# RESEARCH FINDINGS

## CHEMISTRY AND PHYSIOLOGICAL SYSTEMS RESEARCH

**Modulation Of Inflammatory Responses By A Cannabinoid-2-Selective Agonist After Spinal Cord Injury** The goal of the current investigation was to evaluate the mechanisms through which administration of a selective cannabinoid-2 (CB2) agonist (O-1966) modifies inflammatory responses and helps to improve function following spinal cord injury. A comparison of motor function, autonomic function, and inflammatory responses was made between animals treated with O-1966 (5 mg/kg IP) and animals treated with vehicle 1 h and 24 h following contusion injury to the spinal cord. Motor function was significantly improved in the treated animals at each time point during the 14 days of evaluation. The percentage of animals able to spontaneously void their bladder was also greater over the entire study period in the group treated with the selective CB2 agonist. Seven days following injury there was a significant reduction in both hematopoietic and myeloid cell invasion of the spinal cord, and a reduction in the number of immunoreactive microglia. The results of the evaluation of chemokine/cytokine expression and inflammatory cell invasion also demonstrated a significant effect of treatment on inflammatory reactions following injury. Two days after injury, animals treated with O-1966 had significant reductions in CXCL-9 and CXCL-11, and dramatic reductions in IL-23p19 expression and its receptor IL-23r. Treatment with O-1966 also caused inhibition of toll-like receptor expression (TLR1, TLR4, TLR6 and TLR7) following injury. These results demonstrate that the improvement in motor and autonomic function resulting from treatment with a selective CB2 agonist is associated with a significant effect on inflammatory responses in the spinal cord following injury. Adhikary S, Li H, Heller J, Skarica M, Zhang M, Ganea D, Tuma RF. Modulation of inflammatory responses by a cannabinoid-2-selective agonist after spinal cord injury. J Neurotrauma. 2011 Dec; 28(12): 2417-2427. Epub 2011 Oct 4.

**Effects Of Monoamine Releasers With Varying Selectivity For Releasing Dopamine/ Norepinephrine Versus Serotonin On Choice Between Cocaine And Food In Rhesus Monkeys** Monoamine releasers constitute one class of candidate medications for the treatment of cocaine abuse, and concurrent cocaine-versus-food choice procedures are potentially valuable as experimental tools to evaluate the efficacy and safety of candidate medications. This study assessed the choice between cocaine and food by rhesus monkeys during treatment with five monoamine releasers that varied in selectivity to promote the release of dopamine and norepinephrine versus serotonin (5HT) [m-fluoroamphetamine, (+)-phenmetrazine, (+)-methamphetamine, napthylisopropylamine and (±)-fenfluramine]. Rhesus monkeys (n=8) responded under a concurrent-choice schedule of food delivery (1-g pellets, fixed ratio 100 schedule) and cocaine injections (0-0.1 mg/kg/injection, fixed ratio 10 schedule). Cocaine choice dose-effect curves were determined daily during continuous 7-day treatment with saline or with each test compound dose. During saline treatment, cocaine maintained a dose-dependent increase in cocaine choice, and the highest cocaine doses (0.032-0.1 mg/kg/injection) maintained almost exclusive cocaine choice. Efficacy of monoamine releasers to decrease cocaine choice corresponded to their pharmacological selectivity to release dopamine and norepinephrine versus 5HT. None of the releasers reduced cocaine choice or promoted reallocation of responding to food choice to the same extent as when saline was substituted for cocaine. These results extend the range of conditions across which dopamine and norepinephrine-selective releasers have been shown to reduce cocaine self-administration. Banks ML, Blough BE, Negus SS. Effects of

monoamine releasers with varying selectivity for releasing dopamine/norepinephrine versus serotonin on choice between cocaine and food in rhesus monkeys. Behav Pharmacol. 2011 Dec; 22(8): 824-836.

**The Duration Of Nicotine Withdrawal-Associated Deficits In Contextual Fear Conditioning Parallels Changes In Hippocampal High Affinity Nicotinic Acetylcholine Receptor Upregulation** A predominant symptom of nicotine withdrawal is cognitive deficits, yet understanding of the neural basis for these deficits is limited. Withdrawal from chronic nicotine disrupts contextual learning in mice and this deficit is mediated by direct effects of nicotine in the hippocampus. Chronic nicotine treatment upregulates nicotinic acetylcholine receptors (nAChR); however, it is unknown whether upregulation is related to the observed withdrawal-induced cognitive deficits. If a relationship between altered learning and nAChR levels exists, changes in nAChR levels after cessation of nicotine treatment should match the duration of learning deficits. To test this hypothesis, mice were chronically administered 6.3mg/kg/day (freebase) nicotine for 12 days and trained in contextual fear conditioning on day 11 or between 1 to 16 days after withdrawal of treatment. Changes in [(125)I]-epibatidine binding at cytisine-sensitive and cytisine-resistant nAChRs and chronic nicotine-related changes in α4, α7, and β2 nAChR subunit mRNA expression were assessed. Chronic nicotine had no behavioral effect but withdrawal produced deficits in contextual fear conditioning that lasted 4 days. Nicotine withdrawal did not disrupt cued fear conditioning. Chronic nicotine upregulated hippocampal cytisine-sensitive nAChR binding; upregulation continued after cessation of nicotine administration and the duration of upregulation during withdrawal paralleled the duration of behavioral changes. Changes in binding in cortex and cerebellum did not match behavioral changes. No changes in α4, α7, and β2 subunit mRNA expression were seen with chronic nicotine. Thus, nicotine withdrawal-related deficits in contextual learning are time-limited changes that are associated with temporal changes in upregulation of high-affinity nAChR binding. Gould TJ, Portugal GS, André JM, Tadman MP, Marks MJ, Kenney JW, Yildirim E, Adoff M. The duration of nicotine withdrawal-associated deficits in contextual fear conditioning parallels changes in hippocampal high affinity nicotinic acetylcholine receptor upregulation. Neuropharmacology. 2012 Apr; 62(5-6): 2118-2125. Epub 2012 Jan 21.

**Nicotinic Neuromodulation In Auditory Cortex Requires MAPK Activation In 3 Thalamocortical And Intracortical Circuits** Activation of nicotinic acetylcholine receptors (nAChRs) by systemic nicotine enhances sensory-cognitive function and sensory-evoked cortical responses. Although nAChRs mediate fast neurotransmission at many synapses in the nervous system, nicotinic regulation of cortical processing is neuromodulatory. To explore potential mechanisms of nicotinic neuromodulation, the authors examined whether intracellular signal transduction involving mitogen-activated protein kinase (MAPK) contributes to regulation of tone-evoked responses in primary auditory cortex (A1) in the mouse. Systemic nicotine enhanced characteristic frequency (CF) tone-evoked current-source density (CSD) profiles in A1, including the shortest-latency (presumed thalamocortical) current sink in layer 4 and longer-latency (presumed intracortical) sinks in layers 2-4, by increasing response amplitudes and decreasing response latencies. Microinjection of the MAPK kinase (MEK) inhibitor U0126 into the thalamus, targeting the auditory thalamocortical pathway, blocked the effect of nicotine on the initial (thalamocortical) CSD component, but did not block enhancement of longer-latency (intracortical) responses. Conversely, microinjection of U0126 into supragranular layers of A1 blocked nicotine's effect on intracortical, but not thalamocortical, CSD components. Simultaneously with enhancement of CF-evoked responses, responses to spectrally-distant

(nonCF) stimuli were reduced, implying nicotinic "sharpening" of frequency receptive fields, an effect also blocked by MEK inhibition. Consistent with these physiological results, acoustic stimulation with nicotine produced immunolabel for activated MAPK in A1, primarily in layer 2/3 cell bodies. Immunolabel was blocked by intracortical microinjection of the nAChR antagonist dihydro-β-erythroidine, but not methyllycaconitine, implicating α4β2*, but not α7, nAChRs. Thus, activation of MAPK in functionally distinct forebrain circuits-thalamocortical, local intracortical and long-range intracortical-underlies nicotinic neuromodulation of A1. Intskirveli I, Metherate R. Nicotinic neuromodulation in auditory cortex requires MAPK activation in thalamocortical and intracortical circuits. J Neurophysiol. 2012 Feb 22 [epub ahead of print]

**Collegial Ethics: What, Why And How** Collegial ethics (CE) proposes that we support our colleagues whenever possible. It is more of a focus on the feelings of others rather than on our own. In spite of the importance of collegial interactions, CE is not usually taught. Courses in CE need to be developed, and collegial skills need to be identified, taught and practiced. Such skills would include: use of the golden rule, supportive communication, conflict resolution, and even the development of greater courage in our actions. Kuhar MJ. Collegial ethics: what, why and how. Drug Alcohol Depend. 2011 Dec 15; 119(3): 235-238.

**Estrogen Receptors Stimulate Brain Region Specific Metabotropic Glutamate Receptors To Rapidly Initiate Signal Transduction Pathways** Estradiol and other steroid hormones modulate the nervous system and behavior on both acute and long-term time scales. Though estradiol was originally characterized as a regulator of gene expression through the action of nuclear estrogen receptors (ERs) that directly bind DNA, research over the past thirty years has firmly established that estradiol can bind to extra-nuclear ERs associated with the cellular membrane, producing changes in neurons through stimulation of various intracellular signaling pathways. Several studies have determined that the classical ERs, ERα and ERβ, mediate some of these fast-acting signaling pathways through activation of G proteins. Since ERα and ERβ are not G protein-coupled receptors, the mechanisms by which ERs can stimulate signal transduction pathways are a focus of recent research. Here the authors discuss recent studies illustrating one mechanism by which ERα and ERβ initiate these pathways: through direct association with metabotropic glutamate receptors (mGluRs). Estradiol binding to these membrane-localized estrogen receptors results in mGluR signaling independent of glutamate. ERs are organized with mGluRs into functional signaling microdomains via caveolin proteins. The pairing of ERs to specific mGluRs via caveolins is region specific, with ERs being linked to different mGluRs in hippocampal, striatal, and other neurons. It is becoming clear that ER signaling through mGluRs is one important mechanism by which estrogens can modulate neuron and glial physiology, ultimately impacting various aspects of nervous system function. Meitzen J, Mermelstein PG. Estrogen receptors stimulate brain region specific metabotropic glutamate receptors to rapidly initiate signal transduction pathways. J Chem Neuroanat. 2011 Dec; 42(4): 236-241. Epub 2011 Mar 31.

**Morphine Alters M. Bovis Infected Microglia's Ability To Activate Γδ T Lymphocytes** Microglia, the macrophages of the central nervous system (CNS), are both the principle target cells for Mycobacterium infection in the CNS and serve a critical role in defense of the brain. If microglia's functions are altered due to immunosuppressive agents such as opiates, perturbation in defense of the brain may occur, including defense against CNS Tuberculosis. This study was designed to determine if Mycobacterium infected microglia activate γδT lymphocytes and if the

opiate morphine alters the capability of microglia to activate γδT lymphocytes. γδT lymphocytes proliferated, produced IFN-γ, and demonstrated cytolytic response upon exposure to Mycobacterium bovis infected microglia. IFN-γ, and antigen specific cytotoxicity were both markedly impaired due to morphine treatment. Olin M, Choi K, Molitor TW. Morphine alters M. bovis infected microglia's ability to activate γδ T lymphocytes. J Neuroimmune Pharmacol. 2011 Dec; 6(4): 578-584. Epub 2011 Sep 1.

**Genome-Wide Association For Methamphetamine Sensitivity In An Advanced Intercross Mouse Line** Sensitivity to the locomotor stimulant effects of methamphetamine (MA) is a heritable trait that utilizes neurocircuitry also associated with the rewarding effects of drugs. The authors used the power of a C57BL/6J × DBA/2J F(2) intercross (n = 676) and the precision of a C57BL/6J × DBA/2J F(8) advanced intercross line (Aap: B6, D2-G8; or F(8) AIL; n = 552) to identify and narrow quantitative trait loci (QTLs) associated with sensitivity to the locomotor stimulant effects of MA. They used the program QTLRel to simultaneously map QTL in the F(2) and F(8) AIL mice. They identified six genome-wide significant QTLs associated with locomotor activity at baseline and seven genome-wide significant QTLs associated with MA-induced locomotor activation. The average per cent decrease in QTL width between the F(2) and the integrated analysis was 65%. Additionally, these QTLs showed a distinct temporal specificity within each session that allowed us to further refine their locations, and identify one QTL with a 1.8-LOD support interval of 1.47 Mb. Next, they utilized publicly available bioinformatics resources to exploit strain-specific sequence data and strain- and region-specific expression data to identify candidate genes. These results illustrate the power of AILs in conjunction with sequence and gene expression data to investigate the genetic underpinnings of behavioral and other traits. Parker CC, Cheng R, Sokoloff G, Palmer AA. Genome-wide association for methamphetamine sensitivity in an advanced intercross mouse line. Genes Brain Behav. 2012 Feb; 11(1): 52-61. doi: 10.1111/j.1601-183X.2011.00747.x. Epub 2011 Nov 23.

**Drugs Of Abuse Effects On Immunity And Microbial Pathogenesis** Substance abuse remains a serious medical, public health, and social problem. The impact on destructive public health and health costs compounded with the negative consequences of drugs abuse poses a significant toll on the economy. Despite significant advancement of research in the field treatment of and care of patients with substance abuse has lagged behind because of limited education and training of clinicians on substance abuse problems. The goal of the special issue is to provide the current status on the mechanisms underlying the increased prevalence of opportunistic infections in the drug abuse population, to identify important areas where further research would be beneficial and to open new avenues of investigation for therapeutic development. The authors aimed these articles for the benefit of both basic and clinical researchers. Roy S. Drugs of abuse effects on immunity and microbial pathogenesis. J Neuroimmune Pharmacol. 2011 Dec; 6(4): 435-438. Epub 2011 Oct 14.

**Opioid Drug Abuse And Modulation Of Immune Function: Consequences In The Susceptibility To Opportunistic Infections** Infection rate among intravenous drug users (IDU) is higher than the general public, and is the major cause of morbidity and hospitalization in the IDU population. Epidemiologic studies provide data on increased prevalence of opportunistic bacterial infections such as TB and pneumonia, and viral infections such as HIV-1 and hepatitis in the IDU population. An important component in the intravenous drug abuse population and in patients receiving medically indicated chronic opioid treatment is opioid withdrawal. Data on bacterial virulence in the context of opioid withdrawal suggest that mice undergoing withdrawal

had shortened survival and increased bacterial load in response to Salmonella infection. As the body of evidence in support of opioid dependency and its immunosuppressive effects is growing, it is imperative to understand the mechanisms by which opioids exert these effects and identify the populations at risk that would benefit the most from the interventions to counteract opioid immunosuppressive effects. Thus, it is important to refine the existing animal model to closely match human conditions and to cross-validate these findings through carefully controlled human studies. Better understanding of the mechanisms will facilitate the search for new therapeutic modalities to counteract adverse effects including increased infection rates. This review will summarize the effects of morphine on innate and adaptive immunity, identify the role of the mu opioid receptor in these functions and the signal transduction activated in the process. The role of opioid withdrawal in immunosuppression and the clinical relevance of these findings will also be discussed. Roy S, Ninkovic J, Banerjee S, Charboneau RG, Das S, Dutta R, Kirchner VA, Koodie L, Ma J, Meng J, Barke RA. Opioid drug abuse and modulation of immune function: consequences in the susceptibility to opportunistic infections. J Neuroimmune Pharmacol. 2011 Dec; 6(4): 442-465. Epub 2011 Jul 26.

**Profound Reduction In Sensitivity To The Aversive Effects Of Methamphetamine In Mice Bred For High Methamphetamine Intake** Reduced sensitivity to aversive effects of methamphetamine (MA) may increase risk for MA abuse. Studies in two replicate sets of mouse lines that were selectively bred for high and low levels of MA intake support this view. Current studies examined the extent of insensitivity to aversive MA effects of mice bred for high levels of MA drinking. Conditioning procedures in which drugs are delivered shortly after cue exposure have been used to detect aversive drug effects and, in some cases, are more sensitive to such effects. Aversive effects induced by MA injected immediately after exposure to cues from two different sensory modalities were examined. In addition, effects of higher MA doses than those used previously were examined. MA-associated place conditioning utilized tactile cues, whereas MA-induced taste conditioning utilized a novel tastant. Second replicate, MA high drinking (MAHDR-2) and low drinking (MALDR-2) mice were treated with doses of MA up to 4 mg/kg. MAHDR-2 mice were insensitive to aversive effects of MA, except after place conditioning with the 4 mg/kg dose; MALDR-2 mice exhibited sensitivity to aversive effects of MA at doses as low as 1 mg/kg. These studies show that the expression of aversion is dependent upon procedure and MA dose, and that MAHDR-2 mice have markedly reduced sensitivity to the aversive effects of MA. The current and previous results support a strong genetic relationship between level of MA intake and level of sensitivity to aversive effects of MA, a factor that could impact risk for MA use in humans. This article is part of a Special Issue entitled 'Post-Traumatic Stress Disorder'. Shabani S, McKinnon CS, Cunningham CL, Phillips TJ. Profound reduction in sensitivity to the aversive effects of methamphetamine in mice bred for high methamphetamine intake. Neuropharmacology. 2012 Feb; 62(2): 1134-1141. Epub 2011 Nov 18.

**Unpredictable Saccharin Reinforcement Enhances Locomotor Responding To Amphetamine** Drug-naïve, non-deprived rats were trained to lever press for saccharin under fixed-ratio (FR) or variable-ratio (VR) schedules of reinforcement. Rats trained on the VR schedule in which saccharin reinforcement was not predicted by a fixed number of lever presses subsequently showed an enhanced locomotor response to a threshold amphetamine challenge injection (0.5mg/kg IP) administered 2 weeks following the last saccharin session. This finding suggests that chronic exposure to gambling-like conditions of uncertain reinforcement can induce neuroadaptations in brain reward systems that are similar to those produced by repeated psychostimulant exposure and may lead to the development of addictive behaviors. Singer BF,

Scott-Railton J, Vezina P. Unpredictable saccharin reinforcement enhances locomotor responding to amphetamine. Behav Brain Res. 2012 Jan 1; 226(1): 340-344. Epub 2011 Sep 8.

**Stress-Induced Activation Of The Dynorphin/K-Opioid Receptor System In The Amygdala Potentiates Nicotine Conditioned Place Preference** Many smokers describe the anxiolytic and stress-reducing effects of nicotine, the primary addictive component of tobacco, as a principal motivation for continued drug use. Recent evidence suggests that activation of the stress circuits, including the dynorphin/κ-opioid receptor system, modulates the rewarding effects of addictive drugs. In the present study, the authors find that nicotine produced dose-dependent conditioned place preference (CPP) in mice. κ-receptor activation, either by repeated forced swim stress or U50,488 (5 or 10 mg/kg, i.p.) administration, significantly potentiated the magnitude of nicotine CPP. The increase in nicotine CPP was blocked by the κ-receptor antagonist norbinaltorphimine (norBNI) either systemically (10 mg/kg, i.p.) or by local injection in the amygdala (2.5 μg) without affecting nicotine reward in the absence of stress. U50,488 (5 mg/kg, i.p.) produced anxiety-like behaviors in the elevated-plus maze and novel object exploration assays, and the anxiety-like behaviors were attenuated both by systemic nicotine (0.5 mg/kg, s.c.) and local injection of norBNI into the amygdala. Local norBNI injection in the ventral posterior thalamic nucleus (an adjacent brain region) did not block the potentiation of nicotine CPP or the anxiogenic-like effects of κ-receptor activation. These results suggest that the rewarding effects of nicotine may include a reduction in the stress-induced anxiety responses caused by activation of the dynorphin/κ-opioid system. Together, these data implicate the amygdala as a key region modulating the appetitive properties of nicotine, and suggest that κ-opioid antagonists may be useful therapeutic tools to reduce stress-induced nicotine craving. Smith JS, Schindler AG, Martinelli E, Gustin RM, Bruchas MR, Chavkin C. Stress-induced activation of the dynorphin/κ-opioid receptor system in the amygdala potentiates nicotine conditioned place preference. J Neurosci. 2012 Jan 25; 32(4): 1488-1495.

**Histone Deacetylase 5 Limits Cocaine Reward Through Camp-Induced Nuclear Import** Chromatin remodeling by histone deacetylases (HDACs) is a key mechanism regulating behavioral adaptations to cocaine use. The authors report here that cocaine and cyclic adenosine monophosphate (cAMP) signaling induce the transient nuclear accumulation of HDAC5 in rodent striatum. They show that cAMP-stimulated nuclear import of HDAC5 requires a signaling mechanism that involves transient, protein phosphatase 2A (PP2A)-dependent dephosphorylation of a Cdk5 site (S279) found within the HDAC5 nuclear localization sequence. Dephosphorylation of HDAC5 increases its nuclear accumulation, by accelerating its nuclear import rate and reducing its nuclear export rate. Importantly, they show that dephosphorylation of HDAC5 S279 in the nucleus accumbens suppresses the development, but not expression, of cocaine reward behavior in vivo. Together, these findings reveal a molecular mechanism by which cocaine regulates HDAC5 function to antagonize the rewarding impact of cocaine, likely by putting a brake on drug-stimulated gene expression that supports drug-induced behavioral changes. Taniguchi M, Carreira MB, Smith LN, Zirlin BC, Neve RL, Cowan CW. Histone deacetylase 5 limits cocaine reward through cAMP-induced nuclear import. Neuron. 2012 Jan 12; 73(1): 108-120.

**Paraquat Neurotoxicity Is Mediated By The Dopamine Transporter And Organic Cation Transporter-3** The herbicide paraquat (PQ) has increasingly been reported in epidemiological studies to enhance the risk of developing Parkinson's disease (PD). Furthermore, case-control studies report that individuals with genetic variants in the dopamine transporter (DAT, SLC6A)

have a higher PD risk when exposed to PQ. However, it remains a topic of debate whether PQ can enter dopamine (DA) neurons through DAT. The authors report here a mechanism by which PQ is transported by DAT: In its native divalent cation state, PQ(2+) is not a substrate for DAT; however, when converted to the monovalent cation PQ(+) by either a reducing agent or NADPH oxidase on microglia, it becomes a substrate for DAT and is accumulated in DA neurons, where it induces oxidative stress and cytotoxicity. Impaired DAT function in cultured cells and mutant mice significantly attenuated neurotoxicity induced by PQ(+). In addition to DAT, PQ(+) is also a substrate for the organic cation transporter 3 (Oct3, Slc22a3), which is abundantly expressed in non-DA cells in the nigrostriatal regions. In mice with Oct3 deficiency, enhanced striatal damage was detected after PQ treatment. This increased sensitivity likely results from reduced buffering capacity by non-DA cells, leading to more PQ(+) being available for uptake by DA neurons. This study provides a mechanism by which DAT and Oct3 modulate nigrostriatal damage induced by PQ(2+)/PQ(+) redox cycling. Rappold PM, Cui M, Chesser AS, Tibbett J, Grima JC, Duan L, Sen N, Javitch JA, Tieu K. Paraquat neurotoxicity is mediated by the dopamine transporter and organic cation transporter-3. Proc Natl Acad Sci U S A. 2011 Dec 20; 108(51): 20766-20771.

