. Dr. Leggio also gave a talk on "GLP-1 and ghrelin as new targets for alcoholism treatment? A translational overview."

Dr. Amina S. Woods, IRP, gave a talk on "Interaction mechanisms of cellular membrane phospholipids with drugs and proteins" at NIAID in April 2014 and on "Imaging biological applications: Chronic ethanol consumption profoundly alters regional brain ceramide and sphingomyelin content in rodents" at the 62nd ASMS Conference, Baltimore MD.

Dr. Jonathan L. Katz, IRP, presented an invited paper entitled "Combinations of cocaine with other dopamine uptake inhibitors: Assessment of additivity" at the 122nd Annual Meeting of the American Psychological Association (Division 28), August 8, 2014. The session was a tribute to Ronald J. Tallarida, PhD. A book co-edited by Jonathan L. Katz was the winner of the annual award "Docendo Discimus" in Medical and Pharmaceutical Education in Russia. The category of the award was "The Best Textbook for Students in Educational Programs, Postgraduate Education." The full citation of the book is: Bespalov, A., Zvartau, E., Beardsley, P. and Katz, J.L. (Eds.) Textbook on Behavioral Pharmacology, St. Petersburg, Pavlov Medical University Press, 2013. [Фармакология поведения: Хрестоматия / под ред. А.Ю. Беспалова, Э.Э. Звартау, П.Бирдсли, Дж. Катца. – СПб.: Издательство СПбГМУ, 2013. – 466 с.]

Dr. Brandon Harvey, IRP, gave an invited lecture at Stony Brook University and presented work at the Society for Neuroscience Meeting 2014 and Gordon Research Conference on Protein Processing, Trafficking, and Secretion, 2014.

Dr. Elliot Stein, IRP, was an invited speaker at the 4th Biannual Resting State Conference, Boston, MA, September 2014. The title of his talk was "Resting state limbic circuit connectivity predicts early relapse risk after treatment for cocaine addiction."

Dr. Elliot Stein presented a talk entitled "Network and circuit modifications in nicotine addiction" at the MIT- McGovern Institute for Brain Research, September 2014.

Dr. Elliot Stein was invited to speak at the Center for Tobacco Products, Office of Science, FDA, Washington, DC September 2014; his talk was entitled "Neuroimaging Biomarkers of Nicotine Addiction."

Dr. Roy Wise, IRP, gave the History of Neuroscience Lecture at the annual meeting of the Society for Neuroscience.

Dr. Jean Lud Cadet, IRP, presented Grand Rounds and was a visiting professor at Howard University on August 28, 2014. His talk was entitled "Transcription and epigenetic substrates of methamphetamine addiction."

Christie Brannock, IRP, presented "Research opportunities at NIDA IRP" on October 22, 2014 at the Baltimore County Community College STEM fair.

Dr. Jean Lud Cadet presented "Epigenetic and transcriptional bases of food and methamphetamine addiction" at William Patterson University on October 23, 2014. He also talked about diversity in science and the described the Scientific Director's Fellowship for Diversity in Research (SDFDR) to biology and chemistry undergraduate students.

Dr. Oscar Torres, IRP, presented at Society for Neuroscience in Washington D.C. on November 14, 2014. His talk was entitled "Histone deacetylase 2 regulates methamphetamine-induced immediate early gene expression in the nucleus accumbens."

Dr. Jean Lud Cadet presented at Society for Neuroscience in Washington D.C. on November 15, 2014. His talk was entitled "Methamphetamine self-administration produces differential effects on the striatal expression of stress-related genes and histone deacetylases."

Dr. Irina Krasnova, IRP, presented at Society for Neuroscience in Washington D.C. on November 16, 2014. Her talk was "Incubation of methamphetamine and palatable food craving after punishment-induced abstinence."

Dr. Mike McCoy, IRP, presented at Society for Neuroscience in Washington D.C. on November 19, 2014. His talk was "Long-term effects of a single use of methamphetamine administration on the expression of histone deacetylases (HDACs) in the rat nucleus accumbens."