**Opioid Activity Of Spinally Selective Analogues Of N-Naphthoyl-B-Naltrexamine In HEK-293 Cells And Mice** Using the selective mu-kappa agonist, N-naphthoyl-β-naltrexamine 1, as the prototype ligand, a series of closely related naphthalene analogues were synthesized to study the chemical space around the naphthalene moiety in an effort to evaluate how receptor selectivity is affected by chemical modification. Nine analogues (2-10) of compound 1 were synthesized and tested on HEK-293 cells expressing homomeric and heteromeric opioid receptors, and in the mouse tail-flick assay. It was found that a small change in structure produces profound changes in selectivity in this series. This is exemplified by the discovery that introduction of a 6-fluoro group transforms 1 from a selective mu-kappa heteromeric receptor agonist to a delta-preferring agonist 7. The in vivo studies reveal that many of the ligands are more potent spinally than supraspinally and devoid of tolerance. Le Naour M, Lunzer MM, Powers MD, Portoghese PS. Opioid activity of spinally selective analogues of N-naphthoyl-β-naltrexamine in HEK-293 cells and mice J Med Chem. 2012 Jan 26; 55(2): 670-677.

**Serine 77 In The PDZ Domain Of PICK1 Is A Protein Kinase Cα Phosphorylation Site Regulated By Lipid Membrane Binding** PICK1 (protein interacting with C kinase 1) contains an N-terminal protein binding PDZ domain and a C-terminal lipid binding BAR domain. PICK1 plays a key role in several physiological processes, including synaptic plasticity. However, little is known about the cellular mechanisms governing the activity of PICK1 itself. Here the authors show that PICK1 is a substrate in vitro both for PKCα (protein kinase Cα), as previously shown, and for CaMKIIα (Ca(2+)-calmodulin-dependent protein kinase IIα). By mutation of predicted phosphorylation sites, they identify Ser77 in the PDZ domain as a major phosphorylation site for PKCα. Mutation of Ser77 reduced the level of PKCα-mediated phosphorylation ~50%, whereas no reduction was observed upon mutation of seven other predicted sites. Addition of lipid vesicles increased the level of phosphorylation of Ser77 10-fold, indicating that lipid binding is critical for optimal phosphorylation. Binding of PKCα to the PICK1 PDZ domain was not required for phosphorylation, but a PDZ domain peptide ligand reduced the overall level of phosphorylation ~30%. The phosphomimic S77D reduced the extent of cytosolic clustering of eYFP-PICK1 in COS7 cells and thereby conceivably its lipid binding and/or polymerization capacity. The authors propose that PICK1 is phosphorylated at Ser77 by PKCα preferentially when bound to membrane vesicles and that this phosphorylation in turn modulates its cellular

distribution. Ammendrup-Johnsen I, Thorsen TS, Gether U, Madsen KL. Serine 77 in the PDZ domain of PICK1 is a protein kinase Cα phosphorylation site regulated by lipid membrane binding.Biochemistry. 2012 Jan 17; 51(2): 586-596. Epub 2012 Jan 6.

**(±)-2-(N-Tert-Butylamino)-3'-[(125)I]-Iodo-4'-Azidopropiophenone: A Dopamine Transporter And Nicotinic Acetylcholine Receptor Photoaffinity Ligand Based On Bupropion (Wellbutrin, Zyban)** Towards addressing the knowledge gap of how bupropion interacts with the dopamine transporter (DAT) and nicotinic acetylcholine receptors (nAChRs), a ligand was synthesized in which the chlorine of bupropion was isosterically replaced with an iodine and a photoreactive azide was added to the 4'-position of the aromatic ring. Analog (±)-3 (SADU-3-72) demonstrated modest DAT and α4β2 nAChR affinity. A radioiodinated version was shown to bind covalently to hDAT expressed in cultured cells and affinity-purified, lipid-reincorporated human α4β2 neuronal nAChRs. Co-incubation of (±)-[(125)I]-3 with non-radioactive (±)-bupropion or (-)-cocaine blocked labeling of these proteins. Compound (±)-[(125)I]-3 represents the first successful example of a DAT and nAChR photoaffinity ligand based on the bupropion scaffold. Such ligands are expected to assist in mapping bupropion-binding pockets within plasma membrane monoamine transporters and ligand-gated nAChR ion channels. Lapinsky DJ, Aggarwal S, Nolan TL, Surratt CK, Lever JR, Acharya R, Vaughan RA, Pandhare A, Blanton MP. (±)-2-(N-tert-Butylamino)-3'-[(125)I]-iodo-4'-azidopropiophenone: a dopamine transporter and nicotinic acetylcholine receptor photoaffinity ligand based on bupropion (Wellbutrin, Zyban). Bioorg Med Chem Lett. 2012 Jan 1;22(1): 523-526. Epub 2011 Nov 4.

**Truncated G Protein-Coupled Mu Opioid Receptor MOR-1 Splice Variants Are Targets For Highly Potent Opioid Analgesics Lacking Side Effects** Pain remains a pervasive problem throughout medicine, transcending all specialty boundaries. Despite the extraordinary insights into pain and its mechanisms over the past few decades, few advances have been made with analgesics. Most pain remains treated by opiates, which have significant side effects that limit their utility. The authors now describe a potent opiate analgesic lacking the traditional side effects associated with classical opiates, including respiratory depression, significant constipation, physical dependence, and, perhaps most important, reinforcing behavior, demonstrating that it is possible to dissociate side effects from analgesia. Evidence indicates that this agent acts through a truncated, six-transmembrane variant of the G protein-coupled mu opioid receptor MOR-1. Although truncated splice variants have been reported for a number of G protein-coupled receptors, their functional relevance has been unclear. This evidence now suggests that truncated variants can be physiologically important through heterodimerization, even when inactive alone, and can comprise new therapeutic targets, as illustrated by our unique opioid analgesics with a vastly improved pharmacological profile. Majumdar S, Grinnell S, Le Rouzic V, Burgman M, Polikar L, Ansonoff M, Pintar J, Pan YX, Pasternak GW. Truncated G protein-coupled mu opioid receptor MOR-1 splice variants are targets for highly potent opioid analgesics lacking side effects. Proc Natl Acad Sci U S A. 2011 Dec 6; 108(49): 19778-19783. Epub 2011 Nov 21.

**Nicotinic Cholinergic Mechanisms Causing Elevated Dopamine Release And Abnormal Locomotor Behavior** Firing rates of dopamine (DA) neurons in substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) control DA release in target structures such as striatum and prefrontal cortex. DA neuron firing in the soma and release probability at axon terminals are tightly regulated by cholinergic transmission and nicotinic acetylcholine receptors (nAChRs). To

understand the role of α6* nAChRs in DA transmission, the authors studied several strains of mice expressing differing levels of mutant, hypersensitive (leucine 9' to serine [L9'S]) α6 subunits. α6 L9'S mice harboring six or more copies of the hypersensitive α6 gene exhibited spontaneous home-cage hyperactivity and novelty-induced locomotor activity, whereas mice with an equal number of WT and L9'S α6 genes had locomotor activity resembling that of control mice. α6-dependent, nicotine-stimulated locomotor activation was also more robust in high-copy α6 L9'S mice versus low-copy mice. In wheel-running experiments, results were also bi-modal; high-copy α6 L9'S animals exhibited blunted total wheel rotations during each day of a 9-day experiment, but low-copy α6 L9'S mice ran normally on the wheel. Reduced wheel running in hyperactive strains of α6 L9'S mice was attributable to a reduction in both overall running time and velocity. ACh and nicotine-stimulated DA release from striatal synaptosomes in α6 L9'S mice was well-correlated with behavioral phenotypes, supporting the hypothesis that augmented DA release mediates the altered behavior of α6 L9'S mice. This study highlights the precise control that the nicotinic cholinergic system exerts on DA transmission and provides further insights into the mechanisms and consequences of enhanced DA release. Cohen BN, Mackey ED, Grady SR, McKinney S, Patzlaff NE, Wageman CR, McIntosh JM, Marks MJ, Lester HA, Drenan RM. Nicotinic cholinergic mechanisms causing elevated dopamine release and abnormal locomotor behavior.Neuroscience. 2012 Jan 3; 200: 31-41. Epub 2011 Nov 4.

**Allosteric Interactions between δ and κ Opioid Receptors in Peripheral Sensory Neurons** The peripheral δ opioid receptor (DOR) is an attractive target for analgesic drug development. There is evidence that DOR can form heteromers with the κ-opioid receptor (KOR). As drug targets, heteromeric receptors offer an additional level of selectivity and, because of allosteric interactions between protomers, functionality. Here the authors report that selective KOR antagonists differentially altered the potency and/or efficacy of DOR agonists in primary cultures of adult rat peripheral sensory neurons and in a rat behavioral model of thermal allodynia. In vitro, the KOR antagonist nor-binaltorphimine (nor-BNI) enhanced the potency of [D-Pen(2,5)]-enkephalin (DPDPE), decreased the potency of [D-Ala(2),D-Leu(5)]-enkephalin (DADLE), and decreased the potency and efficacy of 4-[(R)-[(2S,5R)-4-allyl-2,5-dimethylpiperazin-1-yl](3-methoxyphenyl)methyl]-N,N-d iethylbenzamide (SNC80) to inhibit prostaglandin E(2) (PGE(2))-stimulated adenylyl cyclase activity. In vivo, nor-BNI enhanced the effect of DPDPE and decreased the effect of SNC80 to inhibit PGE(2)-stimulated thermal allodynia. In contrast to nor-BNI, the KOR antagonist 5'-guanidinonaltrindole (5'-GNTI) reduced the response of DPDPE both in cultured neurons and in vivo. Evidence for DOR-KOR heteromers in peripheral sensory neurons included coimmunoprecipitation of DOR with KOR, a DOR-KOR heteromer selective antibody augmented the antinociceptive effect of DPDPE in vivo, and the DOR-KOR heteromer agonist 6'-GNTI inhibited adenylyl cyclase activity in vitro as well as PGE(2)-stimulated thermal allodynia in vivo. Taken together, these data suggest that DOR-KOR heteromers exist in rat primary sensory neurons and that KOR antagonists can act as modulators of DOR agonist responses most likely through allosteric interactions between the protomers of the DOR-KOR heteromer. Berg KA, Rowan MP, Gupta A, Sanchez TA, Silva M, Gomes I, McGuire BA, Portoghese PS, Hargreaves KM, Devi LA, Clarke WP. Allosteric interactions between δ and κ opioid receptors in peripheral sensory neurons. Mol Pharmacol. 2012 Feb; 81(2): 264-272.

**Spinal Matrix Metalloproteinase 3 Mediates Inflammatory Hyperalgesia Via A Tumor Necrosis Factor-Dependent Mechanism** Matrix metalloproteinases (MMPs) have been implicated in the modulation of synaptic plasticity, glial activation, and long-term potentiation in the CNS. Here we demonstrate for the first time a mechanism for the regulation of nociceptive

processing by spinal MMP-3 during peripheral inflammation. The authors first determined by western blotting that the catalytic (active) form of MMP-3 (cMMP-3) is increased in lumbar spinal cord following peripheral inflammation in rats. The peripheral inflammation-induced thermal hyperalgesia and tactile hypersensitivity was transiently (2-3 h) attenuated by intrathecal (IT) pretreatment with either an MMP-3 inhibitor (NNGH), or a broad spectrum MMP inhibitor (GM6001). In addition, IT delivery of cMMP-3 evoked hypersensitivity, whereas the pro (enzymatically inactive) form of MMP-3 did not. This suggests a pro-algesic effect of spinal MMP-3 mediated by an enzymatic mechanism. This cMMP-3-induced hypersensitivity is concurrent with increased tumor necrosis factor (TNF) in the spinal cord. The hypersensitivity behavior is prevented by intrathecal etanercept (TNF blockade). Treatment with cMMP-3 resulted in an increase in TNF release from spinal primary microglial, but not astrocyte cultures. These findings thus present direct evidence implicating MMP-3 in the coordination of spinal nociceptive processing via a spinal TNF-dependent mechanism. Christianson CA, Fitzsimmons BL, Shim JH, Agrawal A, Cohen SM, Hua XY, Yaksh TL Spinal matrix metalloproteinase 3 mediates inflammatory hyperalgesia via a tumor necrosis factor-dependent mechanism. Neuroscience. 2012 Jan 3; 200: 199-210.

**Anion Activation Site Of Insulin-Degrading Enzyme** Insulin-degrading enzyme (IDE) (insulysin) is a zinc metallopeptidase that metabolizes several bioactive peptides, including insulin and the amyloid β peptide. IDE is an unusual metallopeptidase in that it is allosterically activated by both small peptides and anions, such as ATP. Here, the authors report that the ATP-binding site is located on a portion of the substrate binding chamber wall arising largely from domain 4 of the four-domain IDE. Two variants having residues in this site mutated, IDEK898A,K899A,S901A and IDER429S, both show greatly decreased activation by the polyphosphate anions ATP and PPPi. IDEK898A,K899A,S901A is also deficient in activation by small peptides, suggesting a possible mechanistic link between the two types of allosteric activation. Sodium chloride at high concentrations can also activate IDE. There are no observable differences in average conformation between the IDE-ATP complex and unliganded IDE, but regions of the active site and C-terminal domain do show increased crystallographic thermal factors in the complex, suggesting an effect on dynamics. Activation by ATP is shown to be independent of the ATP hydrolysis activity reported for the enzyme. We also report that IDEK898A,K899A,S901A has reduced intracellular function relative to unmodified IDE, consistent with a possible role for anion activation of IDE activity in vivo. Together, the data suggest a model in which the binding of anions activates by reducing the electrostatic attraction between the two halves of the enzyme, shifting the partitioning between open and closed conformations of IDE toward the open form. Noinaj N, Song ES, Bhasin S, Alper BJ, Schmidt WK, Hersh LB, Rodgers DW Anion activation site of insulin-degrading enzyme. J Biol Chem. 2012 Jan 2; 287(1): 48-57.

**Spinal TLR4 Mediates The Transition To A Persistent Mechanical Hypersensitivity After The Resolution Of Inflammation In Serum-Transferred Arthritis** Persistent pain after resolution of clinically appreciable signs of arthritis poses a therapeutic challenge, and immunosuppressive therapies do not meet this medical need. To investigate this conversion to persistent pain, the authors utilized the K/BxN serum transfer arthritis model, which has persistent mechanical hypersensitivity despite the resolution of visible inflammation. Toll-like receptor (TLR) 4 has been implicated as a potential therapeutic target in neuropathic and other pain models. The authors compared the relative courses of serum transfer arthritis and mechanical hypersensitivity in wild type (WT) and Tlr4(-/-) mice. K/BxN serum transfer induced

similar joint swelling and inflammation from days 4-22 in WT and Tlr4(-/-) mice. Unlike WT mice, Tlr4(-/-) mice displayed a significant reversal in mechanical hypersensitivity and diminished appearance of glial activation markers after resolution of peripheral inflammation. Intrathecal (IT) delivery of a TLR4 antagonist, lipopolysaccharide Rhodobacter sphaeroides (LPS-RS; 10 μg), on days 6, 9, and 12 abrogated the transition to persistent mechanical hypersensitivity in WT arthritic mice, while later administration had no impact. The authors utilized a lipidomics liquid chromatography tandem mass spectrometry methodology to determine spinal cord profiles of bioactive lipid species after early LPS-RS treatment compared to vehicle-treated control animals. WT arthritic mice had reduced spinal levels of the anti-inflammatory prostaglandin 15-deoxy-Δ(12,14)-PGJ(2) (15d-PGJ(2)) on day 6, compared to IT LPS-RS-treated mice. Direct IT application of 15d-PGJ(2) (0.5 μg) on day 6 improved mechanical hypersensitivity in arthritic mice within 15 min. Hence, TLR4 signaling altered spinal bioactive lipid profiles in the serum transfer model and played a critical role in the transition from acute to chronic postinflammatory mechanical hypersensitivity**.** Christianson CA, Dumlao DS, Stokes JA, Dennis EA, Svensson CI, Corr M, Yaksh TL. Spinal TLR4 mediates the transition to a persistent mechanical hypersensitivity after the resolution of inflammation in serum-transferred arthritis. Pain. 2011 Dec; 152(12): 2881-2891.

**Development And In Vitro Characterization Of A Novel Bifunctional M-Agonist/Δ-Antagonist Opioid Tetrapeptide** The development of tolerance to and dependence on opioid analgesics greatly reduces their long-term usefulness. Previous studies have demonstrated that co-administration of a μ-opioid receptor (MOR) agonist and δ-opioid receptor (DOR) antagonist can decrease MOR agonist-induced tolerance and dependence development after chronic exposure. Clinically, a single ligand displaying multiple efficacies (e.g., MOR agonism concurrently with DOR antagonism) would be of increased value over two drugs administered simultaneously. Guided by modeling of receptor-ligand complexes the authors have developed a series of potent non-selective opioid tetrapeptides that have differing efficacy at MOR and DOR. In particular, their lead peptide (KSK-103) binds with equal affinity to MOR and DOR but acts as a MOR agonist with similar efficacy but greater potency than morphine and a DOR antagonist in cellular assays measuring both G protein stimulation and adenylyl cyclase inhibition. Purington LC, Sobczyk-Kojiro K, Pogozheva ID, Traynor JR, Mosberg HI. Development and in vitro characterization of a novel bifunctional μ-agonist/δ-antagonist opioid tetrapeptide. ACS Chem Biol. 2011 Dec 16; 6(12): 1375-1381. doi: 10.1021/cb200263q.

**Inhibiting Fatty Acid Amide Hydrolase Normalizes Endotoxin-Induced Enhanced Gastrointestinal Motility In Mice** Gastrointestinal (GI) motility is regulated in part by fatty acid ethanolamides (FAEs), including the endocannabinoid (EC) anandamide (AEA). The actions of FAEs are terminated by fatty acid amide hydrolase (FAAH). The authors investigated the actions of the novel FAAH inhibitor AM3506 on normal and enhanced GI motility. They examined the effect of AM3506 on electrically-evoked contractility in vitro and GI transit and colonic faecal output in vivo, in normal and FAAH-deficient mice treated with saline or LPS (100 μg·kg(-1), i.p.), in the presence and absence of cannabinoid (CB) receptor antagonists. mRNA expression was measured by quantitative real time-PCR, EC levels by liquid chromatography-MS and FAAH activity by the conversion of [(3)H]-AEA to [(3)H]-ethanolamine in intestinal extracts. FAAH expression was examined by immunohistochemistry. FAAH was dominantly expressed in the enteric nervous system; its mRNA levels were higher in the ileum than the colon. LPS enhanced ileal contractility in the absence of overt inflammation. AM3506 reversed the enhanced electrically-evoked contractions of the ileum through CB(1) and

CB(2) receptors. LPS increased the rate of upper GI transit and faecal output. AM3506 normalized the enhanced GI transit through CB(1) and CB(2) receptors and faecal output through CB(1) receptors. LPS did not increase GI transit in FAAH-deficient mice. Inhibiting FAAH normalizes various parameters of GI dysmotility in intestinal pathophysiology. Inhibition of FAAH represents a new approach to the treatment of disordered intestinal motility. Bashashati M, Storr MA, Nikas SP, Wood JT, Godlewski G, Liu J, Ho W, Keenan CM, Zhang H, Alapafuja SO, Cravatt BF, Lutz B, Mackie K, Kunos G, Patel KD, Makriyannis A, Davison JS, Sharkey KA. Inhibiting fatty acid amide hydrolase normalizes endotoxin-induced enhanced gastrointestinal motility in mice. Br J Pharmacol. 2012 Mar; 165(5): 1556-1571. doi: 10.1111/j.1476-5381.2011.01644.x.

**Contributions Of Neuroimaging To Understanding Sex Differences In Cocaine Abuse** A consistent observation in drug abuse research is that males and females show differences in their response to drugs of abuse. In order to understand the neurobiology underlying cocaine abuse and effective treatments, it is important to consider the role of sex differences. Sex hormones have been investigated in both behavioral and molecular studies, but further evidence addressing drug abuse and dependence in both sexes would expand our knowledge of sex differences in response to drugs of abuse. Neuroimaging is a powerful tool that can offer insight into the biological bases of these differences and meet the challenges of directly examining drug-induced changes in brain function. As such, neuroimaging has drawn much interest in recent years. Specifically, positron emission tomography (PET), single photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI) technology have emerged as effective noninvasive approaches for human and animal models. Studies have revealed sex-specific changes in patterns of brain activity in response to acute cocaine injection and after prolonged cocaine use. SPECT and PET studies have demonstrated changes in the dopamine transporter but are less clear on other components of the dopaminergic system. This review highlights contributions of neuroimaging toward understanding the role of sex differences in the drug abuse field, specifically regarding cocaine, and identifies relevant questions that neuroimaging can effectively address. Andersen ML, Sawyer EK, Howell LL. Contributions of neuroimaging to understanding sex differences in cocaine abuse. Exp Clin Psychopharmacol. 2012 Feb; 20(1): 2-15.

**A Common Single Nucleotide Polymorphism A118G Of The M Opioid Receptor Alters Its N-Glycosylation And Protein Stability** The A118G SNP (single nucleotide polymorphism) of the hMOPR [human MOPR (μ opioid receptor)] gene OPRM1 results in an amino acid substitution (N40D). Subjects homozygous for the 118G allele have been reported to require higher morphine doses to achieve adequate analgesia, and the 118G allele is more prevalent among drug abusers. However, changes in the MOPR protein associated with this SNP are unknown. Using a knockin mouse model (G/G mice; mice homozygous for the 112G allele of MOPR) that possesses the equivalent nucleotide/amino acid substitution (A112G; N38D) of the A118G SNP in the hMOPR gene, the authors investigated the N-linked glycosylation status of thalamic and striatal MOPR in G/G mice compared with A/A mice (wild-type mice homozygous for the 112A allele of MOPR). The molecular mass of MOPR determined by immunoblotting was lower in G/G mice than in A/A mice. Following treatment with peptide N-glycosidase F, which removes all N-linked glycans, both MOPR variants had an identical molecular mass, indicating that this discrepancy was due to a lower level of N-glycosylation of the MOPR in G/G mice. In Chinese-hamster ovary cells stably expressing hMOPRs, 118G/Asp40-hMOPR had a lower molecular mass than 118A/Asn40-hMOPR, which was similarly due to differential N-

glycosylation. Pulse-chase studies revealed that the half-life of the mature form of 118G/Asp40-hMOPR (~12 h) was shorter than that of 118A/Asn40-hMOPR (~28 h). Thus the A118G SNP reduces MOPR N-glycosylation and protein stability. Huang P, Chen C, Mague SD, Blendy JA, Liu-Chen LY. A common single nucleotide polymorphism A118G of the μ opioid receptor alters its N-glycosylation and protein stability Biochem J. 2012 Jan 1; 441(1): 379-386.