Dr. Subramaniam Jayanthi, IRP, presented at Society for Neuroscience in Washington D.C. on November 19, 2014. Her talk was titled "Methamphetamine produces increased neuropeptide gene expression by TET-dependent DNA methylation-hydroxymethylation epigenetic events in the rat nucleus accumbens."

Drs. Kenzie Preston and Yavin Shaham, IRP, organized and chaired a symposium entitled "The role of cues and contexts in adaptive and maladaptive behaviors: From mice to humans" at the NIH Research Festival in September 2014. The symposium featured speakers from NIDA, NIAAA, and NIA. Drs. William Kowalcyzk and Melody Furnari, postdoctoral IRTA fellows in the Treatment Section, also presented their FARE award research at the festival.

Dr. Yavin Shaham gave an invited lecture at the University of California at San Francisco.

Dr. Yavin Shaham organized a session and gave a lecture at the NIH Research Festival.

PLANNED MEETINGS

The NIDA CTN Steering Committee Meeting will be held April 14-16, 2015 in Gaithersburg, MD. **** (Pending approval)***

The National Institute on Drug Abuse (NIDA) will sponsor a Grant-Writing and Career Development Workshop at the **College on Problems of Drug Dependence (CPDD) Annual Scientific Meeting**. This year's conference will be held in **Phoenix, Arizona, on June 13–18, 2015**. The Grant/Career Workshop provides new or junior investigators with information and skills to advance their research careers, with a heavy emphasis on NIDA funding opportunities, grantsmanship, and the grant application process. NIDA will be offering a limited number of travel awards to partially defray the cost of attending this conference. Only NIDA-supported Diversity Supplement recipients, NRSA trainees, and NRSA fellows are eligible for this award. The application deadline for these awards is February 5, 2015.

STAFF HIGHLIGHTS

Staff Awards

Dr. Michael Baumann, IRP, was appointed to the Scientific Advisory Group of the National Drug Early Warning System (NDEWS), a government-sponsored organization which aims to track the availability and misuse of novel synthetic drugs in the United States.

Nina Lopatina, a graduate student in Dr. Schoenbaum's lab, successfully proposed for her dissertation work.

Dr. Samia Noursi, Women and Sex/Gender Differences Research Deputy Coordinator, DCNBR, was invited to join the Editorial Board of Violence Research Digest: Translating Research into Policy and Practice. The Violence Research Digest is a new resource created by the National Partnership to End Interpersonal Violence (NPEIV; www.NPEIV.org), in particular its action team "Translation and Dissemination." The overarching mission of this team is to facilitate communication among researchers, policy makers, service providers and practitioners, in such a way that treatment and policy making is informed by research, and researchers are responsive to input from the field.

Dr. Geoffrey Schoenbaum, IRP, has accepted a position on the Editorial Board of *Biological Psychiatry* as part of his official duties.

Dr. Jean Lud Cadet's doctoral student, **Karina Villalba**, defended her thesis on November 12, 2014. Karina completed her Ph.D. in public health, with specialization in health promotion and disease prevention with a focus in genetics at Florida International University.

Staff Changes

New Appointments

Susan R. B. Weiss, Ph.D. has been selected to be the Director of the new Division of Extramural Research (DER), NIDA. Susan is currently serving as the Associate Director for Scientific Affairs in the Office of the Director, NIDA. In this role, she has done a remarkable job in leading NIDA's operations and program planning for new initiative development and provided scientific recommendations on funding for new grants, including those related to research training and career development. Most notably, Susan has done an outstanding job of planning and managing trans-NIH initiatives, including the Collaborative Research on Addiction at NIH (CRAN) and Brain Research through Advancing Innovative Neurotechnologies (BRAIN) and in planning and spearheading the ABCD study. She was previously the Acting Director of the Office of Science Policy and Communications, and has expertise in communicating to a wide range of stakeholders, allocating funds, and developing strategic plans.