**Morphine, But Not Trauma, Sensitizes To Systemic Acinetobacter Baumannii Infection**
Acinetobacter baumannii is an important nosocomial pathogen in civilian intensive care units. Recently the incidence has increased in wounded military personnel. Morphine is documented in numerous animal studies to be immunosuppressive and to sensitize to infection. The hypotheses were tested that morphine, administered for analgesia in the battlefield, predisposes to Acinetobacter infection, and that the opioid may have an additive or synergistic effect with trauma. To test these hypotheses, an intraperitoneal infection model was established in mice using several Acinetobacter strains. Morphine administered for 48 h by implantation of a slow-release morphine pellet increased mortality compared to animals receiving a placebo pellet, an effect that was blocked by the mu-opioid receptor antagonist, naltrexone. Acinetobacter burdens in the blood, spleens, livers, and lungs of morphine-treated mice, were significantly higher than those in placebo-treated animals, confirming that mortality was due to potentiated growth of the bacteria. There were also elevated levels of pro-inflammatory cytokines in morphine-treated versus placebo-treated mice. Morphine caused a reduction in the total number of cells in the peritoneal cavity, a decrease in the percentage and total numbers of neutrophils, and a decrease in the total number of macrophages. Morphine treatment also suppressed levels of the neutrophil-inducing molecules, IL-17A and KC/CXCL1. However, IL-17A(-/-) mice given morphine were not sensitized to Acintobacter infection to a greater degree than similarly treated wild-type mice. Trauma alone did not sensitize to Acinetobacter infection, and there was no additive effect between morphine and trauma. These results support the hypothesis that morphine potentiates Acinetobacter infection. Breslow JM, Monroy MA, Daly JM, Meissler JJ, Gaughan J, Adler MW, Eisenstein TK. Morphine, but not trauma, sensitizes to systemic Acinetobacter baumannii infection. J Neuroimmune Pharmacol. 2011 Dec; 6(4): 551-565.

**Opioids And HIV/HCV Infection** Since human immunodeficiency virus (HIV) and hepatitis C virus (HCV) share the same modes of transmission and common risk factors for infection, co-infections with HIV and HCV are frequently found in injection drug users (IDUs). IDUs represent one of the largest reservoirs of HIV as well as HCV in the United States. These two pathogens are also likely to be responsible for the highest infectious disease morbidity and mortality rates among IDUs. IDUs frequently involve the abuse of heroin, the most common abused opiate. Opiates have been suggested to have a cofactor role in the immunopathogenesis of HIV disease, as they have the potential to compromise host immune responses and enhances microbial infections. Although in vitro studies have yielded relatively agreeable data that morphine, the active metabolite of heroin, exacerbate HIV infection/replication, epidemiologic studies as well as in vivo non-human primate investigations on the impact of opiate abuse on HIV disease progression have yielded the conflicting data. Given immunomodulation and immunocompromising effect as well as demonstrated impact to enhance HIV replication in vitro, it is reasonable to believe that opiate abuse is a facilitator in HIV and/or HCV disease progression. However, much remain to be learned about the mechanisms of opiate-mediated broad influence on host immunity and viral expression. Thus, more extensive studies are needed in order to determine the effects of different conditions of opiate abuse and to define the understanding of the role of opiate in modulating HIV and/or HCV disease progression. Wang X,

Zhang T, Ho WZ Opioids and HIV/HCV infection. J Neuroimmune Pharmacol. 2011 Dec; 6(4): 477-489. Epub 2011 Jul 14.

**Glutamatergic Input From Specific Sources Influences The Nucleus Accumbens-Ventral Pallidum Information Flow** The nucleus accumbens (NAc) is positioned to integrate signals originating from limbic and cortical areas and to modulate reward-related motor output of various goal-directed behaviours. The major target of the NAc GABAergic output neurons is the ventral pallidum (VP). VP is part of the reward circuit and controls the ascending mesolimbic dopamine system, as well as the motor output structures and the brainstem. The excitatory inputs governing this system converge in the NAc from the prefrontal cortex (PFC), ventral hippocampus (vHC), midline and intralaminar thalamus (TH) and basolateral nucleus of the amygdala (BLA). It is unclear which if any of these afferents innervate the medium spiny neurons of the NAc, that project to the VP. To identify the source of glutamatergic afferents that innervate neurons projecting to the VP, a dual-labelling method was used: Phaseolus vulgaris leucoagglutinin for anterograde and EGFP-encoded adenovirus for retrograde tract-tracing. Within the NAc, anterogradely labelled BLA terminals formed asymmetric synapses on dendritic spines that belonged to medium spiny neurons retrogradely labelled from the VP. TH terminals also formed synapses on dendritic spines of NAc neurons projecting to the VP. However, dendrites and dendritic spines retrogradely labelled from VP received no direct synaptic contacts from afferents originating from mPFC and vHC in the present material, despite the large number of fibres labelled by the anterograde tracer injections. These findings represent the first experimental evidence for a selective glutamatergic innervation of NAc neurons projecting to the VP. The glutamatergic inputs of different origin (i.e. mPFC, vHC, BLA, TH) to the NAc might thus convey different types of reward-related information during goal-directed behaviour, and thereby contribute to the complex regulation of nucleus accumbens functions. Papp E, Borhegyi Z, Tomioka R, Rockland KS, Mody I, Freund TF. Glutamatergic input from specific sources influences the nucleus accumbens-ventral pallidum information flow. Brain Struct Funct. 2012 Jan; 217(1): 37-48. Epub 2011 Jun 5

**Structure of the Human κ-Opioid Receptor in Complex with JDTic** Opioid receptors mediate the actions of endogenous and exogenous opioids on many physiological processes, including the regulation of pain, respiratory drive, mood, and-in the case of κ-opioid receptor (κ-OR)-dysphoria and psychotomimesis. Here the authors report the crystal structure of the human κ-OR in complex with the selective antagonist JDTic, arranged in parallel dimers, at 2.9 Å resolution. The structure reveals important features of the ligand-binding pocket that contribute to the high affinity and subtype selectivity of JDTic for the human κ-OR. Modelling of other important κ-OR-selective ligands, including the morphinan-derived antagonists norbinaltorphimine and 5'-guanidinonaltrindole, and the diterpene agonist salvinorin A analogue RB-64, reveals both common and distinct features for binding these diverse chemotypes. Analysis of site-directed mutagenesis and ligand structure-activity relationships confirms the interactions observed in the crystal structure, thereby providing a molecular explanation for κ-OR subtype selectivity, and essential insights for the design of compounds with new pharmacological properties targeting the human κ-OR. Wu H, Wacker D, Mileni M, Katritch V, Han GW, Vardy E, Liu W, Thompson AA, Huang XP, Carroll FI, Mascarella SW, Westkaemper RB, Mosier PD, Roth BL, Cherezov V, Stevens RC. Structure of the human κ-opioid receptor in complex with JDTic. Nature. 2012 Mar 21. doi: 10.1038/nature10939. [Epub ahead of print]

**Crystal Structure of the μ-Opioid Receptor Bound To A Morphinan Antagonist** Opium is one of the world's oldest drugs, and its derivatives morphine and codeine are among the most used clinical drugs to relieve severe pain. These prototypical opioids produce analgesia as well as many undesirable side effects (sedation, apnoea and dependence) by binding to and activating the G-protein-coupled μ-opioid receptor (μ-OR) in the central nervous system. Here the authors describe the 2.8 Å crystal structure of the mouse μ-OR in complex with an irreversible morphinan antagonist. Compared to the buried binding pocket observed in most G-protein-coupled receptors published so far, the morphinan ligand binds deeply within a large solvent-exposed pocket. Of particular interest, the μ-OR crystallizes as a two-fold symmetrical dimer through a four-helix bundle motif formed by transmembrane segments 5 and 6. These high-resolution insights into opioid receptor structure will enable the application of structure-based approaches to develop better drugs for the management of pain and addiction. Manglik A, Kruse AC, Kobilka TS, Thian FS, Mathiesen JM, Sunahara RK, Pardo L, Weis WI, Kobilka BK, Granier S. Crystal structure of the μ-opioid receptor bound to a morphinan antagonist. Nature. 2012 Mar 21. doi: 10.1038/nature10954. [Epub ahead of print]

**Cannabinoid Receptor Involvement in Stress-Induced Cocaine Reinstatement: Potential Interaction with Noradrenergic Pathways** This study examined the role of endocannabinoid signaling in stress-induced reinstatement of cocaine seeking and explored the interaction between noradrenergic and endocannabinergic systems in the process. A well-validated preclinical model for human relapse, the rodent conditioned place preference assay, was used. Cocaine-induced place preference was established in C57BL/6 mice using injections of 15 mg/kg cocaine. Following extinction of preference for the cocaine-paired environment, reinstatement of place preference was determined following 6 min of swim stress or cocaine injection (15 mg/kg, i.p.). The role of endocannabinoid signaling was studied using the cannabinoid antagonist AM-251 (3 mg/kg, i.p.). Another cohort of mice was tested for reinstatement following administration of the cannabinoid agonist CP 55,940 (10, 20, or 40 μg/kg, i.p.). The alpha-2 adrenergic antagonist BRL-44408 (5 mg/kg, i.p.) with or without CP 55,940 (20 μg/kg) was administered to a third group of mice. The authors found that: (1) AM-251 blocked forced swim-induced, but not cocaine-induced, reinstatement of cocaine-seeking behavior; (2) the cannabinoid agonist CP 55,940 did not reinstate cocaine-seeking behavior when administered alone but did synergize with a non-reinstating dose of the alpha-2 adrenergic antagonist BRL-44408 to cause reinstatement. These results are consistent with the hypothesis that stress exposure triggers the endogenous activation of CB1 receptors and that activation of the endocannabinoid system is required for the stress-induced relapse of the mice to cocaine seeking. Further, the data suggest that the endocannabinoid system interacts with noradrenergic mechanisms to influence stress-induced reinstatement of cocaine-seeking behavior. This article is part of a Special Issue entitled: Stress, Emotional Behavior and the Endocannabinoid System. Vaughn LK, Mantsch JR, Vranjkovic O, Stroh G, Lacourt M, Kreutter M, Hillard CJ. Neuroscience. 2012 Mar 1; 204: 117-124.

**Kalirin Binds the NR2B Subunit of the NMDA Receptor, Altering its Synaptic Localization and Function** The ability of dendritic spines to change size and shape rapidly is critical in modulating synaptic strength; these morphological changes are dependent upon rearrangements of the actin cytoskeleton. Kalirin-7 (Kal7), a Rho guanine nucleotide exchange factor localized to the postsynaptic density (PSD), modulates dendritic spine morphology in vitro and in vivo. Kal7 activates Rac and interacts with several PSD proteins, including PSD-95, DISC-1, AF-6, and Arf6. Mice genetically lacking Kal7 (Kal7(KO)) exhibit deficient hippocampal long-term

potentiation (LTP) as well as behavioral abnormalities in models of addiction and learning. Purified PSDs from Kal7(KO) mice contain diminished levels of NR2B, an NMDA receptor subunit that plays a critical role in LTP induction. Here the authors demonstrate that Kal7(KO) animals have decreased levels of NR2B-dependent NMDA receptor currents in cortical pyramidal neurons as well as a specific deficit in cell surface expression of NR2B. Additionally, they demonstrate that the genotypic differences in conditioned place preference and passive avoidance learning seen in Kal7(KO) mice are abrogated when animals are treated with an NR2B-specific antagonist during conditioning. Finally, they identify a stable interaction between the pleckstrin homology domain of Kal7 and the juxtamembrane region of NR2B preceding its cytosolic C-terminal domain. Binding of NR2B to a protein that modulates the actin cytoskeleton is important, as NMDA receptors require actin integrity for synaptic localization and function. These studies demonstrate a novel and functionally important interaction between the NR2B subunit of the NMDA receptor and Kalirin, proteins known to be essential for normal synaptic plasticity. Kiraly DD, Lemtiri-Chlieh F, Levine ES, Mains RE, Eipper BA. Kalirin binds the NR2B subunit of the NMDA receptor, altering its synaptic localization and function. J Neurosci 2011 Aug 31; 31(35): 12554-12565.

**Mass Spectrometric Characterization of Human N-Acylethanolamie-hydrolyzing Acid Amidase** N-Acylethanolamine-hydrolyzing acid amidase (NAAA) is a lysosomal enzyme that primarily degrades palmitoylethanolamine (PEA), a lipid amide that inhibits inflammatory responses. The authors developed a HEK293 cell line stably expressing the NAAA pro-enzyme (zymogen) and a single step chromatographic purification of the protein from the media. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry MALDI-TOF MS analysis of the zymogen (47.7 kDa) treated with peptide-N-glycosidase F (PNGase F) identified 4 glycosylation sites, and acid cleavage of the zymogen into α- and β-subunits (14.6 and 33.3 kDa) activated the enzyme. Size exclusion chromatography estimated the mass of the active enzyme as 45 ± 3 kDa, suggesting formation of an α/β heterodimer. MALDI-TOF MS fingerprinting covered more than 80% of the amino acid sequence, including the N-terminal peptides, and evidence for the lack of a disulfide bond between subunits. The significance of the cysteine residues was established by their selective alkylation resulting in almost complete loss of activity. The purified enzyme was kinetically characterized with PEA and a novel fluorogenic substrate, N-(4-methyl coumarin) palmitamide (PAMCA). The production of sufficient quantities of NAAA and a high throughput assay could be useful in discovering novel inhibitors and determining the structure and function of this enzyme. West JM, Zvonok N., Whitten KM, Wood JT, Makriyannis A. Mass Spectrometric Characterization of Human N-Acylethanolamie-hydrolyzing Acid Amidase. J Proeome Res. 2012 Feb 3; 11(2): 972-981. Epub 2012 Jan 3.

**Nicotinic Neuromodulation In Auditory Cortex Requires MAPK Activation In Thalamocortical And Intracortical Circuits** Activation of nicotinic acetylcholine receptors (nAChRs) by systemic nicotine enhances sensory cognitive function and sensory-evoked cortical responses. Although nAChRs mediate fast neurotransmission at many synapses in the nervous system, nicotinic regulation of cortical processing is neuromodulatory. To explore potential mechanisms of nicotinic neuromodulation, the authors examined whether intracellular signal transduction involving mitogen-activated protein kinase (MAPK) contributes to regulation of tone-evoked responses in primary auditory cortex(A1) in the mouse. Systemic nicotine enhanced characteristic frequency (CF) tone-evoked current-source density (CSD) profiles in A1, including the shortest-latency (presumed thalamocortical) current sink in layer 4 and longer-latency (presumed intracortical) sinks in layers 2-4, by increasing response amplitudes and

decreasing response latencies. Microinjection of the MAPK kinase (MEK) inhibitor U0126 into the thalamus, targeting the auditory thalamocortical pathway, blocked the effect of nicotine on the initial (thalamocortical) CSD component, but did not block enhancement of longer-latency (intracortical) responses. Conversely, microinjection of U0126 into supragranular layers of A1 blocked nicotine's effect on intracortical, but not thalamocortical, CSD components. Simultaneously with enhancement of CF-evoked responses, responses to spectrally-distant (nonCF) stimuli were reduced, implying nicotinic "sharpening" of frequency receptive fields, an effect also blocked by MEK inhibition. Consistent with these physiological results, acoustic stimulation with nicotine produced immunolabel for activated MAPK in A1, primarily in layer 2/3 cell bodies. Immunolabel was blocked by intracortical microinjection of the nAChR antagonist dihydro-□-erythroidine, but not methyllycaconitine, implicating □4□2*, but not □7, nAChRs. Thus, activation of MAPK in functionally distinct forebrain circuits—thalamocortical, local intracortical and long-range intracortical—underlies nicotinic neuromodulation of A1.
Intskirveli I, Metherate R. Nicotinic neuromodulation in auditory cortex requires MAPK activation in thalamocortical and intracortical circuits. J Neurophysiol. 2012 Feb 22. [Epub ahead of print]

## GENETICS AND MOLECULAR NEUROBIOLOGY RESEARCH

**μ- and δ-Opioid-Related Processes in the Accumbens Core And Shell Differentially Mediate The Influence Of Reward-Guided And Stimulus-Guided Decisions On Choice** Two motivational processes affect choice between actions: (1) changes in the reward value of the goal or outcome of an action and (2) changes in the predicted value of an action based on outcome-related stimuli. Here, the authors evaluated the role of μ-opioid receptor (MOR) and δ-opioid receptor (DOR) in the nucleus accumbens in the way these motivational processes influence choice using outcome revaluation and pavlovian-instrumental transfer tests. They first examined the effect of genetic deletion of MOR and DOR in specific knock-out mice. They then assessed the effect of infusing the MOR antagonist d-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH(2) (CTAP) or the DOR antagonist naltrindole into the core or shell subregions of the nucleus accumbens on these tests in rats. They found that, whereas MOR knock-outs showed normal transfer, they failed to show a selective outcome revaluation effect. Conversely, DOR knock-outs showed normal revaluation but were insensitive to the influence of outcome-related cues on choice. This double dissociation was also found regionally within the nucleus accumbens in rats. Infusion of naltrindole into the accumbens shell abolished transfer but had no effect on outcome revaluation and did not influence either effect when infused into the accumbens core. Conversely, infusion of CTAP into the accumbens core abolished sensitivity to outcome revaluation but had no effect on transfer and did not influence either effect when infused into the accumbens shell. These results suggest that reward-based and stimulus-based values exert distinct motivational influences on choice that can be doubly dissociated both neuroanatomically and neurochemically at the level of the nucleus accumbens. Laurent V, Leung B, Maidment N, Balleine BW. μ- and δ-opioid-related processes in the accumbens core and shell differentially mediate the influence of reward-guided and stimulus-guided decisions on choice J Neurosci. 2012 Feb 1; 32(5): 18775-18783.

**Plasticity Of Mouse Enteric Synapses Mediated Through Endocannabinoid And Purinergic Signaling** The enteric nervous system (ENS) possesses extensive synaptic connections which integrate information and provide appropriate outputs to coordinate the activity of the gastrointestinal tract. The regulation of enteric synapses is not well understood. Cannabinoid (CB)(1) receptors inhibit the release of acetylcholine (ACh) in the ENS, but their role in the synapse is not understood. The authors tested the hypothesis that enteric CB(1) receptors provide inhibitory control of excitatory neurotransmission in the ENS. Intracellular microelectrode recordings were obtained from mouse myenteric plexus neurons. Interganglionic fibers were stimulated with a concentric stimulating electrode to elicit synaptic events on to the recorded neuron. Differences between spontaneous and evoked fast synaptic transmission was examined within preparations from CB(1) deficient mice (CB(1)(-/-)) and wild-type (WT) littermate controls. Cannabinoid receptors were colocalized on terminals expressing the vesicular ACh transporter and the synaptic protein synaptotagmin. A greater proportion of CB(1)(-/-) neurons received spontaneous fast excitatory postsynaptic potentials than neurons from WT preparations. The CB(1) agonist WIN55,212 depressed WT synapses without any effect on CB(1)(-/-) synapses. Synaptic activity in response to depolarization was markedly enhanced at CB(1)(-/-) synapses and after treatment with a CB(1) antagonist in WT preparations. Activity-dependent liberation of a retrograde purine messenger was demonstrated to facilitate synaptic transmission in CB(1)(-/-) mice. Cannabinoid receptors inhibit transmitter release at enteric synapses and depress synaptic strength basally and in an activity-dependent manner. These actions help explain accelerated intestinal transit observed in the absence of CB(1) receptors. Plasticity of

mouse enteric synapses mediated through endocannabinoid and purinergic signaling. Hons IM, Storr MA, Mackie K, Lutz B, Pittman QJ, Mawe GM, Sharkey KA. Neurogastroenterol Motil. 2012 Mar; 24(3): e113-124. doi: 10.1111/j.1365-2982.2011.01860.x. Epub 2012 Jan 11.

**Dynamic Loss Of Surface-Expressed AMPA Receptors In Mouse Cortical And Striatal Neurons During Anesthesia** Ionotropic glutamate receptors, especially the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor subtype, undergo dynamic trafficking between the surface membrane and intracellular organelles. This trafficking activity determines the efficacy and strength of excitatory synapses and is subject to modulation by changing synaptic inputs. Given the possibility that glutamate receptors in the central nervous system might be a sensitive target of anesthetic agents, this study investigated the possible impact of anesthesia on trafficking and subcellular expression of AMPA receptors in adult mouse brain neurons in vivo. The authors found that anesthesia induced by a systemic injection of pentobarbital did not alter total protein levels of three AMPA receptor subunits (GluR1-3) in cortical neurons. However, an anesthetic dose of pentobarbital reduced GluR1 and GluR3 proteins in the surface pool and elevated these proteins in the intracellular pool of cortical neurons. The similar redistribution of GluR1/3 was observed in mouse striatal neurons. Pentobarbital did not significantly alter GluR2 expression in the two pools. Chloral hydrate at an anesthetic dose also reduced surface GluR1/3 expression and increased intracellular levels of these proteins. The effect of pentobarbital on subcellular distribution of AMPA receptors was reversible. Altered subcellular distribution of GluR1/3 returned to normal levels after the anesthesia subsided. These data indicate that anesthesia induced by pentobarbital and chloral hydrate can alter AMPA receptor trafficking in both cortical and striatal neurons. This alteration is characterized by the concurrent loss and addition of GluR1/3 subunits in the respective surface and intracellular pools. Carino C, Fibuch EE, Mao LM, Wang JQ. Dynamic loss of surface-expressed AMPA receptors in mouse cortical and striatal neurons during anesthesia. J Neurosci Res. 2012 Jan; 90(1): 315-323. doi: 10.1002/jnr.22749.