Dave Daubert will serve as Acting Executive Officer. Dave has a very productive 12 year history at NIDA including being Deputy Executive Officer (since January 2014) in which role he has excelled. Additionally he is the principal on several NIH-level groups and is a respected member of NIH's executive community.

New Employees

Kim DiFonzo joined the Public Information and Liaison Branch (PILB), Office of Science Policy and Communications (OSPC), in January 2015, after working as a contractor in NIDA's press office for the past six years. She is currently serving as the Deputy Press Officer where she is responsible for daily media inquiries on a wide variety of issues related to drug addiction research; preparing spokespeople for media interviews; assisting with the implementation of media outreach campaigns and events; and writing and editing various press materials. Kim has more than 20 years of public relations experience in healthcare communications and media relations. Prior to NIDA, Ms. DiFonzo worked in the public relations office at the American Psychological Association, wrote public relations materials on behalf of the President of the American Nurses Association, served as a national spokesperson for the blood services program at the American Red Cross, and managed the Campaign on Clinical Depression while at Burson-Marsteller.

Dr. Emily Einstein joined the Science Policy Branch, Office of Science Policy and Communications as Health Science Policy Analyst on January 12, 2015. Prior to joining OSPC, Dr. Einstein completed her time as an AAAS Science and Technology Policy Fellow in the Office of Autism Research Coordination at NIMH. Dr. Einstein earned her B.S. in biology and English at the College of William and Mary, and her Ph.D. in neuroscience at Yale University. Her graduate research was focused on the molecular and cellular mechanisms of psychiatric disorders, with an emphasis on the basal ganglia circuitry that underlies drug addiction. Dr. Einstein also has an interest in evidence-based undergraduate course design, serving as the scientific coordinator of the Yale Teaching Center, as an HHMI teaching fellow with the Yale Center for Scientific Teaching, and as a facilitator for the National Academies Summer Institutes.

David Marzilli joined NIDA's Office of Management in September 2014. David attended University of Massachusetts for his undergraduate degree and Catholic University of America for law school. Before coming to NIDA, David clerked for judges in both the Montgomery County Circuit Court and the Rhode Island Superior Court. He now serves as a contract specialist in the NIDA R&D Contracts Management Branch.

Dr. Susan McGuire joined NIDA as a Scientific Review Officer on September 21, 2014. Previously, she was employed by the University of Illinois at Chicago and the US Veterans Administration where she served as a Research Health Scientist at the Edward Hines Jr. VA Hospital in Maywood, IL, a Chicago suburb. Susan set up an independent lab at Loyola University Medical School in Chicago. There, she conducted pre-clinical research aimed at understanding neuroinflammation and the effects of diet in aging, brain injury, and neurodegenerative disease using animal models of multiple sclerosis (EAE), Parkinson's disease, neural transplantation and repair, Alzheimer's disease, and traumatic brain injury. In addition to VA funding, Dr. McGuire was funded by NIH, the Alzheimer's Association and various private agencies. Susan served as a peer reviewer for both CSR and NCCAM. She was also a member and officer of the American Society for Neurochemistry.

Shirley Simson joined the Public Information and Liaison Branch (PILB), Office of Science Policy and Communications (OSPC), in October 2014, after working as a contractor in NIDA's press office for the past eight years. She is currently serving as the Press Officer managing the day-to-day operations of the press office. Ms. Simson has more than 20 years of experience developing, managing and implementing successful public relations programs, with an emphasis on health communication and social marketing. Ms. Simson's career has included work for a wide range of government agencies, including the Substance Abuse and Mental Health Services Administration, the Centers for Disease Control and Prevention, the Food and Drug Administration, and the U.S. Department of Transportation. She also spent two years as a media spokesperson for the national headquarters of the American Red Cross.