**Effect of ΔFosB Overexpression On Opioid And Cannabinoid Receptor-Mediated Signaling In The Nucleus Accumbens** The stable transcription factor ΔFosB is induced in the nucleus accumbens (NAc) by chronic exposure to several drugs of abuse, and transgenic expression of ΔFosB in the striatum enhances the rewarding properties of morphine and cocaine. However, the mechanistic basis for these observations is incompletely understood. The authors used a bitransgenic mouse model with inducible expression of ΔFosB in dopamine D(1) receptor/dynorphin-containing striatal neurons to determine the effect of ΔFosB expression on opioid and cannabinoid receptor signaling in the NAc. Results showed that mu opioid-mediated G-protein activity and inhibition of adenylyl cyclase were enhanced in the NAc of mice that expressed ΔFosB. Similarly, kappa opioid inhibition of adenylyl cyclase was enhanced in the ΔFosB expressing mice. In contrast, cannabinoid receptor-mediated signaling did not differ between mice overexpressing ΔFosB and control mice. These findings suggest that opioid and cannabinoid receptor signaling are differentially modulated by expression of ΔFosB, and indicate that ΔFosB expression might produce some of its effects via enhanced mu and kappa opioid receptor signaling in the NAc. Sim-Selley LJ, Cassidy MP, Sparta A, Zachariou V, Nestler EJ, Selley DE. Effect of ΔFosB overexpression on opioid and cannabinoid receptor-mediated signaling in the nucleus accumbens. Neuropharmacology. 2011 Dec; 61(8): 1470-1476. Epub 2011 Sep 3.

**Activation Of Nociceptin/Orphanin FQ Peptide Receptors Disrupts Visual But Not Auditory Sensorimotor Gating In BALB/Cbyj Mice: Comparison To Dopamine Receptor Agonists** Nociceptin/orphanin FQ (N/OFQ) peptide and its receptor (NOP receptor) have been implicated in a host of brain functions and diseases, but the contribution of this neuropeptide system to behavioral processes of relevance to psychosis has not been investigated. The authors examined the effect of the NOP receptor antagonists, Compound 24 and J-113397, and the synthetic agonist, Ro64-6198, on time function (2-2000 ms prepulse-pulse intervals) of acoustic (80 dB/10 ms prepulse) and visual (1000 Lux/20 ms prepulse) prepulse inhibition of startle reflex (PPI), a preattentive sensory filtering mechanism that is central to perceptual and mental integration. The effects of the dopamine D1-like receptor agonist, SKF-81297, the D2-like receptor agonist, quinelorane, and the mixed D1/D2 agonist, apomorphine, were studied for comparison. When acoustic stimulus was used as prepulse, BALB/cByJ mice displayed a monotonic time function of PPI, and consistent with previous studies, apomorphine and SKF-81279 induced PPI impairment, whereas quinelorane had no effect. None of the NOP receptor ligands was effective on acoustic PPI. When flash light was used as prepulse, BALB/cByJ mice displayed a bell-shaped time function of PPI and all dopamine agonists were active. Ro64-6198 was also effective in reducing visual PPI. NOP receptor antagonists showed no activity but blocked disruptive effect of Ro64-6198. Finally, coadministration of the typical antipsychotic, haloperidol, attenuated PPI impairment induced by Ro64-6198, revealing involvement of a dopaminergic component. These findings show that pharmacological stimulation of NOP or dopamine D2-like receptors is more potent in disrupting visual than acoustic PPI in mice, whereas D1-like receptor activation disrupts both. They further suggest that dysfunction of N/OFQ transmission may be implicated in the pathogenesis of psychotic manifestations. Ces A, Reiss D, Walter O, Wichmann J, Prinssen EP, Kieffer BL, Ouagazzal AM. Activation of nociceptin/orphanin FQ peptide receptors disrupts visual but not auditory sensorimotor gating in BALB/cByJ mice: comparison to dopamine receptor agonists. Neuropsychopharmacology. 2012 Jan; 37(2): 378-389. doi: 10.1038/npp.2011.175.

**Negative Regulation Of Adiponectin Secretion By Receptor Interacting Protein 140 (RIP140)** RIP140 (receptor-interacting protein 140) is highly expressed in mature adipocytes and functions as a co-repressor for gene expression involved in lipid and glucose metabolism. In adipocytes, activated PKCε (Protein kinase C epsilon) phosphorylates nuclear RIP140 which is then subsequently arginine methylated and exported to the cytoplasm. In the cytoplasm, RI140 can elicit additional activities. Here the authors report a new functional role for cytoplasmic RIP140 in adipocyte in regulating adiponectin secretion. Targeting cytoplasmic RIP140 by knocking down RIP140 itself or its nuclear export trigger, PKCε, promotes the secretion of adiponectin without affecting the production or oligomerization of adiponectin. Consequentially, conditioned media from either RIP140- or PKCε-silenced adipocytes, which contain higher levels of adiponectin, enhance glucose uptake in C2C12 cells and reduce gluconeogenesis in HepG2 cells. Further, these effects can be inhibited by an adiponectin-neutralizing antibody. The effect of cytoplasmic RIP140 in regulating adiponectin secretion is via interacting with AS160, a known RIP140-interacting protein. This study reveals a new functional role for cytoplasmic RIP140 in modulating adiponectin vesicle secretion, and suggests that targeting cytoplasmic RIP140 may be a potentially effective therapeutic strategy to improve adiponectin secretion and possibly to manage metabolic disorders. Ho PC, Wei LN. Negative regulation of adiponectin secretion by receptor interacting protein 140 (RIP140). Cell Signal. 2012 Jan; 24(1): 71-76. Epub 2011 Aug 18.

**Tol2 Gene Trap Integrations In The Zebrafish Amyloid Precursor Protein Genes appa and aplp2 Reveal Accumulation Of Secreted APP At the Embryonic Veins** The single spanning transmembrane amyloid precursor protein (APP) and its proteolytic product, amyloid-beta (Ab) peptide, have been intensely studied due to their role in the pathogenesis of Alzheimer's disease. However, the biological role of the secreted ectodomain of APP, which is also generated by proteolytic cleavage, is less well understood. Here, the authors report Tol2 red fluorescent protein (RFP) transposon gene trap integrations in the zebrafish amyloid precursor protein a (appa) and amyloid precursor-like protein 2 (aplp2) genes. The transposon integrations are predicted to disrupt the appa and aplp2 genes to primarily produce secreted ectodomains of the corresponding proteins that are fused to RFP. These results indicate the Appa-RFP and Aplp2 fusion proteins are likely secreted from the central nervous system and accumulate in the embryonic veins independent of blood flow. The zebrafish appa and aplp2 transposon insertion alleles will be useful for investigating the biological role of the secreted form of APP. Liao HK, Wang Y, Noack Watt KE, Wen Q, Breitbach J, Kemmet CK, Clark KJ, Ekker SC, Essner JJ, McGrail M. Tol2 gene trap integrations in the zebrafish amyloid precursor protein genes appa and aplp2 reveal accumulation of secreted APP at the embryonic veins. Dev Dyn. 2012 Feb; 241(2): 415-425.

**The Lineage-Specific Gene Ponzr1 Is Essential For Zebrafish Pronephric And Pharyngeal Arch Development** The Homeobox (Hox) and Paired box (Pax) gene families are key determinants of animal body plans and organ structure. In particular, they function within regulatory networks that control organogenesis. How these conserved genes elicit differences in organ form and function in response to evolutionary pressures is incompletely understood. The authors molecularly and functionally characterized one member of an evolutionarily dynamic gene family, plac8 onzin related protein 1 (ponzr1), in the zebrafish. ponzr1 mRNA is expressed early in the developing kidney and pharyngeal arches. Using ponzr1-targeting morpholinos, the authors show that ponzr1 is required for formation of the glomerulus. Loss of ponzr1 results in a nonfunctional glomerulus but retention of a functional pronephros, an arrangement similar to the aglomerular kidneys found in a subset of marine fish. ponzr1 is integrated into the pax2a pathway, with ponzr1 expression requiring pax2a gene function, and proper pax2a expression requiring normal ponzr1 expression. In addition to pronephric function, ponzr1 is required for pharyngeal arch formation. The authors functionally demonstrate that ponzr1 can act as a transcription factor or co-factor, providing the first molecular mode of action for this newly described gene family. Together, this work provides experimental evidence of an additional mechanism that incorporates evolutionarily dynamic, lineage-specific gene families into conserved regulatory gene networks to create functional organ diversity. Bedell VM, Person AD, Larson JD, McLoon A, Balciunas D, Clark KJ, Neff KI, Nelson KE, Bill BR, Schimmenti LA, Beiraghi S, Ekker SC. The lineage-specific gene ponzr1 is essential for zebrafish pronephric and pharyngeal arch development. Development. 2012 Feb; 139(4): 793-804.

**Regulator Of Calmodulin Signaling Knockout Mice Display Anxiety-Like Behavior And Motivational Deficits** Regulator of calmodulin (CaM) signaling (RCS), when phosphorylated by protein kinase A (PKA) on Ser55, binds to CaM and inhibits CaM-dependent signaling. RCS expression is high in the dorsal striatum, nucleus accumbens and amygdala, suggesting that the protein is involved in limbic-striatal function. To test this hypothesis, the authors examined RCS knockout (KO) mice in behavioral models dependent on these brain areas. Mice were tested for food-reinforced instrumental conditioning and responding under a progressive ratio (PR) schedule of reinforcement and in models of anxiety (elevated plus maze and open field). While

RCS KO mice showed normal acquisition of a food-motivated instrumental response, they exhibited a lower breakpoint value when tested on responding under a PR schedule of reinforcement. RCS KO mice also displayed decreased exploration in both the open arms of an elevated plus maze and in the center region of an open field, suggesting an enhanced anxiety response. Biochemical studies revealed a reduction in the levels of dopamine and cAMP-regulated phosphoprotein (DARPP-32) in the striatum of RCS KO mice. DARPP-32 is important in reward-mediated behavior, suggestive of a possible role for DARPP-32 in mediating some of the effects of RCS. Together these results implicate a novel PKA-regulated phosphoprotein, RCS, in the etiology of motivational deficits and anxiety. Davis MM, Olausson P, Greengard P, Taylor JR, Nairn AC. Regulator of calmodulin signaling knockout mice display anxiety-like behavior and motivational deficits. Eur J Neurosci. 2012 Jan; 35(2): 300-308.

**Variation In OPRM1 And Risk Of Suicidal Behavior In Drug-Dependent Individuals**
Completed suicide and nonfatal suicide-related outcomes (SROs), such as suicidal ideation and attempts, are heritable. A recent genetic association study in a sample of suicide victims reported a protective effect of the G allele of Asn40Asp (rs1799971) on risk for completed suicide. The authors examined the association of three OPRM1 single nucleotide polymorphisms (SNPs) (rs1799971, rs609148, and rs648893) with SRO in 426 European Americans, using GEE logistic regression analysis to examine the association of a lifetime history of SRO. There was no allelic association with the SRO phenotypes. A larger sample may be needed to identify risk variants that convey SRO risk. OPRM1 may not be important in the risk of SRO. Arias AJ, Chan G, Gelernter J, Farrer L, Kranzler HR. Variation in OPRM1 and risk of suicidal behavior in drug-dependent individuals. Am J Addict. 2012 Jan-Feb; 21(1): 5-10.

**M(3): An Improved SNP Calling Algorithm for Illumina BeadArray Data** Genotype calling from high-throughput platforms such as Illumina and Affymetrix is a critical step in data processing, so that accurate information on genetic variants can be obtained for phenotype-genotype association studies. A number of algorithms have been developed to infer genotypes from data generated through the Illumina BeadStation platform, including GenCall, GenoSNP, Illuminus and CRLMM. Most of these algorithms are built on population-based statistical models to genotype every SNP in turn, such as GenCall with the GenTrain clustering algorithm, and require a large reference population to perform well. These approaches may not work well for rare variants where only a small proportion of the individuals carry the variant. A fundamentally different approach, implemented in GenoSNP, adopts a single nucleotide polymorphism (SNP)-based model to infer genotypes of all the SNPs in one individual, making it an appealing alternative to call rare variants. However, compared to the population-based strategies, more SNPs in GenoSNP may fail the Hardy-Weinberg Equilibrium test. To take advantage of both strategies, the authors propose a two-stage SNP calling procedure, named the modified mixture model (M(3)), to improve call accuracy for both common and rare variants. The effectiveness of their approach is demonstrated through applications to genotype calling on a set of HapMap samples used for quality control purpose in a large case-control study of cocaine dependence. The increase in power with M(3) is greater for rare variants than for common variants depending on the model. Li G, Gelernter J, Kranzler HR, Zhao H. M(3): an improved SNP calling algorithm for Illumina BeadArray data. Bioinformatics. 2012 Feb 1; 28(3): 358-365.

**Zfishbook: Connecting You To A World Of Zebrafish Revertible Mutants** zfishbook is an internet-based openly accessible database of revertible protein trap gene-breaking transposon (GBT) insertional mutants in the zebrafish, Danio rerio. In these lines, a monomeric red fluorescent protein (mRFP) is encoded by an artificial 3' exon, resulting in a translational fusion to endogenous loci. The natural transparency of the zebrafish embryo and larvae greatly facilitates the expression annotation of tagged loci using new capillary-based SCORE imaging methods. Molecular annotation of each line is facilitated by cloning methods such as 5'-Rapid Amplification of cDNA Ends (RACE) and inverse polymerase chain reaction (PCR). zfishbook (http://zfishbook.org) represents a central hub for molecular, expression and mutational information about GBT lines from the International Zebrafish Protein Trap Consortium (IZPTC) that includes researchers from around the globe. zfishbook is open to community-wide contributions including expression and functional annotation. zfishbook also represents a central location for information on how to obtain these lines from diverse members of the IZPTC and integration within other zebrafish community databases including Zebrafish Information Network (ZFIN), Ensembl and National Center for Biotechnology Information. Clark KJ, Argue DP, Petzold AM, Ekker SC. zfishbook: connecting you to a world of zebrafish revertible mutants. Nucleic Acids Res. 2012 Jan; 40(Database issue):D907-11.

**Rare Missense Variants In CHRNB4 Are Associated With Reduced Risk Of Nicotine Dependence** Genome-wide association studies have identified common variation in the CHRNA5-CHRNA3-CHRNB4 and CHRNA6-CHRNB3 gene clusters that contribute to nicotine dependence. However, the role of rare variation in risk for nicotine dependence in these nicotinic receptor genes has not been studied. The authors undertook pooled sequencing of the coding regions and flanking sequence of the CHRNA5, CHRNA3, CHRNB4, CHRNA6 and CHRNB3 genes in African American and European American nicotine-dependent smokers and smokers without symptoms of dependence. Carrier status of individuals harboring rare missense variants at conserved sites in each of these genes was then compared in cases and controls to test for an association with nicotine dependence. Missense variants at conserved residues in CHRNB4 are associated with lower risk for nicotine dependence in African Americans and European Americans (AA P = 0.0025, odds-ratio (OR) = 0.31, 95% confidence-interval (CI) = 0.31-0.72; EA P = 0.023, OR = 0.69, 95% CI = 0.50-0.95). Furthermore, these individuals were found to smoke fewer cigarettes per day than non-carriers (AA P = 6.6 × 10(-5), EA P = 0.021). Given the possibility of stochastic differences in rare allele frequencies between groups replication of this association is necessary to confirm these findings. The functional effects of the two CHRNB4 variants contributing most to this association (T375I and T91I) and a missense variant in CHRNA3 (R37H) in strong linkage disequilibrium with T91I were examined in vitro. The minor allele of each polymorphism increased cellular response to nicotine (T375I P = 0.01, T91I P = 0.02, R37H P = 0.003), but the largest effect on in vitro receptor activity was seen in the presence of both CHRNB4 T91I and CHRNA3 R37H (P = 2 × 10(-6)). Haller G, Druley T, Vallania FL, Mitra RD, Li P, Akk G, Steinbach JH, Breslau N, Johnson E, Hatsukami D, Stitzel J, Bierut LJ, Goate AM. Rare missense variants in CHRNB4 are associated with reduced risk of nicotine dependence. Hum Mol Genet. 2012 Feb 1; 21(3): 647-655.

**Chromosome 20 Shows Linkage With DSM-IV Nicotine Dependence In Finnish Adult Smokers** Chromosome 20 has previously been associated with nicotine dependence (ND) and smoking cessation. The authors' aim was to replicate and extend these findings. METHODS: First, a total of 759 subjects belonging to 206 Finnish families were genotyped with 18 microsatellite markers residing on chromosome 20, in order to replicate previous linkage

findings. Then, the replication data were combined to an existing whole-genome linkage data resulting in a total of 1,302 genotyped subjects from 357 families. ND diagnosed by DSM-IV criteria, the Fagerström Test for Nicotine Dependence (FTND) score, and the lifetime maximum number of cigarettes smoked within a 24-hr period (MaxCigs24) were used as phenotypes in the nonparametric linkage analyses. The authors replicated previously reported linkage to DSM-IV ND, with a maximum logarithm of odd (LOD) score of 3.8 on 20p11, with females contributing more (maximum LOD [MLOD] score 3.4 on 20q11) than males (MLOD score 2.6 on 20p11). With the combined sample, a suggestive LOD score of 2.3 was observed for DSM-IV ND on 20p11. Sex-specific analyses revealed that the signal was driven by females with a maximum LOD score of 3.3 (on 20q11) versus LOD score of 1.3 in males (on 20q13) in the combined sample. No significant linkage signals were obtained for FTND or MaxCigs24. These results provide further evidence that chromosome 20 harbors genetic variants influencing ND in adult smokers. Keskitalo-Vuokko K, Hällfors J, Broms U, Pergadia ML, Saccone SF, Loukola A, Madden PA, Kaprio J. Chromosome 20 shows linkage with DSM-IV nicotine dependence in Finnish adult smokers. Nicotine Tob Res. 2012 Feb; 14(2): 153-160.

**Childhood Adversity Increases Risk For Nicotine Dependence And Interacts With A5 Nicotinic Acetylcholine Receptor Genotype Specifically In Males** The relative importance of specific genetic and environmental factors in regulating nicotine dependence (ND) risk, including the effects on specific forms of childhood adversity on smoking risk, have been understudied. Genome-wide association studies and rodent models have demonstrated that the α5 nicotinic acetylcholine receptor gene (CHRNA5) is important in regulating nicotine intake. Childhood adversity increases the methylation level of the CHRNA5 promoter region in European Americans (EAs), an effect that was observed only in males (Zhang et al, submitted for publication). In view of this potential sex difference in the effects of early life experience on smoking, the authors investigated the presence of a sex-specific gene-by-environment effect of this marker on ND risk. A nonsynonymous SNP in CHRNA5 previously associated to ND and several related traits, rs16969968, was genotyped in 2206 EAs (1301 men and 905 women). The main and interactive effects of childhood adversity and rs16969968 genotype on diagnosis of ND and ND defined by dichotomized Fagerstrom test for ND (FTND) scores were explored. Men and women were analyzed separately to test for sex differences. Childhood adversity significantly increased ND risk in both sexes, and the effect in women was twice than that in men. Significant interactive effects of childhood adversity and rs16969968 genotype were observed in men (ND: OR=1.80, 95% CI=1.18-2.73, P=0.0044; FTND: OR=1.79, 95% CI=1.11-2.88, P=0.012). No interaction was found in women. This study provides evidence of a sex-specific gene × environment effect of CHRNA5 and childhood adversity on the risk for ND. Xie P, Kranzler HR, Zhang H, Oslin D, Anton RF, Farrer LA, Gelernter J. Childhood adversity increases risk for nicotine dependence and interacts with α5 nicotinic acetylcholine receptor genotype specifically in males. Neuropsychopharmacology. 2012 Feb; 37(3): 669-676.

**A CRHR1 Haplotype Moderates The Effect Of Adverse Childhood Experiences On Lifetime Risk Of Major Depressive Episode In African-American Women** Adverse childhood experiences (ACEs) increase the risk for adult depression and substance dependence, possibly mediated by the corticotropin-releasing hormone type 1 receptor (CRHR1). In some studies, a three-SNP "T-A-T" haplotype in CRHR1, which encodes CRHR1, exerted a protective moderating effect on risk of depression in adults with ACEs. Other studies have shown a main or moderating effect of SNPs in CRHR1 on alcohol consumption. The authors tested the moderating effects of the three-SNP haplotype on lifetime risk of a major depressive episode

(MDE) and alcohol dependence (AD) in 1,211 European-Americans (EAs) and 1,869 African-Americans (AAs), most of whom had a lifetime substance use disorder. There were no significant main or interaction effects of the TAT haplotype on AD. There was a significant interaction of ACE by TAT on risk of depression only in AA women (P = 0.005); each copy of the TAT haplotype reduced the odds of MDE by almost 40% (OR = 0.63). In AA women without an ACE and two TAT haplotypes, the risk of MDE was increased (OR = 1.51 for each copy). These findings in relation to the TAT haplotype of CRHR1 extend those obtained in other populations to a largely substance-dependent one. The complex structure of CRHR1 may help to explain why some variants in the gene moderate the effects of an ACE only on depression risk while others moderate the effect of an ACE only on AD risk. Kranzler HR, Feinn R, Nelson EC, Covault J, Anton RF, Farrer L, Gelernter J. A CRHR1 haplotype moderates the effect of adverse childhood experiences on lifetime risk of major depressive episode in African-American women. Am J Med Genet B Neuropsychiatr Genet. 2011 Dec; 156B(8): 960-968. doi: 10.1002/ajmg.b.31243.

**FACS Purification Of Immunolabeled Cell Types From Adult Rat Brain** Molecular analysis of brain tissue is greatly complicated by having many different classes of neurons and glia interspersed throughout the brain. Fluorescence-activated cell sorting (FACS) has been used to purify selected cell types from brain tissue. However, its use has been limited to brain tissue from embryos or transgenic mice with promoter-driven reporter genes. To overcome these limitations, the authors developed a FACS procedure for dissociating intact cell bodies from adult wild-type rat brains and sorting them using commercially available antibodies against intracellular and extracellular proteins. As an example, they isolated neurons using a NeuN antibody and confirmed their identity using microarray and real time PCR of mRNA from the sorted cells. This FACS procedure allows rapid, high-throughput, quantitative assays of molecular alterations in identified cell types with widespread applications in neuroscience. Guez-Barber D, Fanous S, Harvey BK, Zhang Y, Lehrmann E, Becker KG, Picciotto MR, Hope BT. FACS purification of immunolabeled cell types from adult rat brain. J Neurosci Methods. 2012 Jan 15; 203(1): 10-18. Epub 2011 Sep 3.