Amanda Wasson joined NIDA on 11/2/2014. Before coming to the Washington D.C. area, Amanda worked at the Davis Monthan Air Force Base in Tucson, Arizona for almost 4 years. She worked as a Social Services Assistant for the Medical Operations Squadron, Mental Health Flight. She assisted with the management of the Family Advocacy program. Amanda will provide administrative support to all of the Branch Chiefs at Office of Management; assist in acceptance, tracking, acknowledgment, and administrations of donations to the NIDA Gift fund; backup to NIDA Executive Secretariat when needed; data calls; and other duties as assigned.

Anna Wheeler joined NIDA in September 2014 as an Ethics Program Specialist. She received a bachelor of science degree from Louisiana State University and a juris doctor from Tulane University. She practiced as an attorney for two years before working at the United States Attorney's Office for the District of Columbia Appellate Division as a legal assistant.

Departures

Glenda Conroy, CPA, MBA, PMP, NIDA's Executive Officer and Associate Director for Management has agreed to serve as the permanent Director of NIH OMA starting December 28, 2014. In January 2012, Glenda became NIDA's Executive Officer; during this period of time Glenda has worked diligently and creatively to strengthen the NIDA OM Team including the COAC. Her efforts let to significant improvements in the administrative and managerial structure of NIDA; for which I am very grateful. In her new capacity Glenda will continue to support NIDA.

Dave Daubert will serve as Acting Executive Officer. Dave has a very productive 12 year history at NIDA including being Deputy Executive Officer (since January 2014) in which role he has excelled. Additionally he is the principal on several NIH-level groups and is a respected member of NIH's executive community.

Dr. Sheri Grabus left the Public Information and Liaison Branch (PILB), Office of Science Policy and Communications (OSPC), in December 2014, to relocate with her family to Florida. Dr. Grabus joined the Office of Science Policy and Communications (OSPC) in November 2010 as the NIDA Deputy Press Officer and began managing the press team in early 2013, bringing a strong science background to NIDA's media outreach efforts. Dr. Grabus was trained as a neuroscientist and has a Ph.D. from American University in Psychopharmacology and Neuroscience. As a postdoc at Virginia Commonwealth University, she designed mouse models of nicotine dependence and

reward, and studied nicotinic agonists, antagonists, and bupropion. She has also taught at the college level—including courses in psychology, substance abuse prevention and treatment, and she has lectured on drug dependence, pharmacology and drugs and pain control. Prior to joining NIDA, Sheri served as Executive Director for a small-town Chamber of Commerce and was in charge of all marketing, public relations, sales and media relations.

Jessica Cotto, M.P.H. left the Science Policy Branch, Office of Science Policy and Communications (OSPC), in October 2014, to serve as a Health Science Policy Analyst in the Office of Science Policy, Engagement, Education, and Communication at NHLBI where she provides 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 joined the Science Policy Branch of the Office of Science Policy and Communications as an Epidemiologist in January 2009. Her primary responsibilities included analyzing data and synthesizing information from disparate sources to identify trends related to substance abuse. She was also responsible for analyzing data on the use of prescription medications and for overseeing and monitoring the contract that provides this information. 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.

Dr. Jessica Chambers of the Behavioral and Integrative Treatment Branch left NIDA on December 3, 2014 for personal reasons. She had directed the branch's portfolio in adolescent treatment and had contributed significantly to NIDA for several years.

Dr. Lisa Onken, Branch Chief of the Behavioral and Integrative Treatment Branch, has left NIDA on January 9, 2015 to establish a behavioral treatment program at the National Institute on Aging. She has contributed to NIDA significantly throughout the 27 years of her tenure here. She has provided leadership both at NIDA and at the NIH on numerous initiatives including the NIH Roadmap and NIH Common Fund, particularly most recently on the Science of Behavior Change initiatives. She has helped shape an entire field and has advanced substance abuse treatment substantially. Rarely are sustained contributions made that have such a significant impact as hers. Her leadership has been recognized at the NIH as well as by national organizations with several awards, citations, and commendations.