**Phosphodiesterase 4 Inhibition Enhances The Dopamine D1 Receptor/PKA/DARPP-32 Signaling Cascade In Frontal Cortex** Alteration of dopamine neurotransmission in the prefrontal cortex, especially hypofunction of dopamine D1 receptors, contributes to psychotic symptoms and cognitive deficit in schizophrenia. D1 receptors signal through the cAMP/PKA second messenger cascade, which is modulated by phosphodiesterase (PDE) enzymes that hydrolyze and inactivate cyclic nucleotides. Though several PDEs are expressed in cortical neurons, the PDE4 enzyme family (PDE4A-D) has been implicated in the control of cognitive function. The best studied isoform, PDE4B, interacts with a schizophrenia susceptibility factor, disrupted in schizophrenia 1 (DISC1). The authors explore the control of mouse frontal cortex dopamine D1 receptor signaling and associated behavior by PDE4. Inhibition of PDE4 by rolipram induced activation of cAMP/PKA signaling in cortical slices and in vivo, leading to the phosphorylation of DARPP-32 and other postsynaptic and presynaptic PKA-substrates. Rolipram also enhanced DARPP-32 phosphorylation invoked by D1 receptor activation. Immunohistochemical studies demonstrated PDE4A, PDE4B, and PDE4D expression in DARPP-32-positive neurons in layer VI of frontal cortex, most likely in D1 receptor-positive, glutamatergic corticothalamic pyramidal neurons. Furthermore, the ability of rolipram treatment to improve the performance of mice in a sensorimotor gating test was DARPP-32-dependent. PDE4, which is co-expressed with DARPP-32 in D1 receptor-positive cortical pyramidal

neurons in layer VI, modulates the level of D1 receptor signaling and DARPP-32 phosphorylation in the frontal cortex, likely influencing cognitive function. These biochemical and behavioral actions of PDE4 inhibitors may contribute to the hypothesized antipsychotic actions of this class of compounds. Kuroiwa M, Snyder GL, Shuto T, Fukuda A, Yanagawa Y, Benavides DR, Nairn AC, Bibb JA, Greengard P, Nishi A. Phosphodiesterase 4 inhibition enhances the dopamine D1 receptor/PKA/DARPP-32 signaling cascade in frontal cortex. Psychopharmacology (Berl). 2012 Feb; 219(4): 1065-1079. Epub 2011 Aug 11.

**Genome-Wide Association Study Of Major Depressive Disorder: New Results, Meta-Analysis, And Lessons Learned** Major depressive disorder (MDD) is a common complex disorder with a partly genetic etiology. The authors conducted a genome-wide association study of the MDD2000+ sample (2431 cases, 3673 screened controls and >1 M imputed single-nucleotide polymorphisms (SNPs)). No SNPs achieved genome-wide significance either in the MDD2000+ study, or in meta-analysis with two other studies totaling 5763 cases and 6901 controls. These results imply that common variants of intermediate or large effect do not have main effects in the genetic architecture of MDD. Suggestive but notable results were (a) gene-based tests suggesting roles for adenylate cyclase 3 (ADCY3, 2p23.3) and galanin (GAL, 11q13.3); published functional evidence relates both of these to MDD and serotonergic signaling; (b) support for the bipolar disorder risk variant SNP rs1006737 in CACNA1C (P=0.020, odds ratio=1.10); and (c) lack of support for rs2251219, a SNP identified in a meta-analysis of affective disorder studies (P=0.51). They estimate that sample sizes 1.8- to 2.4-fold greater are needed for association studies of MDD compared with those for schizophrenia to detect variants that explain the same proportion of total variance in liability. Larger study cohorts characterized for genetic and environmental risk factors accumulated prospectively are likely to be needed to dissect more fully the etiology of MDD. Wray NR, Pergadia ML, Blackwood DH, Penninx BW, Gordon SD, Nyholt DR, Ripke S, MacIntyre DJ, McGhee KA, Maclean AW, Smit JH, Hottenga JJ, Willemsen G, Middeldorp CM, de Geus EJ, Lewis CM, McGuffin P, Hickie IB, van den Oord EJ, Liu JZ, Macgregor S, McEvoy BP, Byrne EM, Medland SE, Statham DJ, Henders AK, Heath AC, Montgomery GW, Martin NG, Boomsma DI, Madden PA, Sullivan PF. Genome-wide association study of major depressive disorder: new results, meta-analysis, and lessons learned. Mol Psychiatry. 2012 Jan; 17(1): 36-48. doi: 10.1038/mp.2010.109. Epub 2010 Nov 2.

**Generation Of A Synthetic Memory Trace** The authors investigated the effect of activating a competing, artificially generated, neural representation on encoding of contextual fear memory in mice. They used a c-fos-based transgenic approach to introduce the hM(3)D(q) DREADD receptor (designer receptor exclusively activated by designer drug) into neurons naturally activated by sensory experience. Neural activity could then be specifically and inducibly increased in the hM(3)D(q)-expressing neurons by an exogenous ligand. When an ensemble of neurons for one context (ctxA) was artificially activated during conditioning in a distinct second context (ctxB), mice formed a hybrid memory representation. Reactivation of the artificially stimulated network within the conditioning context was required for retrieval of the memory, and the memory was specific for the spatial pattern of neurons artificially activated during learning. Similar stimulation impaired recall when not part of the initial conditioning. Garner AR, Rowland DC, Hwang SY, Baumgaertel K, Roth BL, Kentros C, Mayford M. Generation of a synthetic memory trace. Science. 2012 Mar 23; 335(6075): 1513-1516.

**High-Resolution Genetic Mapping Using The Mouse Diversity Outbred Population** The JAX Diversity Outbred population is a new mouse resource derived from partially inbred Collaborative Cross strains and maintained by randomized outcrossing. As such, it segregates the same allelic variants as the Collaborative Cross but embeds these in a distinct population architecture in which each animal has a high degree of heterozygosity and carries a unique combination of alleles. Phenotypic diversity is striking and often divergent from phenotypes seen in the founder strains of the Collaborative Cross. Allele frequencies and recombination density in early generations of Diversity Outbred mice are consistent with expectations based on simulations of the mating design. The authors describe analytical methods for genetic mapping using this resource and demonstrate the power and high mapping resolution achieved with this population by mapping a serum cholesterol trait to a 2-Mb region on chromosome 3 containing only 11 genes. Analysis of the estimated allele effects in conjunction with complete genome sequence data of the founder strains reduced the pool of candidate polymorphisms to seven SNPs, five of which are located in an intergenic region upstream of the Foxo1 gene. Svenson KL, Gatti DM, Valdar W, Welsh CE, Cheng R, Chesler EJ, Palmer AA, McMillan L, Churchill GA. High-resolution genetic mapping using the mouse diversity outbred population. Neuron. 2011 Dec 22; 72(6): 977-990.

**Role for mTOR Signaling And Neuronal Activity In Morphine-Induced Adaptations In Ventral Tegmental Area Dopamine Neurons** While the abuse of opiate drugs continues to rise, the neuroadaptations that occur with long-term drug exposure remain poorly understood. The authors describe here a series of chronic morphine-induced adaptations in ventral tegmental area (VTA) dopamine neurons, which are mediated via downregulation of AKT-mTORC2 (mammalian target of rapamycin complex-2). Chronic opiates decrease the size of VTA dopamine neurons in rodents, an effect seen in humans as well, and concomitantly increase the excitability of the cells but decrease dopamine output to target regions. Chronic morphine decreases mTORC2 activity, and overexpression of Rictor, a component of mTORC2, prevents morphine-induced changes in cell morphology and activity. Further, local knockout of Rictor in VTA decreases DA soma size and reduces rewarding responses to morphine, consistent with the hypothesis that these adaptations represent a mechanism of reward tolerance. Together, these findings demonstrate a novel role for AKT-mTORC2 signaling in mediating neuroadaptations to opiate drugs of abuse. Mazei-Robison MS, Koo JW, Friedman AK, Lansink CS, Robison AJ, Vinish M, Krishnan V, Kim S, Siuta MA, Galli A, Niswender KD, Appasani R, Horvath MC, Neve RL, Worley PF, Snyder SH, Hurd YL, Cheer JF, Han MH, Russo SJ, Nestler EJ. Role for mTOR signaling and neuronal activity in morphine-induced adaptations in ventral tegmental area dopamine neurons. Nicotine Tob Res. 2012 Jan 12. [Epub ahead of print]

**Varenicline Blocks β2*-nAChR-Mediated Response and Activates β4*-nAChR-Mediated Responses in Mice In Vivo** The smoking cessation aid, varenicline, has higher affinity for the alpha4beta2-subtype of the nicotinic acetylcholine receptor (α4β2*-nAChR) than for other subtypes of nAChRs by in vitro assays. The mechanism of action of acute varenicline was studied in vivo to determine (a) subtype activation associated with physiological effects and (b) dose relationship as an antagonist of nicotine. Acute doses of saline, nicotine, and varenicline were given to mice, and locomotor depression and hypothermia were measured. Subunit null mutant mice as well as selective antagonists were used to study mode of action of varenicline as an agonist. Varenicline as an antagonist of nicotine was also investigated. Varenicline evokes locomotor depression and hypothermia at higher doses than necessary for nicotine. Null mutation of the α7- or β2-nAChR subunit did not decrease the effectiveness of varenicline; however, null

mutation of the β4 subunit significantly decreased the magnitude of the varenicline effect. Effects of the highest dose studied were blocked by mecamylamine (general nAChR antagonist) and partially antagonized by hexamethonium (largely peripheral nAChR antagonist). No significant block was seen with ondansetron antagonist of 5-hydroxytryptamine 3 receptor. Using a dose of nicotine selective for β2*-nAChR subtype effects with these tests, dose-dependent antagonism by varenicline was seen. Effective inhibitory doses were determined and appear to be in a range consistent with binding affinity or desensitization of β2*-nAChRs. Varenicline acts as a functional antagonist of β2*-nAChRs, blocking certain effects of nicotine. At higher doses, varenicline is an agonist of β4*-nAChRs producing physiological changes in mice. Ortiz NC, O'Neill HC, Marks MJ, Grady SR. Varenicline blocks β2*-nAChR-mediated response and activates β4*-nAChR-mediated responses in mice in vivo**.** J Neurosci. 2012 Feb 15; 32(7): 2352-2356.

**Visualizing Neuromodulation In Vivo: TANGO-Mapping Of Dopamine Signaling Reveals Appetite Control Of Sugar Sensing** Behavior cannot be predicted from a "connectome" because the brain contains a chemical "map" of neuromodulation superimposed upon its synaptic connectivity map. Neuromodulation changes how neural circuits process information in different states, such as hunger or arousal. Here the authors describe a genetically based method to map, in an unbiased and brain-wide manner, sites of neuromodulation under different conditions in the Drosophila brain. This method, and genetic perturbations, reveal that the well-known effect of hunger to enhance behavioral sensitivity to sugar is mediated, at least in part, by the release of dopamine onto primary gustatory sensory neurons, which enhances sugar-evoked calcium influx. These data reinforce the concept that sensory neurons constitute an important locus for state-dependent gain control of behavior and introduce a methodology that can be extended to other neuromodulators and model organisms. Inagaki HK, Ben-Tabou de-Leon S, Wong AM, Jagadish S, Ishimoto H, Barnea G, Kitamoto T, Axel R, Anderson DJ Visualizing neuromodulation in vivo: TANGO-mapping of dopamine signaling reveals appetite control of sugar sensing.. Cell. 2012 Feb 3; 148(3): 583-595.

**Dopamine D4 Receptor Gene Variation Moderates The Efficacy Of Bupropion For Smoking Cessation** Smokers (≥10 cigarettes per day, N=331) of European ancestry taking part in a double-blind placebo-controlled randomized trial of 12 weeks of treatment with bupropion along with counseling for smoking cessation were genotyped for a variable number of tandem repeats polymorphism in exon III of the dopamine D4 receptor gene. Generalized estimating equations predicting point-prevalence abstinence at end of treatment and 2, 6 and 12 months after the end of treatment indicated that bupropion (vs placebo) predicted increased odds of abstinence. The main effect of Genotype was not significant. A Genotype × Treatment interaction (P=0.005) showed that bupropion predicted increased odds of abstinence in long-allele carriers (odds ratios (OR)=1.31, P<0.0001), whereas bupropion was not associated with abstinence among short-allele homozygotes (OR=1.06, P=0.23). The Genotype × Treatment interaction remained when controlling for demographic and clinical covariates (P=0.01) and in analyses predicting continuous abstinence (P's≤0.054). Bupropion may be more efficacious for smokers who carry the long allele, which is relevant to personalized pharmacogenetic treatment approaches. Leventhal AM, David SP, Brightman M, Strong D, McGeary JE, Brown RA, Lloyd-Richardson EE, Munafò M, Uhl GR, Niaura R. Dopamine D4 receptor gene variation moderates the efficacy of bupropion for smoking cessation. Pharmacogenomics J. 2012 Feb; 12(1): 86-92. doi: 10.1038/tpj.2010.64. Epub 2010 Jul 27.

**A Plasma Biomarker Signature of Immune Activation in HIV Patients on Antiretroviral Therapy** Immune activation is a strong predictor of disease progression in HIV infection. Combinatorial plasma biomarker signatures that represent surrogate markers of immune activation in both viremic and aviremic HIV patients on combination antiretroviral therapy (cART) have not been defined. Here, the authors identify a plasma inflammatory biomarker signature that distinguishes between both viremic and aviremic HIV patients on cART and healthy controls and examine relationships of this signature to markers of disease progression. Multiplex profiling and ELISA were used to detect 15 cytokines/chemokines, soluble IL-2R (sIL-2R), and soluble CD14 (sCD14) in plasma from 57 HIV patients with CD4 nadir <300 cells/μl and 29 healthy controls. Supervised and unsupervised analyses were used to identify biomarkers explaining variance between groups defined by HIV status or drug abuse. Relationships between biomarkers and disease markers were examined by Spearman correlation. The majority (91%) of HIV subjects were on cART, with 38% having undetectable viral loads (VL). Hierarchical clustering identified a biomarker cluster in plasma consisting of two interferon-stimulated gene products (CXCL9 and CXCL10), T cell activation marker (sIL-2R), and monocyte activation marker (sCD14) that distinguished both viremic and aviremic HIV patients on cART from controls ($p<0.0001$) and were top-ranked in variables important in projection plots. IL-12 and CCL4 were also elevated in viremic and aviremic patients compared to controls ($p<0.05$). IL-12 correlated with IFNα, IFNγ, CXCL9, and sIL-2R ($p<0.05$). CXCL10 correlated positively with plasma VL and percentage of CD16+ monocytes, and inversely with CD4 count ($p=0.001$, $<0.0001$, and 0.04, respectively). A plasma inflammatory biomarker signature consisting of CXCL9, CXCL10, sIL-2R, and sCD14 may be useful as a surrogate marker to monitor immune activation in both viremic and aviremic HIV patients on cART during disease progression and therapeutic responses. Kamat A, Misra V, Cassol E, Ancuta P, Yan Z, Li C, Morgello S, Gabuzda D. PLoS One. 2012; 7(2): e30881. Epub 2012 Feb 17.

**Differential Regulation of MeCP2 Phosphorylation in the CNS by Dopamine and Serotonin** Systemic administration of amphetamine (AMPH) induces phosphorylation of MeCP2 at Ser421 (pMeCP2) in select populations of neurons in the mesolimbocortical brain regions. Because AMPH simultaneously activates multiple monoamine neurotransmitter systems, here the authors examined the ability of dopamine (DA), serotonin (5-HT), and norepinephrine (NE) to induce pMeCP2. Selective blockade of the DA transporter (DAT) or the 5-HT transporter (SERT), but not the NE transporter (NET), was sufficient to induce pMeCP2 in the CNS. DAT blockade induced pMeCP2 in the prelimbic cortex (PLC) and nucleus accumbens (NAc), whereas SERT blockade induced pMeCP2 only in the NAc. Administration of selective DA and 5-HT receptor agonists was also sufficient to induce pMeCP2; however, the specific combination of DA and 5-HT receptors activated determined the regional- and cell-type specificity of pMeCP2 induction. The D(1)-class DA receptor agonist SKF81297 induced pMeCP2 widely; however, coadministration of the D(2)-class agonist quinpirole restricted the induction of pMeCP2 to GABAergic interneurons of the NAc. Intra-striatal injection of the adenylate cyclase activator forskolin was sufficient to induce pMeCP2 in medium-spiny neurons, suggesting that the combinatorial regulation of cAMP by different classes of DA and 5-HT receptors may contribute to the cell-type specificity of pMeCP2 induction. Consistent with the regulation of pMeCP2 by multiple monoamine neurotransmitters, genetic disruption of any single monoamine transporter in DAT-, SERT-, and NET-knockout mice failed to eliminate AMPH-induced pMeCP2 in the NAc. Together, these studies indicate that combinatorial signaling through DA and 5-HT receptors can regulate the brain region- and cell-type specific pMeCP2 in the CNS. Hutchinson AN, Deng JV, Aryal DK, Wetsel WC, West AE.Differential regulation of MeCP2

phosphorylation in the CNS by dopamine and serotonin. Neuropsychopharmacology. 2012 Jan; 37(2): 321-337. doi: 10.1038/npp.2011.190.

**T-Cell Receptor Signaling Enhances Transcriptional Elongation From Latent HIV Proviruses By Activating P-Tefb Through An ERK-Dependent Pathway** Latent human immunodeficiency virus (HIV) proviruses are thought to be primarily reactivated in vivo through stimulation of the T-cell receptor (TCR). Activation of the TCR induces multiple signal transduction pathways, leading to the ordered nuclear migration of the HIV transcription initiation factors NF-κB (nuclear factor κB) and NFAT (nuclear factor of activated T-cells), as well as potential effects on HIV transcriptional elongation. The authors have monitored the kinetics of proviral reactivation using chromatin immunoprecipitation assays to measure changes in the distribution of RNA polymerase II in the HIV provirus. Surprisingly, in contrast to TNF-α (tumor necrosis factor α) activation, where early transcription elongation is highly restricted due to rate-limiting concentrations of Tat, efficient and sustained HIV elongation and positive transcription elongation factor b (P-TEFb) recruitment are detected immediately after the activation of latent proviruses through the TCR. Inhibition of NFAT activation by cyclosporine had no effect on either HIV transcription initiation or elongation. However, examination of P-TEFb complexes by gel-filtration chromatography showed that TCR signaling led to the rapid dissociation of the large inactive P-TEFb:7SK RNP (small nuclear RNA 7SK ribonucleoprotein) complex and the release of active low-molecular-weight P-TEFb complexes. Both P-TEFb recruitment to the HIV long terminal repeat and enhanced HIV processivity were blocked by the ERK (extracellular-signal-regulated kinase) inhibitor U0126, but not by AKT (serine/threonine protein kinase Akt) and PI3K (phosphatidylinositol 3-kinase) inhibitors. In contrast to treatment with HMBA (hexamethylene bisacetamide) and DRB (5,6-dichlorobenzimidazole 1-β-ribofuranoside), which disrupt the large 7SK RNP complex but do not stimulate early HIV elongation, TCR signaling provides the first example of a physiological pathway that can shift the balance between the inactive P-TEFb pool and the active P-TEFb pool and thereby stimulate proviral reactivation. Kim YK, Mbonye U, Hokello J, Karn J. T-cell receptor signaling enhances transcriptional elongation from latent HIV proviruses by activating P-TEFb through an ERK-dependent pathway. Nat Struct Mol Biol. 2012 Jan 15; 19(2): 207-211. doi: 10.1038/nsmb.2197.

**Experimental Conditions Can Obscure The Second High-Affinity Site In LeuT** Neurotransmitter:Na(+) symporters (NSSs), the targets of antidepressants and psychostimulants, recapture neurotransmitters from the synapse in a Na(+)-dependent symport mechanism. The crystal structure of the NSS homolog LeuT from Aquifex aeolicus revealed one leucine substrate in an occluded, centrally located (S1) binding site next to two Na(+) ions. Computational studies combined with binding and flux experiments identified a second substrate (S2) site and a molecular mechanism of Na(+)-substrate symport that depends upon the allosteric interaction of substrate molecules in the two high-affinity sites. Here the authors show that the S2 site, which has not yet been identified by crystallographic approaches, can be blocked during preparation of detergent-solubilized LeuT, thereby obscuring its crucial role in Na(+)-coupled symport. This finding points to the need for caution in selecting experimental environments in which the properties and mechanistic features of membrane proteins can be delineated. Quick M, Shi L, Zehnpfennig B, Weinstein H, Javitch JA. Experimental conditions can obscure the second high-affinity site in LeuT. Neuropsychopharmacology. 2012 Feb; 37(3): 707-722. doi: 10.1038/npp.2011.248. Epub 2011 Oct 26.

**CBP In The Nucleus Accumbens Regulates Cocaine-Induced Histone Acetylation And Is Critical For Cocaine-Associated Behaviors** Cocaine exposure triggers molecular events that lead to long-lasting changes in brain structure and function. These changes can lead to the development of persistent and robust behavioral adaptations that characterize addiction. Recent evidence suggests the regulation of transcription via chromatin modification, such as histone acetylation, has an important role in the development of addictive behavior. Histone acetylation is regulated by histone acetyltransferases (HATs), which acetylate histones and promote transcription, and histone deacetylases (HDACs), which remove acetyl groups and silence transcription. Studies have demonstrated that HDACs may negatively regulate cocaine-induced behaviors, but very little is known about the role of specific HATs in long-lasting drug-induced plasticity. The histone acetyltransferase CREB-binding protein (CBP) mediates transcriptional activation by recruiting basal transcription machinery and acetylating histones. CBP is a critically important chromatin-modifying enzyme involved in regulating gene expression required for long-term plasticity and memory. However, the role of CBP in cocaine-induced behaviors remains largely unknown. The authors examined the role of CBP in drug-induced plasticity using CBP-FLOX genetically modified mice in combination with adeno-associated virus expressing Cre-recombinase to generate focal homozygous deletions of Cbp in the nucleus accumbens (NAc). A complete loss of CBP in NAc neurons results in decreased histone acetylation and significantly altered c-fos expression in response to cocaine. Furthermore, the deletion of CBP in the NAc correlates with significant impairments in cocaine sensitivity and context-cocaine associated memory. This is the first study to demonstrate a definitive role for CBP in modulating gene expression that may subserve drug-seeking behaviors. Malvaez M, Mhillaj E, Matheos DP, Palmery M, Wood MA. CBP in the nucleus accumbens regulates cocaine-induced histone acetylation and is critical for cocaine-associated behaviors. J Neurosci. 2011 Nov 9; 31(45): 16458-16463.

**Plasticity Of Prefrontal Attention Circuitry: Upregulated Muscarinic Excitability In Response To Decreased Nicotinic Signaling Following Deletion Of A5 Or B2 Subunits** Attention depends on cholinergic stimulation of nicotinic and muscarinic acetylcholine receptors in the medial prefrontal cortex. Pyramidal neurons in layer VI of this region express cholinergic receptors of both families and play an important role in attention through their feedback projections to the thalamus. Here, the authors investigate how nicotinic and muscarinic cholinergic receptors affect the excitability of these neurons using whole-cell recordings in acute brain slices of prefrontal cortex. Since attention deficits have been documented in both rodents and humans having genetic abnormalities in nicotinic receptors, they focus in particular on how the cholinergic excitation of layer VI neurons is altered by genetic deletion of either of two key nicotinic receptor subunits, the accessory α5 subunit or the ligand-binding β2 subunit. They find that the cholinergic excitation of layer VI neurons is dominated by nicotinic receptors in wild-type mice and that the reduction or loss of this nicotinic stimulation is accompanied by a surprising degree of plasticity in excitatory muscarinic receptors. These findings suggest that disrupting nicotinic receptors fundamentally alters the mechanisms and timing of excitation in prefrontal attentional circuitry. Tian MK, Bailey CD, De Biasi M, Picciotto MR, Lambe EK. Plasticity of prefrontal attention circuitry: upregulated muscarinic excitability in response to decreased nicotinic signaling following deletion of α5 or β2 subunits. PLoS One. 2012; 7(2): e31031. Epub 2012 Feb 16.

**Receptor Heteromerization Expands The Repertoire Of Cannabinoid Signaling In Rodent Neurons** A fundamental question in G protein coupled receptor biology is how a single ligand acting at a specific receptor is able to induce a range of signaling that results in a variety of physiological responses. The authors focused on Type 1 cannabinoid receptor ($CB_1R$) as a model GPCR involved in a variety of processes spanning from analgesia and euphoria to neuronal development, survival and differentiation. They examined receptor dimerization as a possible mechanism underlying expanded signaling responses by a single ligand and focused on interactions between $CB_1R$ and delta opioid receptor (DOR). Using co-immunoprecipitation assays as well as analysis of changes in receptor subcellular localization upon co-expression, they show that $CB_1R$ and DOR form receptor heteromers. They find that heteromerization affects receptor signaling since the potency of the $CB_1R$ ligand to stimulate G-protein activity is increased in the absence of DOR, suggesting that the decrease in $CB_1R$ activity in the presence of DOR could, at least in part, be due to heteromerization. They also find that the decrease in activity is associated with enhanced PLC-dependent recruitment of arrestin3 to the $CB_1R$-DOR complex, suggesting that interaction with DOR enhances arrestin-mediated $CB_1R$ desensitization. Additionally, presence of DOR facilitates signaling via a new $CB_1R$-mediated anti-apoptotic pathway leading to enhanced neuronal survival. Taken together, these results support a role for $CB_1R$-DOR heteromerization in diversification of endocannabinoid signaling and highlight the importance of heteromer-directed signal trafficking in enhancing the repertoire of GPCR signaling. Rozenfeld R, Bushlin I, Gomes I, Tzavaras N, Gupta A, Neves S, Battini L, Gusella GL, Lachmann A, Ma'ayan A, Blitzer RD, Devi LA. Receptor heteromerization expands the repertoire of cannabinoid signaling in rodent neurons. PLoS One. 2012; 7(1): e29239. Epub 2012 Jan 3.

## FUNCTIONAL NEUROSCIENCE RESEARCH

**Predator Stress Engages Corticotropin-Releasing Factor And Opioid Systems To Alter The Operating Mode Of Locus Coeruleus Norepinephrine Neurons** The norepinephrine nucleus, locus coeruleus (LC), has been implicated in cognitive aspects of the stress response, in part through its regulation by the stress-related neuropeptide, corticotropin-releasing factor (CRF). LC neurons discharge in tonic and phasic modes that differentially modulate attention and behavior. Here, the effects of exposure to an ethologically relevant stressor, predator odor, on spontaneous (tonic) and auditory-evoked (phasic) LC discharge were characterized in unanesthetized rats. Similar to the effects of CRF, stressor presentation increased tonic LC discharge and decreased phasic auditory-evoked discharge, thereby decreasing the signal-to-noise ratio of the sensory response. This stress-induced shift in LC discharge toward a high tonic mode was prevented by a CRF antagonist. Moreover, CRF antagonism during stress unmasked a large decrease in tonic discharge rate that was opioid mediated because it was prevented by pretreatment with the opiate antagonist, naloxone. Elimination of both CRF and opioid influences with an antagonist combination rendered LC activity unaffected by the stressor. These results demonstrate that both CRF and opioid afferents are engaged during stress to fine-tune LC activity. The predominant CRF influence shifts the operational mode of LC activity toward a high tonic state that is thought to facilitate behavioral flexibility and may be adaptive in coping with the stressor. Simultaneously, stress engages an opposing opioid influence that restrains the CRF influence and may facilitate recovery toward pre-stress levels of activity. Changes in the balance of CRF:opioid regulation of the LC could have consequences for stress vulnerability. Curtis AL, Leiser SC, Snyder K, Valentino RJ. Predator stress engages corticotropin-releasing factor and opioid systems to alter the operating mode of locus coeruleus norepinephrine neurons. Neuropharmacology. 2012 Mar; 62(4): 1737-1745. Epub 2011 Dec 23.

**Response of Limbic Neurotensin Systems To Methamphetamine Self-Administration** Methamphetamine (METH) abuse is personally and socially devastating. Although effects of METH on dopamine (DA) systems likely contribute to its highly addictive nature, no medications are approved to treat METH dependence. Thus, the authors and others have studied the METH-induced responses of neurotensin (NT) systems. NT is associated with inhibitory feedback action on DA projections, and NT levels are elevated in both the nucleus accumbens and dorsal striatum after noncontingent treatment with high doses of METH. In the present study, the authors used a METH self-administration (SA) model (linked to lever pressing) to demonstrate that substitution of an NT agonist for METH, while not significantly affecting motor activity, dramatically reduced lever pressing but was not self-administered per se. They also found that nucleus accumbens NT levels were elevated via a D1 mechanism after five sessions in rats self-administering METH (SAM), with a lesser effect in corresponding yoked rats. Extended (15 daily sessions) exposure to METH SA manifested similar NT responses; however, more detailed analyses revealed (i) 15 days of METH SA significantly elevated NT levels in the nucleus accumbens shell and dorsal striatum, but not the nucleus accumbens core, with a lesser effect in the corresponding yoked METH rats; (ii) the elevation of NT in both the nucleus accumbens shell and dorsal striatum significantly correlated with the total amount of METH received in the self-administering, but not the corresponding yoked METH rats; and (iii) an NT agonist blocked, but an NT antagonist did not alter, lever-pressing behavior on day 15 in SAM rats. After 5 days in SAM animals, NT levels were also elevated in the ventral tegmental area,

but not frontal cortex of rats self-administering METH. Hanson GR, Hoonakker AJ, Alburges ME, McFadden LM, Robson CM, Frankel PS. Response of limbic neurotensin systems to methamphetamine self-administration. Neuroscience. 2012 Feb 17; 203: 99-107. Epub 2012 Jan 2.

**Glutamatergic Transmission In Schizophrenia: From Basic Research To Clinical Practice** The past 20 years have seen the glutamatergic hypothesis go from theory to phase III trials of novel mechanism antipsychotics. The authors review the recent literature on glutamatergic theory, covering assessment and genetic studies, as well as drug development in animals and humans. Although evidence continues to accumulate in support of glutamate hypotheses, further research continues to be required and interactions with other key systems need to be explored. Kantrowitz J, Javitt DC. Glutamatergic transmission in schizophrenia: from basic research to clinical practice. Curr Opin Psychiatry. 2012 Mar; 25(2): 96-102.

**Estrogen Effects On The Brain: Actions Beyond The Hypothalamus Via Novel Mechanisms** From its origins in how the brain controls the endocrine system via the hypothalamus and pituitary gland, neuroendocrinology has evolved into a science that now includes hormone action on many aspects of brain function. These actions involve the whole central nervous system and not just the hypothalamus. Advances in our understanding of cellular and molecular actions of steroid hormones have gone beyond the important cell nuclear actions of steroid hormone receptors to include signaling pathways that intersect with other mediators such as neurotransmitters and neuromodulators. This has, in turn, broadened the search for and identification of steroid receptors to include nonnuclear sites in synapses, dendrites, mitochondria, and glial cells, as well as cell nuclei. The study of estrogen receptors and estrogen actions on processes related to cognition, mood, autonomic regulation, pain, and neuroprotection, among other functions, has led the way in this new view of hormone actions on the brain. In this review, we summarize past and current work in our laboratory on this topic. This exciting and growing field involving many laboratories continues to reshape our ideas and approaches to neuroendocrinology both at the bench and the bedside. McEwen BS, Akama KT, Spencer-Segal JL, Milner TA, Waters EM. Estrogen effects on the brain: actions beyond the hypothalamus via novel mechanisms. Behav Neurosci. 2012 Feb; 126(1): 4-16.

**Apomorphine-Evoked Redistribution Of Neurokinin-3 Receptors In Dopaminergic Dendrites And Neuronal Nuclei Of The Rat Ventral Tegmental Area** Mammalian neurokinin-3 (NK(3)) receptors of the tachykinin family of neuropeptides have been shown to activate dopaminergic neurons of the ventral tegmental area (VTA), a midbrain area displaying dopaminergic dysfunctional activity in schizophrenia. The recent finding of NK(3) receptors in VTA neuronal nucleus highlights a new level of neuromodulation, in addition to the traditional tachykinin-induced NK(3) receptor internalization and activation of second messenger signaling pathways. The function of nuclear NK(3) receptors is still unknown. It is also unclear how dopaminergic activation is affecting the NK(3) receptor distribution in the VTA. In the present study, trafficking of the NK(3) receptor in somatodendritic profiles of dopaminergic and non-dopaminergic neurons of the rat VTA was investigated following acute systemic administration of the dopamine D(1)/D(2) receptor agonist apomorphine. VTA sections were dual immunolabeled for the NK(3) receptor (immunogold) and the dopamine synthesizing enzyme tyrosine hydroxylase (TH, immunoperoxidase). Electron microscopic quantifications of somatic

and dendritic densities of NK(3) immunogold particles with or without TH immunolabeling were compared in vehicle-injected or apomorphine-injected rats. In dopaminergic (TH) neurons, apomorphine evoked a significant increase in NK(3) receptor densities in cytoplasmic and nuclear portions of the soma. These changes were accompanied by a respective decrease and increase in plasmalemmal and cytoplamic NK(3) receptor densities in dopaminergic dendrites. In non-TH neurons, presumably GABAergic neurons of the VTA, the NK(3) receptor densities in somata and dendrites were not significantly altered by apomorphine. The results suggest that dopaminergic receptor activation is inducing a rapid mobilization of NK(3) receptors in VTA dopaminergic neurons. The apomorphine-evoked NK(3) receptors plasticity might reflect dendritic internalization and translocation of NK(3) receptors toward the soma and nucleus. This trafficking is not observed in non-dopaminergic neurons of the VTA. The selective apomorphine-evoked redistribution of VTA NK(3) receptors might have important implications in normal or pathological conditions such as schizophrenia. Misono K, Lessard A. Apomorphine-evoked redistribution of neurokinin-3 receptors in dopaminergic dendrites and neuronal nuclei of the rat ventral tegmental area. Neuroscience. 2012 Feb 17; 203: 27-38. Epub 2011 Dec 22.

**Estradiol Acts Via Estrogen Receptors Alpha And Beta On Pathways Important For Synaptic Plasticity In The Mouse Hippocampal Formation** Estradiol affects hippocampal-dependent spatial memory and underlying structural and electrical synaptic plasticity in female mice and rats. Using estrogen receptor (ER) alpha and beta knockout mice and wild-type littermates, the authors investigated the role of ERs in estradiol effects on multiple pathways important for hippocampal plasticity and learning. Six hours of estradiol administration increased immunoreactivity for phosphorylated Akt throughout the hippocampal formation, whereas 48 h of estradiol increased immunoreactivity for phosphorylated TrkB receptor. Estradiol effects on phosphorylated Akt and TrkB immunoreactivities were abolished in ER alpha and ER beta knockout mice. Estradiol also had distinct effects on immunoreactivity for post-synaptic density 95 (PSD-95) and brain derived-neurotrophic factor (BDNF) mRNA in ER alpha and beta knockout mice. Thus, estradiol acts through both ERs alpha and beta in several subregions of the hippocampal formation. The different effects of estradiol at 6 and 48 h indicate that several mechanisms of estrogen receptor signaling contribute to this female hormone's influence on hippocampal synaptic plasticity. By further delineating these mechanisms, we will better understand and predict the effects of endogenous and exogenous ovarian steroids on mood, cognition, and other hippocampal-dependent behaviors. Spencer-Segal JL, Tsuda MC, Mattei L, Waters EM, Romeo RD, Milner TA, McEwen BS, Ogawa S. Neuroscience. 2012 Jan 27; 202: 131-146. Epub 2011 Nov 23.

**Prenatal Cocaine Exposure Alters Progenitor Cell Markers In The Subventricular Zone Of The Adult Rat Brain** Long-term consequences of early developmental exposure to drugs of abuse may have deleterious effects on the proliferative plasticity of the brain. The purpose of this study was to examine the long-term effects of prenatal exposure to cocaine, using the IV route of administration and doses that mimic the peak arterial levels of cocaine use in humans, on the proliferative cell types of the subventricular zones (SVZ) in the adult (180 days-old) rat brain. Employing immunocytochemistry, the expression of GFAP(+) (type B cells) and nestin(+)

(GFAP(-)) (type C and A cells) staining was quantified in the subcallosal area of the SVZ. GFAP(+) expression was significantly different between the prenatal cocaine treated group and the vehicle (saline) control group. The prenatal cocaine treated group possessed significantly lower GFAP(+) expression relative to the vehicle control group, suggesting that prenatal cocaine exposure significantly reduced the expression of type B neural stem cells of the SVZ. In addition, there was a significant sex difference in nestin(+) expression with females showing approximately 8-13% higher nestin(+) expression compared to the males. More importantly, a significant prenatal treatment condition (prenatal cocaine, control) by sex interaction in nestin(+) expression was confirmed, indicating different effects of cocaine based on sex of the animal. Specifically, prenatal cocaine exposure eliminated the basal difference between the sexes. Collectively, the present findings suggest that prenatal exposure to cocaine, when delivered via a protocol designed to capture prominent features of recreational usage, can selectively alter the major proliferative cell types in the subcallosal area of the SVZ in an adult rat brain, and does so differently for males and females. Patel DA, Booze RM, Mactutus CF. Prenatal cocaine exposure alters progenitor cell markers in the subventricular zone of the adult rat brain. Int J Dev Neurosci. 2012 Feb; 30(1): 1-9. Epub 2011 Nov 17.

**Methamphetamine Self-Administration Causes Persistent Striatal Dopaminergic Alterations And Mitigates The Deficits Caused By A Subsequent Methamphetamine Exposure** Preclinical studies have demonstrated that repeated methamphetamine (METH) injections (referred to herein as a "binge" treatment) cause persistent dopaminergic deficits. A few studies have also examined the persistent neurochemical impact of METH self-administration in rats, but with variable results. These latter studies are important because: 1) they have relevance to the study of METH abuse; and 2) the effects of noncontingent METH treatment do not necessarily predict effects of contingent exposure. Accordingly, the present study investigated the impact of METH self-administration on dopaminergic neuronal function. Results revealed that self-administration of METH, given according to a regimen that produces brain METH levels comparable with those reported postmortem in human METH abusers (0.06 mg/infusion; 8-h sessions for 7 days), decreased striatal dopamine transporter (DAT) uptake and/or immunoreactivity as assessed 8 or 30 days after the last self-administration session. Increasing the METH dose per infusion did not exacerbate these deficits. These deficits were similar in magnitude to decreases in DAT densities reported in imaging studies of abstinent METH abusers. It is noteworthy that METH self-administration mitigated the persistent deficits in dopaminergic neuronal function, as well as the increases in glial fibrillary acidic protein immunoreactivity, caused by a subsequent binge METH exposure. This protection was independent of alterations in METH pharmacokinetics, but may have been attributable (at least in part) to a pretreatment-induced attenuation of binge-induced hyperthermia. Taken together, these results may provide insight into the neurochemical deficits reported in human METH abusers. McFadden LM, Hadlock GC, Allen SC, Vieira-Brock PL, Stout KA, Ellis JD, Hoonakker AJ, Andrenyak DM, Nielsen SM, Wilkins DG, Hanson GR, Fleckenstein AE. Methamphetamine self-administration causes persistent striatal dopaminergic alterations and mitigates the deficits caused by a subsequent methamphetamine exposure. J Pharmacol Exp Ther. 2012 Feb; 340(2): 295-303. Epub 2011 Oct 27.

**Corticotropin-Releasing Factor In The Norepinephrine Nucleus, Locus Coeruleus, Facilitates Behavioral Flexibility** Corticotropin-releasing factor (CRF), the stress-related neuropeptide, acts as a neurotransmitter in the brain norepinephrine nucleus, locus coeruleus (LC), to activate this system during stress. CRF shifts the mode of LC discharge from a phasic to a high tonic state that is thought to promote behavioral flexibility. To investigate this, the effects of CRF administered either intracerebroventricularly (30-300 ng, i.c.v.) or directly into the LC (intra-LC; 2-20 ng) were examined in a rat model of attentional set shifting. CRF differentially affected components of the task depending on dose and route of administration. Intracerebroventricular CRF impaired intradimensional set shifting, reversal learning, and extradimensional set shifting (EDS) at different doses. In contrast, intra-LC CRF did not impair any aspect of the task. The highest dose of CRF (20 ng) facilitated reversal learning and the lowest dose (2 ng) improved EDS. The dose-response relationship for CRF on EDS performance resembled an inverted U-shaped curve with the highest dose having no effect. Intra-LC CRF also elicited c-fos expression in prefrontal cortical neurons with an inverted U-shaped dose-response relationship. The number of c-fos profiles was positively correlated with EDS performance. Given that CRF excites LC neurons, the ability of intra-LC CRF to activate prefrontal cortical neurons and facilitate EDS is consistent with findings implicating LC-norepinephrine projections to medial prefrontal cortex in this process. Importantly, the results suggest that CRF release in the LC during stress facilitates shifting of attention between diverse stimuli in a dynamic environment so that the organism can adapt an optimal strategy for coping with the challenge. Snyder K, Wang WW, Han R, McFadden K, Valentino RJ. Corticotropin-releasing factor in the norepinephrine nucleus, locus coeruleus, facilitates behavioral flexibility. Neuropsychopharmacology. 2012 Jan; 37(2): 520-530. doi: 10.1038/npp.2011.218. Epub 2011 Oct 12.

**Influence Of Estradiol On Functional Brain Organization For Working Memory** Working memory is a cognitive function that is affected by aging and disease. To better understand the neural substrates for working memory, the present study examined the influence of estradiol on working memory using functional magnetic resonance imaging. Pre-menopausal women were tested on a verbal n-back task during the early (EF) and late follicular (LF) phases of the menstrual cycle. Although brain activation patterns were similar across the two phases, the most striking pattern that emerged was that estradiol had different associations with the two hemispheres. Increased activation in left frontal circuitry in the LF phase was associated with increased estradiol levels and decrements in working memory performance. In contrast, increased activation in right hemisphere regions in the LF phase was associated with improved task performance. The present study showed that better performance in the LF than the EF phase was associated with a pattern of reduced recruitment of the left-hemisphere and increased recruitment of the right-hemisphere in the LF compared to EF phase. The authors speculate that estradiol interferes with left-hemisphere working-memory processing in the LF phase, but that recruitment of the right hemisphere can compensate for left-hemisphere interference. This may be related to the proposal that estradiol can reduce cerebral asymmetries by modulating transcallosal communication (Hausmann, 2005). Joseph JE, Swearingen JE, Corbly CR, Curry TE Jr, Kelly TH. Influence of estradiol on functional brain organization for working memory. Neuroimage. 2012 Feb 1; 59(3): 2923-2931. Epub 2011 Oct 1.

**A Common Single Nucleotide Polymorphism A118G Of The M Opioid Receptor Alters Its N-Glycosylation And Protein Stability** The A118G SNP (single nucleotide polymorphism) of the hMOPR [human MOPR (μ opioid receptor)] gene OPRM1 results in an amino acid substitution (N40D). Subjects homozygous for the 118G allele have been reported to require higher morphine doses to achieve adequate analgesia, and the 118G allele is more prevalent among drug abusers. However, changes in the MOPR protein associated with this SNP are unknown. Using a knockin mouse model (G/G mice; mice homozygous for the 112G allele of MOPR) that possesses the equivalent nucleotide/amino acid substitution (A112G; N38D) of the A118G SNP in the hMOPR gene, the authors investigated the N-linked glycosylation status of thalamic and striatal MOPR in G/G mice compared with A/A mice (wild-type mice homozygous for the 112A allele of MOPR). The molecular mass of MOPR determined by immunoblotting was lower in G/G mice than in A/A mice. Following treatment with peptide N-glycosidase F, which removes all N-linked glycans, both MOPR variants had an identical molecular mass, indicating that this discrepancy was due to a lower level of N-glycosylation of the MOPR in G/G mice. In Chinese-hamster ovary cells stably expressing hMOPRs, 118G/Asp40-hMOPR had a lower molecular mass than 118A/Asn40-hMOPR, which was similarly due to differential N-glycosylation. Pulse-chase studies revealed that the half-life of the mature form of 118G/Asp40-hMOPR (~12 h) was shorter than that of 118A/Asn40-hMOPR (~28 h). Thus the A118G SNP reduces MOPR N-glycosylation and protein stability. Huang P, Chen C, Mague SD, Blendy JA, Liu-Chen LY. A common single nucleotide polymorphism A118G of the μ opioid receptor alters its N-glycosylation and protein stability. Biochem J. 2012 Jan 1; 441(1): 379-386.

**Acetylcholine α7 Nicotinic And Dopamine D(2) Receptors Are Targeted To Many Of The Same Postsynaptic Dendrites And Astrocytes In The Rodent Prefrontal Cortex** The alpha-7 nicotinic acetylcholine receptor (α7nAChR) and the dopamine D(2) receptor (D(2) R) are both implicated in attentional processes and cognition, mediated in part through the prefrontal cortex (PFC). The authors examined the dual electron microscopic immunolabeling of α7nAChR and either D(2) R or the vesicular acetylcholine transporter (VAChT) in rodent PFC to assess convergent functional activation sites. Immunoreactivity (ir) for α7nAChR and/or D(2) R was seen in the same as well as separate neuronal and glial profiles. At least half of the dually labeled profiles were somata and dendrites, while most labeled axon terminals expressed only D(2) R-ir. The D(2) R-labeled terminals were without synaptic specializations or formed inhibitory or excitatory-type synapses with somatodendritic profiles, some of which expressed the α7nAChR and/or D(2) R. Astrocytic glial processes comprised the majority of nonsomatodendritic α7nAChR or α7nAChR and D(2) R-labeled profiles. Glial processes containing α7nAChR-ir were frequently located near VAChT-labeled terminals and also showed perisynaptic and perivascular associations. The authors conclude that in rodent PFC α7nACh and D(2) R activation can dually modulate (1) postsynaptic dendritic responses within the same or separate but synaptically linked neurons in which the D(2) R has the predominately presynaptic distribution, and (2) astrocytic signaling that may be crucial for synaptic transmission and functional hyperemia. Duffy AM, Fitzgerald ML, Chan J, Robinson DC, Milner TA, Mackie K, Pickel VM. Acetylcholine α7 nicotinic and dopamine D(2) receptors are targeted to many of the same postsynaptic dendrites and astrocytes in the rodent prefrontal cortex. Synapse. 2011 Dec; 65(12): 1350-1367. doi: 10.1002/syn.20977.