Retirements

Dr. Debra Grossman of the Behavioral and Integrative Treatment Branch retired on January 30, 2015. Debra oversaw a large portfolio of grants on smoking, tobacco, and smoking cessation. She had over 34.5 years of Federal service, and her contributions to the branch, division and institute have been numerous. In addition to promoting behavioral and integrative treatment research, she was extremely involved in NIDA's training programs.

GRANTEE HONORS

Dr. Kirill Martemyanov, a NIDA grantee in neuroscience from the Scripps Research Institute, has received the 2014 Cogan award from the Association for Research in Vision and Ophthalmology (ARVO) for his contributions to the field of G-protein signaling pertaining to photoreceptors and ON-bipolar cells, important in vision research.

Dr. Christopher R. McCurdy was elected as a fellow of American Association of Pharmaceutical Scientists (AAPS), AAPS Meeting 2014. He was recognized for his research on the development of medications for pain from natural products

UNC School of Medicine researcher **Dr. Bryan L. Roth**, the Michael Hooker Distinguished Professor of Protein Therapeutics and Translational Proteomics in the Department of Pharmacology, has been elected to the Institute of Medicine. Dr. Roth, is a world-renowned scientist best known for creating an innovative scientific method that allows neuroscientists to manipulate and study brain circuits in health and disease.

Dr. Xiang-Qun Xie, was awarded the Research Achievement Award in Drug Discovery and Development Interface at the 2014 AAPS meeting. Dr. Xie was recognized for his pioneering research for developing diseases-specific chemogenomics databases and cloud computing drug target identification platform for "Big Data to Knowledge" translational research. Dr. Xie was earlier mentored by Dr. Alex Makriyannis.

Dr. Nurul Zaveri was elected as a fellow of AAPS 2014 and was recognized for her contributions on the development of nociception analogs for pain treatment and smoking cessation.

In Memoriam

Dr. Steven R. Goldberg, NIDA IRP Senior Investigator and Chief of the Pre-Clinical Pharmacology Section, passed away on November 25, 2014. Throughout his career Steve made countless outstanding contributions to our understanding of the behavioral and neuropharmacological mechanisms triggered by drugs of abuse and in the words of NIDA Director Nora Volkow, in her message to NIDA staff "... left us with the nagging feeling that the best was yet to come." Steve conducted research in animals on environmental, historical, and pharmacological determinants of the behavioral and cardiovascular effects of psychoactive drugs, with an emphasis in recent years on the psychoactive marijuana constituent delta-9-tetrahydrocannbinol (THC), the endogenous cannabinoid anandamide, the psychoactive tobacco constituent nicotine, and the psychostimulant methamphetamine. Steve collaborated extensively with many U.S. and European labs and published more than 370 empirical papers, reviews, and book chapters. He and his group developed many experimental procedures and identified various neuropharmacological mechanisms of drug reward and relapse that laboratories around the world have capitalized upon. Steve's research goal was to elucidate behavioral and neuropharmacological mechanisms that underlie the actions of legal (nicotine) and illicit (marijuana and methamphetamine) drugs of abuse, develop pharmacological treatment approaches to abuse of these drugs, and to develop new medications that maximize positive actions of cannabinoids, in particular, without their negative actions such as abuse liability and cognitive impairment. Steve received his Ph.D. from the University of Michigan and conducted his dissertation on the role of withdrawal states and conditioning in morphine self-administration in monkeys which appeared in two seminal papers published in Science in 1969. During the 1970s, he conducted research at Harvard Medical School where he and his colleagues developed procedures to study drug self-administration in laboratory animals that are still regarded as the gold standard in the addiction field. Steve joined the Addiction Research Center in 1979, and over the last several decades his research has continued to make important contributions to the field, including the first conclusive demonstrations that nicotine and THC are readily self-administered by non-human primates. Steve was also a visiting professor and adjunct faculty at Johns Hopkins University, Georgetown University, the University of Maryland, and the University of Cagliari in Italy. Beyond his outstanding scientific achievements, Steve will surely be remembered as an exceptionally generous and honest person, an excellent mentor and role model to his trainees, and a fantastic collaborator.