**Meal Schedule Influences Food Restriction-Induced Locomotor Sensitization To Methamphetamine** Traditional protocols for inducing sensitization to psychostimulants use an intermittent or "binge"-like drug administration, and binge eating behavior is comorbid with drug abuse in humans. Food restriction increases the reinforcing properties and self-administration of many drugs of abuse. The present study tested the hypotheses that (1) food restriction induces sensitization to the locomotor stimulation observed in response to methamphetamine and (2) a binge-like feeding schedule during food restriction produces increased sensitization compared to equally restricted mice fed in three daily meals. Male DBA/2J mice were fed ad libitum or were food restricted to either an 8% or 16% loss of body weight. Additionally, the food-restricted mice were divided into two groups that were fed in either one meal (binge) or three equal-sized meals (meal). After the reduced body weight was stable, mice were tested for locomotor activity following saline and methamphetamine (1 mg/kg) injections. Both 16% body weight loss groups exhibited sensitization to methamphetamine. Opposite to the authors' hypothesis, the 8% meal but not the 8% binge food-restricted group demonstrated locomotor sensitization. Serum corticosterone levels were significantly higher in the meal-fed groups when compared to the binge- and ad libitum-fed groups. These results support a role for feeding schedule and plasma corticosterone levels in food restriction-induced enhancement of the effects of methamphetamine. Sharpe AL, Klaus JD, Beckstead MJ. Meal schedule influences food restriction-induced locomotor sensitization to methamphetamine. Psychopharmacology (Berl). 2012 Feb; 219(3): 795-803.

**Cannabinoids Inhibit Migration Of Microglial-Like Cells To The HIV Protein Tat** Microglia are a population of macrophage-like cells in the central nervous system (CNS) which, upon infection by the human immunodeficiency virus (HIV), secrete a plethora of inflammatory factors, including the virus-specified trans-activating protein Tat. Tat has been implicated in HIV neuropathogenesis since it elicits chemokines, cytokines, and a chemotactic response from microglia. It also harbors a β-chemokine receptor binding motif, articulating a mode by which it acts as a migration stimulus. Since select cannabinoids have anti-inflammatory properties, cross the blood-brain barrier, and target specific receptors, they have potential to serve as agents for dampening untoward neuroimmune responses. The aim of this study was to investigate the effect of select cannabinoids on the migration of microglial-like cells toward Tat. Using a mouse BV-2 microglial-like cell model, it was demonstrated that the exogenous cannabinoids Delta-9-tetrahydrocannabinol (THC) and CP55940 exerted a concentration-related reduction in the migration of BV-2 cells towards Tat. A similar inhibitory response was obtained when the endogenous cannabinoid 2-arachidonoylglycerol (2-AG) was used. The CB(2) receptor (CB2R) antagonist SR144528, but not the CB(1) receptor (CB1R) antagonist SR141716A, blocked this inhibition of migration. Similarly, CB2R knockdown with small interfering RNA reversed the cannabinoid-mediated inhibition. In addition, the level of the β-chemokine receptor CCR-3 was reduced and its intracellular compartmentation was altered. These results indicate that cannabinoid-mediated inhibition of BV-2 microglial-like cell migration to Tat is linked functionally to the CB2R. Furthermore, the results indicate that activation of the CB2R leads to altered expression and compartmentation of the β-chemokine receptor CCR-3. Fraga D, Raborn ES, Ferreira GA, Cabral GA. Cannabinoids inhibit migration of microglial-like cells to the HIV protein Tat. J Neuroimmune Pharmacol. 2011 Dec; 6(4): 566-577. Epub 2011 Jul 7.

**Alterations In AMPA Receptor Subunits And Tarps In The Rat Nucleus Accumbens Related To The Formation Of $Ca^{2+}$-Permeable AMPA Receptors During The Incubation Of Cocaine Craving** Cue-induced cocaine seeking intensifies or incubates after withdrawal from extended access cocaine self-administration, a phenomenon termed incubation of cocaine craving. The expression of incubated craving is mediated by $Ca^{2+}$-permeable AMPA receptors (CP-AMPARs) in the nucleus accumbens (NAc). Thus, CP-AMPARs are a potential target for therapeutic intervention, making it important to understand mechanisms that govern their accumulation. Here the authors used subcellular fractionation and biotinylation of NAc tissue to examine the abundance and distribution of AMPAR subunits, and GluA1 phosphorylation, in the incubation model. They also studied two transmembrane AMPA receptor regulatory proteins (TARPs), γ-2 and γ-4. Their results, together with earlier findings, suggest that some of the new CP-AMPARs are synaptic. These are probably associated with γ-2, but they are loosely tethered to the PSD. Levels of GluA1 phosphorylated at serine 845 (pS845 GluA1) were significantly increased in biotinylated tissue and in an extrasynaptic membrane-enriched fraction. These results suggest that increased synaptic levels of CP-AMPARs may result in part from an increase in pS845 GluA1 in extrasynaptic membranes, given that S845 phosphorylation primes GluA1-containing AMPARs for synaptic insertion and extrasynaptic AMPARs supply the synapse. Some of the new extrasynaptic CP-AMPARs are likely associated with γ-4, rather than γ-2. The maintenance of CP-AMPARs in NAc synapses during withdrawal is accompanied by activation of CaMKII and ERK2 but not CaMKI. Overall, AMPAR plasticity in the incubation model shares some features with better described forms of synaptic plasticity, although the timing of the phenomenon and the persistence of related neuroadaptations are significantly different. Ferrario CR, Loweth JA, Milovanovic M, Ford KA, Galiñanes GL, Heng LJ, Tseng KY, Wolf ME. Alterations in AMPA receptor subunits and TARPs in the rat nucleus accumbens related to the formation of $Ca^{2+}$-permeable AMPA receptors during the incubation of cocaine craving. Neuropharmacology. 2011 Dec; 61(7): 1141-1151. Epub 2011 Jan 27.

**Differential Dopamine Release Dynamics In The Nucleus Accumbens Core And Shell Track Distinct Aspects Of Goal-Directed Behavior For Sucrose** Mesolimbic dopamine projections to the nucleus accumbens (NAc) have been implicated in goal-directed behaviors for natural rewards and in learning processes involving cue-reward associations. The NAc has been traditionally subdivided into two anatomically distinct sub-regions with different functional properties: the shell and the core. The aim of the present study was to characterize rapid dopamine transmission across the two NAc sub-regions during cue-signaled operant behavior for a natural (sucrose) reward in rats. Using fast-scan cyclic voltammetry (FSCV) the authors observed differences in the magnitude and dynamics of dopamine release events between the shell and core. Specifically, although cue-evoked dopamine release was observed in both sub-regions, it was larger and longer lasting in the shell compared with the core. Further, secondary dopamine release events were observed following the lever press response for sucrose in the NAc shell, but not the core. These findings demonstrate that the NAc displays regional specificity in dopamine transmission patterns during cued operant behavior for natural reward. Cacciapaglia F, Saddoris MP, Wightman RM, Carelli RM. Differential dopamine release dynamics in the nucleus accumbens core and shell track distinct aspects of goal-directed behavior for sucrose. Neuropharmacology. 2012 Apr; 62(5-6): 2050-2056. Epub 2012 Jan 12.

**Plasticity Of Mouse Enteric Synapses Mediated Through Endocannabinoid And Purinergic Signaling** The enteric nervous system (ENS) possesses extensive synaptic connections which integrate information and provide appropriate outputs to coordinate the activity of the gastrointestinal tract. The regulation of enteric synapses is not well understood. Cannabinoid (CB)(1) receptors inhibit the release of acetylcholine (ACh) in the ENS, but their role in the synapse is not understood. The authors tested the hypothesis that enteric CB(1) receptors provide inhibitory control of excitatory neurotransmission in the ENS. Intracellular microelectrode recordings were obtained from mouse myenteric plexus neurons. Interganglionic fibers were stimulated with a concentric stimulating electrode to elicit synaptic events on to the recorded neuron. Differences between spontaneous and evoked fast synaptic transmission was examined within preparations from CB(1) deficient mice (CB(1)(-/-)) and wild-type (WT) littermate controls. Cannabinoid receptors were colocalized on terminals expressing the vesicular ACh transporter and the synaptic protein synaptotagmin. A greater proportion of CB(1)(-/-) neurons received spontaneous fast excitatory postsynaptic potentials than neurons from WT preparations. The CB(1) agonist WIN55,212 depressed WT synapses without any effect on CB(1)(-/-) synapses. Synaptic activity in response to depolarization was markedly enhanced at CB(1)(-/-) synapses and after treatment with a CB(1) antagonist in WT preparations. Activity-dependent liberation of a retrograde purine messenger was demonstrated to facilitate synaptic transmission in CB(1)(-/-) mice. Cannabinoid receptors inhibit transmitter release at enteric synapses and depress synaptic strength basally and in an activity-dependent manner. These actions help explain accelerated intestinal transit observed in the absence of CB(1) receptors. Hons IM, Storr MA, Mackie K, Lutz B, Pittman QJ, Mawe GM, Sharkey KA. Plasticity of mouse enteric synapses mediated through endocannabinoid and purinergic signaling. Neurogastroenterol Motil. 2012 Mar; 24(3): e113-124. doi: 10.1111/j.1365-2982.2011.01860.x.

**Riluzole And Gabapentinoids Activate Glutamate Transporters To Facilitate Glutamate-Induced Glutamate Release From Cultured Astrocytes** The authors have recently demonstrated that the glutamate transporter activator riluzole paradoxically enhanced glutamate-induced glutamate release from cultured astrocytes. They further showed that both riluzole and the α(2)δ subunit ligand gabapentin activated descending inhibition in rats by increasing glutamate receptor signaling in the locus coeruleus and hypothesized that these drugs share common mechanisms to enhance glutamate release from astrocytes. In the present study, they examined the effects of riluzole and gabapentin on glutamate uptake and release and glutamate-induced Ca(2+) responses in primary cultures of astrocytes. Riluzole and gabapentin facilitated glutamate-induced glutamate release from astrocytes and significantly increased glutamate uptake, the latter being completely blocked by the non-selective glutamate transporter blocker DL-threo-β-benzyloxyaspartic acid (DL-TBOA). Riluzole and gabapentin also enhanced the glutamate-induced increase in intracellular Ca(2+) concentrations. Some α(2)δ subunit ligands, pregabalin and L-isoleucine, enhanced the glutamate-induced Ca(2+) response, whereas another, 3-exo-aminobicyclo[2.2.1]heptane-2-exo-carboxylic acid (ABHCA), did not. The enhancement of glutamate-induced intracellular Ca(2+) response by riluzole and gabapentin was blocked by the DL-TBOA and an inhibitor of Na(+)/Ca(2+) exchange, 2-[2-[4-(4-nitrobenzyloxy) phenyl]ethyl]isothiurea (KB-R7943). Gabapentin's enhancement of Ca(2+) increase was specific to glutamate stimulation, as it was not mimicked with stimulation by ATP. These results suggest that riluzole and gabapentin enhance Na(+)-glutamate co-transport through glutamate transporters, induce subsequent Ca(2+) influx via the reverse mode of Na(+)/Ca(2+) exchange,

and thereby facilitate Ca(2+)-dependent glutamate release by glutamate in astrocytes. The present study also demonstrates a novel target of gabapentinoid action in astrocytes other than α(2)δ subunits in neurons. Yoshizumi M, Eisenach JC, Hayashida K. Riluzole and gabapentinoids activate glutamate transporters to facilitate glutamate-induced glutamate release from cultured astrocytes. Eur J Pharmacol. 2012 Feb 29; 677(1-3): 87-92. Epub 2011 Dec 21.

**Depletion Of Endogenous Noradrenaline Does Not Prevent Spinal Cord Plasticity Following Peripheral Nerve Injury** The present study examined the role of endogenous noradrenaline on glial and neuronal plasticity in the spinal cord in rats after peripheral nerve injury. An intrathecal injection of dopamine-β-hydroxylase antibody conjugated to saporin (DβH-saporin) completely depleted noradrenergic axons in the spinal cord and also reduced noradrenergic neurons in the locus coeruleus (A6) and A5 noradrenergic nucleus in the brainstem and noradrenergic axons in the paraventricular nucleus of the hypothalamus. DβH-saporin treatment itself did not alter mechanical withdrawal threshold, but enhanced mechanical hypersensitivity and intrathecal clonidine analgesia after L5-L6 spinal nerve ligation. In the spinal dorsal horn of spinal nerve ligation rats, DβH-saporin treatment increased choline acetyltransferase immunoreactivity as well as immunoreactivity in microglia of ionized calcium binding adaptor molecule 1[IBA1] and in astrocytes of glial fibrillary acidic protein, and brain-derived nerve growth factor content. DβH-saporin treatment did not, however, alter the fractional release of acetylcholine from terminals by dexmedetomidine after nerve injury. These results suggest that endogenous tone of noradrenergic fibers is not necessary for the plasticity of α2-adrenoceptor analgesia and glial activation after nerve injury, but might play an inhibitory role on glial activation. This study demonstrates that endogenous noradrenaline modulates plasticity of glia and cholinergic neurons in the spinal cord after peripheral nerve injury and hence influences the pathophysiology of spinal cord changes associated with neuropathic pain. Hayashida K, Peters CM, Gutierrez S, Eisenach JC. Depletion of endogenous noradrenaline does not prevent spinal cord plasticity following peripheral nerve injury. J Pain. 2012 Jan; 13(1): 49-57. Epub 2011 Dec 11.

**Regulation Of Neuronal Ferritin Heavy Chain, A New Player In Opiate-Induced Chemokine Dysfunction** The heavy chain subunit of ferritin (FHC), a ubiquitous protein best known for its iron-sequestering activity as part of the ferritin complex, has recently been described as a novel inhibitor of signaling through the chemokine receptor CXCR4. Levels of FHC as well as its effects on CXCR4 activation increase in cortical neurons exposed to mu-opioid receptor agonists such as morphine, an effect likely specific to neurons. Major actions of CXCR4 signaling in the mature brain include a promotion of neurogenesis, activation of pro-survival signals, and modulation of excitotoxic pathways; thus, FHC up-regulation may contribute to the neuronal dysfunction often associated with opiate drug abuse. This review summarizes our knowledge of neuronal CXCR4 function, its regulation by opiates and the role of FHC in this process, and known mechanisms controlling FHC production. The authors speculate on the mechanism involved in FHC regulation by opiates and offer FHC as a new target in opioid-induced neuropathology. Abt AC, Meucci O. Regulation of neuronal ferritin heavy chain, a new player in opiate-induced chemokine dysfunction. J Neuroimmune Pharmacol. 2011 Dec; 6(4): 466-476. Epub 2011 Apr 5.

**A Novel Non-CB1/TRPV1 Endocannabinoid-Mediated Mechanism Depresses Excitatory Synapses On Hippocampal CA1 Interneurons** Endocannabinoids (eCBs) mediate various forms of synaptic plasticity at excitatory and inhibitory synapses in the brain. The eCB anandamide binds to several receptors including the transient receptor potential vanilloid 1 (TRPV1) and cannabinoid receptor 1 (CB1). The authors recently identified that TRPV1 is required for long-term depression at excitatory synapses on CA1 hippocampal stratum radiatum interneurons. Here they performed whole-cell patch clamp recordings from CA1 stratum radiatum interneurons in rat brain slices to investigate the effect of the eCB anandamide on excitatory synapses as well as the involvement of Group I metabotropic glutamate receptors (mGluRs), which have been reported to produce eCBs endogenously. Application of the nonhydrolysable anandamide analog R-methanandamide depressed excitatory transmission to CA1 stratum radiatum interneurons by ~50%. The Group I mGluR agonist DHPG also depressed excitatory glutamatergic transmission onto interneurons to a similar degree, and this depression was blocked by the mGluR5 antagonist MPEP (10 μM) but not by the mGluR1 antagonist CPCCOEt (50 μM). Interestingly, however, neither DHPG-mediated nor R-methanandamide-mediated depression was blocked by the TRPV1 antagonist capsazepine (10 μM), the CB1 antagonist AM-251 (2 μM) or a combination of both, suggesting the presence of a novel eCB receptor or anandamide target at excitatory hippocampal synapses. DHPG also occluded R-methanandamide depression, suggesting the possibility that the two drugs elicit synaptic depression via a shared signaling mechanism. Collectively, this study illustrates a novel CB1/TRPV1-independent eCB pathway present in the hippocampus that mediates depression at excitatory synapses on CA1 stratum radiatum interneurons. Edwards JG, Gibson HE, Jensen T, Nugent F, Walther C, Blickenstaff J, Kauer JA. A novel non-CB1/TRPV1 endocannabinoid-mediated mechanism depresses excitatory synapses on hippocampal CA1 interneurons. Hippocampus. 2012 Feb; 22(2): 209-221. doi: 10.1002/hipo.20884. Epub 2010 Nov 10.

**Anabolic Androgenic Steroid Abuse: Multiple Mechanisms Of Regulation Of GABAergic Synapses In Neuroendocrine Control Regions Of The Rodent Forebrain** Anabolic androgenic steroids (AAS) are synthetic derivatives of testosterone originally developed for clinical purposes but are now predominantly taken at suprapharmacological levels as drugs of abuse. To date, almost 100 different AAS compounds that vary in metabolic fate and physiological effects have been designed and synthesised. Although they are administered for their ability to enhance muscle mass and performance, untoward side effects of AAS use include changes in reproductive and sexual behaviours. Specifically, AAS, depending on the type of compound administered, can delay or advance pubertal onset, lead to irregular oestrous cyclicity, diminish male and female sexual behaviours, and accelerate reproductive senescence. Numerous brains regions and neurotransmitter signalling systems are involved in the generation of these behaviours, and are potential targets for both chronic and acute actions of the AAS. However, critical to all of these behaviours is neurotransmission mediated by GABA(A) receptors within a nexus of interconnected forebrain regions that includes the medial preoptic area, the anteroventral periventricular nucleus and the arcuate nucleus of the hypothalamus. The authors review how exposure to AAS alters GABAergic transmission and neural activity within these forebrain regions, taking advantage of in vitro systems and both wild-type and genetically altered mouse strains, aiming to better understand how these synthetic steroids affect the neural systems that underlie the regulation of reproduction and the expression of sexual behaviours. Oberlander JG, Porter DM, Penatti CA, Henderson LP. Anabolic androgenic steroid abuse: multiple

mechanisms of regulation of GABAergic synapses in neuroendocrine control regions of the rodent forebrain. J Neuroendocrinol. 2012 Jan; 24(1): 202-214. doi: 10.1111/j.1365-2826.2011.02151.x.

**Dopamine Receptor Blockade Attenuates The General Incentive Motivational Effects Of Noncontingently Delivered Rewards And Reward-Paired Cues Without Affecting Their Ability To Bias Action Selection** Environmental cues affect our behavior in a variety of ways. Despite playing an invaluable role in guiding our daily activities, such cues also appear to trigger the harmful, compulsive behaviors that characterize addiction and other disorders of behavioral control. In instrumental conditioning, rewards and reward-paired cues bias action selection and invigorate reward-seeking behaviors, and appear to do so through distinct neurobehavioral processes. Although reward-paired cues are known to invigorate performance through a dopamine-dependent incentive motivational process, it is not known if dopamine also mediates the influence of rewards and reward-paired cues over action selection. The current study contrasted the effects of systemic administration of the nonspecific dopamine receptor antagonist flupentixol on response invigoration and action bias in Pavlovian-instrumental transfer, a test of cue-elicited responding, and in instrumental reinstatement, a test of noncontingent reward-elicited responding. Hungry rats were trained on two different stimulus-outcome relationships (eg, tone-grain pellets and noise-sucrose solution) and two different action-outcome relationships (eg, left press-grain and right press-sucrose). At test, the authors found that flupentixol pretreatment blocked the response invigoration generated by the cues but spared their ability to bias action selection to favor the action whose outcome was signaled by the cue being presented. The response-biasing influence of noncontingent reward deliveries was also unaffected by flupentixol. Interestingly, although flupentixol had a modest effect on the immediate response invigoration produced by those rewards, it was particularly potent in countering the lingering enhancement of responding produced by multiple reward deliveries. These findings indicate that dopamine mediates the general incentive motivational effects of noncontingent rewards and reward-paired cues but does not support their ability to bias action selection. Ostlund SB, Maidment NT. Dopamine receptor blockade attenuates the general incentive motivational effects of noncontingently delivered rewards and reward-paired cues without affecting their ability to bias action selection. Neuropsychopharmacology. 2012 Jan; 37(2): 508-519. doi: 10.1038/npp.2011.217. Epub 2011 Sep 14.

**Withdrawal From Chronic Nicotine Exposure Alters Dopamine Signaling Dynamics In The Nucleus Accumbens** Unaided attempts to quit smoking commonly fail during the first 2 weeks of the nicotine withdrawal syndrome. Alterations in dopamine (DA) signaling correlate with withdrawal from chronic nicotine exposure, but those changes have not been well-characterized. Mice were administered nicotine in their drinking water for 4 or 12 weeks. Then nicotine was withheld for 1 to 10 days while DA signaling was characterized with in vivo microdialysis or fast-scan cyclic voltammetry. Upon withdrawal of nicotine, the basal DA concentration in the nucleus accumbens decreased as measured by microdialysis. The length of time that the low basal DA state lasted depended on the length of the chronic nicotine treatment. Microdialysis indicated that acute re-exposure to nicotine during withdrawal temporarily reversed this hypodopaminergic state. Voltammetry measurements supported the microdialysis results by showing that nicotine withdrawal decreased tonic and phasic DA release. The basal DA concentration and tonic DA signals, however, were disproportionately lower than the phasic

DA signals. Therefore, the phasic/tonic DA signaling ratio was increased during the withdrawal period. The relative increase in the sensitivity of DA release to phasic stimulation suggests an increase in the signal-to-noise relationship of DA signaling during the withdrawal period. Therefore, the DA signal produced by acute nicotine re-exposure produces a DA response that might reinforce relapse to drug use (i.e., smoking). Because the basal DA concentration is low during withdrawal, therapies aimed at elevating the background DA signal represent a reasonable treatment strategy for nicotine-dependent individuals attempting to quit. Zhang L, Dong Y, Doyon WM, Dani JA. Withdrawal from chronic nicotine exposure alters dopamine signaling dynamics in the nucleus accumbens. Biol Psychiatry. 2012 Feb 1; 71(3): 184-191.

## BEHAVIORAL AND COGNITIVE NEUROSCIENCES RESEARCH

**Substance Use After Participation In Laboratory Studies Involving Smoked Cocaine Self-Administration** Laboratory studies in which drugs of abuse are self- or experimenter-administered to non-treatment-seeking research volunteers provide valuable data about new pharmacotherapies for substance use disorders, as well as behavioral and performance data for understanding the neurobiology of drug abuse. This paper analyzed follow-up data from six smoked cocaine self-administration laboratory studies, in order to determine whether changes in substance use occurred 1 and 3 months after study participation compared to pre-study baseline. Ninety-eight healthy, non-treatment-seeking cocaine users were admitted to inpatient and combined inpatient/outpatient studies lasting from 12 to 105 days. The studies allowed participants to self-administer repeated doses of smoked cocaine (0, 6, 12, 25, and/or 50mg per dose) on multiple occasions. Participants returned for follow-up at 1 and 3 months, at which time self-reported consumption of cocaine, alcohol, marijuana, and nicotine was assessed. Compared to baseline ($374.04/week, S.D. $350.09), cocaine use significantly decreased at 1 month ($165.13/week, S.D. $165.56) and 3 months ($118.59/week, S.D. $110.48) after study participation ($p<0.001$; results based on the 39 participants who completed all 3 time points). This decrease was not accompanied by a change in other drug use, e.g., a compensatory increase in alcohol, marijuana or nicotine use. Study participation was not associated with increased post-study cocaine, alcohol, marijuana, or nicotine use. Thus, human laboratory models of cocaine self-administration, conducted in non-treatment-seeking research volunteers, are relatively safe, and study participation does not exacerbate ongoing drug use. Kalapatapu RK, Bedi G, Haney M, Evans SM, Rubin E, Foltin RW. Drug Alcohol Depend. 2012 Jan 1;120(1-3):162-167. http://www.ncbi.nlm.nih.gov/pubmed/21840650

**Delay Discounting In Rhesus Monkeys: Equivalent Discounting Of More And Less Preferred Sucrose Concentrations** Humans discount larger amounts of a delayed reinforcer less steeply than smaller amounts, but studies with pigeons and rats have yet to reveal such a magnitude effect, suggesting that the effect may be unique to humans. The present study examined whether the magnitude effect is observed in a species phylogenetically closer to humans, by comparing the rates at which rhesus monkeys discounted 10% and 20% concentrations of sucrose. There were no systematic differences in the rates at which the monkeys discounted the two sucrose concentrations, despite the fact that they strongly preferred the 20% concentration. Interestingly, the monkeys discounted delayed sucrose at a rate higher than was observed with delayed cocaine, and lower than was observed with delayed saccharin in previous studies (Freeman et al. Behavioural Processes, 82, 214-218, 2009; Woolverton et al. Experimental and Clinical Psychopharmacology, 15, 238-244, 2007). Taken together, these findings suggest that although both quantitative and qualitative differences can affect monkeys' preferences between immediate reinforcers, qualitative differences between types of reinforcers (e.g., sucrose vs. cocaine) can affect monkeys' discounting rates in a way that quantitative differences within a reinforcer (e.g., 10% vs. 20% sucrose) do not. Freeman KB, Nonnemacher JE, Green L, Myerson J, Woolverton WL. Learn Behav. 2012 Mar;40(1):54-60. http://www.ncbi.nlm.nih.gov/pubmed/21870212

**Increased Intra-Individual Reaction Time Variability In Cocaine-Dependent Subjects: Role Of Cocaine-Related Cues** Neuroimaging data suggest that impaired performance on response inhibition and information processing tests in cocaine-dependent subjects is related to prefrontal and frontal cortical dysfunction and that dysfunction in these brain areas may underlie some aspects of cocaine addiction. In subjects with attention-deficit hyperactivity disorder and other psychiatric disorders, the Intra-Individual Reaction Time Variability (IIRTV) has been associated with frontal cortical dysfunction. In the present study, we evaluated IIRTV parameters in cocaine-dependent subjects vs. controls using a cocaine Stroop task. Fifty control and 123 cocaine-dependent subjects compiled from three studies completed a cocaine Stroop task. Standard deviation (SD) and coefficient of variation (CV) for reaction times (RT) were calculated for both trials with neutral and trials with cocaine-related words. The parameters mu, sigma, and tau were calculated using an ex-Gaussian analysis employed to characterize variability in RTs. The ex-Gaussian analysis divides the RTs into normal (mu, sigma) and exponential (tau) components. Using robust regression analysis, cocaine-dependent subjects showed greater SD, CV and Tau on trials with cocaine-related words compared to controls ($p<0.05$). However, in trials with neutral words, there was no evidence of group differences in any IIRTV parameters ($p>0.05$). The Wilcoxon matched-pairs signed-rank test showed that for cocaine-dependent subjects, both SD and tau were larger in trials with cocaine-related words than in trials with neutral words ($p<0.05$). The observation that only cocaine-related words increased IIRTV in cocaine-dependent subjects suggests that cocaine-related stimuli might disrupt information processing subserved by prefrontal and frontal cortical circuits. Liu S, Lane SD, Schmitz JM, Green CE, Cunningham KA, Moeller FG. Addict Behav. 2012 Feb;37(2):193-197. http://www.ncbi.nlm.nih.gov/pubmed/22047976

**Effects Of The GABAB Receptor-Positive Modulators CGP7930 And Rac-BHFF In Baclofen- And In GHB-Discriminating Pigeons** In vivo effects of GABA(B) receptor-positive modulators suggest them to have therapeutic potential to treat central nervous system disorders such as anxiety and drug abuse. Although these effects are thought to be mediated by positive modulation of GABA(B) receptors, such modulation has been examined primarily in vitro. This study further examined the in vivo properties of the GABA(B) receptor-positive modulators, 2,6-di-tert-butyl-4-(3-hydroxy-2,2-dimethylpropyl) phenol (CGP7930) and (R,S)-5,7-di-tert-butyl-3-hydroxy-3-trifluoromethyl-3H-benzofuran-2-one (rac-BHFF). In pigeons discriminating baclofen from saline, γ-hydroxybutyrate (GHB) produced 100% baclofen-appropriate responding, and the GABA(B) antagonist 3-aminopropyl(dimethoxymethyl) phosphinic acid (CGP35348) blocked the effects of both drugs. CGP7930 and rac-BHFF produced at most 41% and 74% baclofen-appropriate responding, respectively, and enhanced the discriminative stimulus effects of baclofen, but not of GHB. In pigeons discriminating GHB from saline, CGP7930 and rac-BHFF produced at most 1% and 49% GHB-appropriate responding, respectively, and enhanced the effects of baclofen, but not of GHB. Enhancement of the discriminative stimulus effects of baclofen by rac-BHFF and CGP7930 is further evidence of their effectiveness as GABA(B) receptor-positive modulators in vivo. Further, lack of complete substitution of the positive modulators rac-BHFF and CGP7930 for baclofen and GHB suggests that their discriminative stimulus effects differ from those of GABA(B) receptor agonists. Finally, together with converging evidence that the GABA(B) receptor populations mediating the effects of baclofen and GHB are not identical, the present findings suggest that these populations differ in their susceptibility to positive modulatory effects. Such differences could allow for more selective

therapeutic targeting of the GABA(B) system. Koek W, France CP, Cheng K, Rice KC. J Pharmacol Exp Ther. 2012 Feb 7. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/22319197

**Parent-Adolescent Conflict Interaction And Adolescent Alcohol Use** One important factor in adolescents' development of problem alcohol use is their family environment. Yet, the mechanisms that relate parenting to youth alcohol use are not well characterized. This study employed a naturalistic laboratory-based approach to observe parenting behaviors (support, structure, criticism) and adolescents' physiological and emotional responses to parent-adolescent interactions to examine associations with adolescent alcohol use. Fifty eight 10-16year olds and their parents completed a 10minute Parent Adolescent Interaction Task (PAIT) in which they discussed a mutually highly-rated conflict topic. Parental support, structure, and criticism were coded from the interaction. Adolescents' heart rate (HR), blood pressure (BP), reported emotions, and salivary cortisol were assessed before, during, and after the interaction. Findings indicated that lower parental structure and support were associated with youth's greater diastolic BP and anger arousal in response to the PAIT. Furthermore, higher HR, systolic BP, and cortisol responses to the interaction were associated with youth's alcohol use. Findings suggest that heightened emotional and physiological responses to parent-adolescent conflict interactions in youth may be one pathway by which parenting is associated with adolescent alcohol use and risk for abuse. Chaplin TM, Sinha R, Simmons JA, Healy SM, Mayes LC, Hommer RE, Crowley MJ. Parent-adolescent conflict interactions and adolescent alcohol use. Addictive Behaviors. 2012 January 13 (Epub ahead of print].

**Escalation Of Methamphetamine Self-Administration In Adolescent And Adult Rats**
Methamphetamine (METH) use has increased substantially in the last 10 years and poses a serious health concern, especially for young populations. Drug abuse primarily begins during adolescence, when uninhibited and excessive and drug intake is a common occurrence; thus, understanding the developmental patterns of addiction during this critical period is an essential step in its prevention. In the present study, the effect of age on the vulnerability to METH abuse was examined using a rat model of bingeing (i.e., escalation). Adolescent and adult rats were compared during short (ShA, 2-h) and long-access (LgA, 6-h) to METH self-administration. On postnatal (PN) days 23 (adolescents) and 90 (adults), rats were implanted with i.v. catheters and trained to lever press for infusions of METH (0.05mg/kg) during 2-h sessions. Once the rats reached a steady rate of METH self-administration, they were divided into ShA or LgA groups and allowed to self-administer METH for 15 additional days. Results indicated that adolescent rats earned significantly more infusions than adults under the LgA condition, but the age groups did not differ during ShA. Adolescents, but not adults, also significantly increased (i.e., escalated) METH self-administration across the 15 days of testing under the LgA condition. Further analysis indicated excessive responding during infusions in the LgA METH-exposed adolescents compared to the other groups, suggesting elevated impulsivity or motivation for drug. These results demonstrate that adolescents are more vulnerable to the escalation of METH than adults during LgA. Anker JJ, Baron TR, Zlebnik NE, Carroll ME. Escalation of methamphetamine self-administration in adolescent and adult rats. Drug Alcohol Depend. 2012 Feb 1. [Epub ahead of print]

**Effects Of Progesterone On Escalation Of Intravenous Cocaine Self-Administration In Rats Selectively Bred For High Or Low Saccharin Intake** Progesterone decreases cocaine self-administration in women and in female rats. In a previous study using rats selectively bred for high (HiS) or low (LoS) saccharin intake, HiS rats escalated their cocaine intake compared with LoS rats. The authors'goal was to examine the effects of progesterone on the escalation of cocaine self-administration in HiS and LoS rats. Four groups of female rats were compared: HiS P (progesterone treated), LoS P, HiS VEH (vehicle treated), and LoS VEH. Rats were trained to self-administer 0.8 mg/kg cocaine intravenously under a fixed-ratio 1 schedule during daily short-access (ShA) 2-h sessions. Rats then self-administered three randomly-presented doses of cocaine (0.2, 0.4, and 1.6 mg/kg), and then had daily 6-h long-access (LgA) sessions with 0.4 mg/kg of cocaine for 21 days. Cocaine intake was then reassessed with the four doses under the ShA condition. Throughout the experiment, rats were treated with daily subcutaneous injections of progesterone (0.5 mg/kg) or an equal volume of vehicle 30 min before each session. During the initial ShA condition, HiS rats earned more cocaine infusions than LoS rats at all doses, and during the subsequent LgA condition, HiS rats escalated cocaine intake, whereas the LoS rats maintained a steady rate. Progesterone treatment potentiated escalation of cocaine intake in the HiS rats but had an opposite effect on LoS rats, attenuating their cocaine self-administration. Results from the post-LgA dose-response ShA condition indicated that both LoS and HiS vehicle-treated and progesterone-treated rats earned more infusions than pre-LgA, but mainly at low doses. These results suggest that genetic differences in drug abuse vulnerability contribute differentially to treatment outcomes during escalation, a critical phase of the drug abuse process. Anker JJ, Holtz NA, Carroll ME. Effects of progesterone on escalation of intravenous cocaine self-administration in rats selectively bred for high or low saccharin intake. Behav Pharmacol. 2012 Apr; 23(2): 205-210.

**Eating High Fat Chow Enhances The Locomotor-Stimulating Effects Of Cocaine In Adolescent And Adult Female Rats** Dopamine systems vary through development in a manner that can impact drugs acting on those systems. Dietary factors can also impact the effects of drugs acting on dopamine systems. This study examined whether eating high fat chow alters locomotor effects of cocaine (1-56 mg/kg) in adolescent and adult female rats. Cocaine was studied in rats (n = 6/group) with free access to standard (5.7% fat) or high fat (34.3%) chow or restricted access to high fat chow (body weight matched to rats eating standard chow). After 1 week of eating high fat chow (free or restricted access), sensitivity to cocaine was significantly increased in adolescent and adult rats, compared with rats eating standard chow. Sensitivity to cocaine was also increased in adolescent rats with restricted, but not free, access to high fat chow for 4 weeks. When adolescent and adult rats that previously ate high fat chow ate standard chow, sensitivity to cocaine returned to normal. In adolescent and adult female rats eating high fat chow, but not those eating standard chow, sensitivity to cocaine increased progressively over once weekly tests with cocaine (i.e., sensitization) in a manner that was not statistically different between adolescents and adults. These results show that eating high fat chow alters sensitivity of female rats to acutely administered cocaine and also facilitates the development of sensitization to cocaine. That the type of food consumed can increase drug effects might have relevance to vulnerability to abuse cocaine in the female population. Baladi MG, Koek W, Aumann M, Velasco F, France CP. Eating high fat chow enhances the locomotor-stimulating effects of cocaine in adolescent and adult female rats. Psychopharmacology (Berl). 2012 Mar 15. [Epub ahead of print]

**Drinking Sucrose Enhances Quinpirole-Induced Yawning In Rats** Food and drugs can activate brain dopamine systems and sensitivity to the effects of drugs acting on those systems is influenced by amount and content of food consumed. This study examined the effects of drinking sucrose on behavioral effects of the direct-acting dopamine receptor agonist quinpirole. Male Sprague-Dawley rats (n=6/group) had free access to water or 10% sucrose and quinpirole dose-response curves (yawning and hypothermia) were generated weekly for 8 weeks. Subsequently, all rats drank water for 8 weeks with quinpirole dose-response curves determined on weeks 9, 10, and 16. In rats drinking sucrose, the ascending (D3 receptor-mediated), but not descending (D2 receptor-mediated), limb of the yawning dose-response curve shifted leftward. The D3 receptor-selective antagonist PG01037 shifted the ascending limb of the dose-response curve to the right in all rats. When rats that previously drank sucrose drank water, their sensitivity to quinpirole did not return to normal. Quinpirole-induced hypothermia was not different between groups. These data show that drinking sucrose increases sensitivity to a dopamine D3, but not D2, receptor-mediated effect and that this change is long lasting. Dopamine receptors mediate the effects of many drugs and the actions of those drugs are likely impacted by dietary factors. Baladi MG, Newman AH, Thomas YM, France CP. Drinking sucrose enhances quinpirole-induced yawning in rats. Behav Pharmacol. 2011 Dec;22(8):773-8.

**Deficits In Default Mode Network Activity Preceding Error In Cocaine Dependent Individuals** Cocaine dependence is associated with cognitive deficits and altered task-related cerebral activation in cognitive performance (see Li and Sinha, 2008, for a review). Relatively little is known whether these individuals are also impaired in regional brain activation of the default mode network (DMN). The authors demonstrated previously that greater activation of the default brain regions precedes errors in a stop signal task performed by healthy controls (SST, Li et al., 2007). They seek to determine whether individuals with cocaine dependence are impaired in DMN activity, specifically activity preceding error, as compared to the healthy people. They also examine the relation to years of cocaine use. Individuals with cocaine dependence (CD, n=23) and demographics-matched healthy controls (HC, n=27) performed a SST that employed a tracking procedure to adjust the difficulty of stop trials and elicit errors approximately half of the time. Blood oxygenation level dependent (BOLD) signals of go trials preceding stop error as compared to those preceding stop success trials were extracted with generalized linear models using statistical parametric mapping. HC showed activation of bilateral precuneus and posterior cingulate cortices and ventromedial prefrontal cortex (vmPFC) preceding errors during the SST. In contrast, despite indistinguishable stop signal performance, CD did not show these error predicting activations. Furthermore, the effect size of error-preceding vmPFC activation was inversely correlated with years of cocaine use. These findings indicate DMN deficits and could potentially add to our understanding of the effects of chronic cocaine use on cerebral functions in cocaine dependence. Work to further clarify potential changes in functional connectivity and gray matter volume is warranted to understand the relevance of DMN to the pathology of cocaine misuse. Bednarski SR, Zhang S, Hong KI, Sinha R, Rounsaville BJ, Li CS. Deficits in default mode network activity preceding error in cocaine dependent individuals. Drug Alcohol Depend. 2011 Dec 15;119(3):e51-7. Epub 2011 Jun 23.

**Dopaminergic Enhancement Of Local Food-Seeking Is Under Global Homeostatic Control** Recent work has implicated dopaminergic mechanisms in overeating and obesity with some researchers suggesting parallels between the dopamine dysregulation associated with addiction and an analogous dysregulation in obesity. The precise role of dopamine in mediating reward and reinforcement, however, remains controversial. In contrast to drugs of abuse, pursuit of a natural reward, such as food, is regulated by homeostatic processes that putatively maintain a stable energy balance keeping unrestrained consumption and reward pursuit in check. Understanding how the reward system is constrained by or escapes homeostatic regulation is a critical question. The widespread use of food restriction to motivate animal subjects in behavior paradigms precludes investigation of this relationship as the homeostatic system is locked into deficit mode. In the present study, the authors examined the role of dopamine in modulating adaptive feeding behavior in semi-naturalistic homecage paradigms where mice earn all of their food from lever pressing. They compared consumption and meal patterning between hyperdopaminergic dopamine transporter knock-down and wild-type mice in two paradigms that introduce escalating costs for procuring food. The authors found that hyperdopaminergic mice exhibited similar demand elasticity, weight loss and energy balance in response to cost. However, the dopamine transporter knock-down mice showed clear differences in meal patterning. Consistent with expectations of enhanced motivation, elevated dopamine increased the meal size and reduced intrameal cost sensitivity. Nonetheless, this did not alter the overall energy balance. The authors conclude that elevated dopamine enhances the incentive or willingness to work locally within meals without shifting the energy balance, enhancing global food-seeking or generating an energy surplus. Beeler JA, Frazier CR, Zhuang X. Dopaminergic enhancement of local food-seeking is under global homeostatic control. Eur J Neurosci. 2012 Jan;35(1): 146-159. doi: 10.1111/j.1460-9568.2011.07916.x. Epub 2011 Nov 27.

**Corticotrophin Releasing Factor (CRF) Induced Reinstatement Of Cocaine Seeking In Male And Female Rats** Significant sex differences have been demonstrated in clinical and preclinical studies of cocaine addiction, with some of the most consistent differences noted in regard to the role of stress and craving. The current study examined stress-induced reinstatement of cocaine seeking in male and female rats in an animal model of relapse using corticotropin-releasing factor (CRF) administration. Both male and female rats demonstrated increased cocaine seeking in response to CRF. CRF-induced reinstatement was highly variable across both male and female rats, and further analysis revealed a subpopulation that was particularly sensitive to CRF (high responders). Female high responders displayed significantly increased responding to CRF compared to males. Individual differences in stress responsivity could thus contribute to the likelihood of relapse, with females showing greater heterogeneity to stress-induced relapse. Buffalari DM, Baldwin CK, Feltenstein MW, See RE. Corticotrophin releasing factor (CRF) induced reinstatement of cocaine seeking in male and female rats. Physiol Behav. 2012 Jan 18;105(2):209-214. Epub 2011 Aug 24.

**Differential Dopamine Release Dynamics In The Nucleus Accumbens Core And Shell Track Distinct Aspects Of Goal-Directed Behavior For Sucrose** Mesolimbic dopamine projections to the nucleus accumbens (NAc) have been implicated in goal-directed behaviors for natural rewards and in learning processes involving cue-reward associations. The NAc has been traditionally subdivided into two anatomically distinct sub-regions with different functional properties: the shell and the core. The aim of the present study was to characterize rapid

dopamine transmission across the two NAc sub-regions during cue-signaled operant behavior for a natural (sucrose) reward in rats. Using fast-scan cyclic voltammetry (FSCV) the authors observed differences in the magnitude and dynamics of dopamine release events between the shell and core. Specifically, although cue-evoked dopamine release was observed in both sub-regions, it was larger and longer lasting in the shell compared with the core. Further, secondary dopamine release events were observed following the lever press response for sucrose in the NAc shell, but not the core. These findings demonstrate that the NAc displays regional specificity in dopamine transmission patterns during cued operant behavior for natural reward. Cacciapaglia F, Saddoris MP, Wightman RM, Carelli RM. Differential dopamine release dynamics in the nucleus accumbens core and shell track distinct aspects of goal-directed behavior for sucrose. Neuropharmacology. 2012 Apr; 62(5-6): 2050-2056. Epub 2012 Jan 12.

**Cocaine Abstinence Alters Nucleus Accumbens Firing Dynamics During Goal-Directed Behaviors For Cocaine And Sucrose** Distinct subsets of nucleus accumbens (NAc) neurons differentially encode goal-directed behaviors for natural vs. drug rewards [R. M. Carelli et al. (2000) The Journal of Neuroscience, 20, 4255-4266], and the encoding of cocaine-seeking is altered following cocaine abstinence [J. A. Hollander & R. M. Carelli (2007) The Journal of Neuroscience, 27, 3535-3539]. Here, electrophysiological recording procedures were used to determine if the selective encoding of natural vs. cocaine reward by NAc neurons is: (i) maintained when the natural reinforcer is a highly palatable sweet tastant and (ii) altered by cocaine abstinence. Rats (n=14) were trained on a multiple schedule of sucrose reinforcement and cocaine self-administration (2-3 weeks) and NAc activity was recorded during the task before and after 30 days of cocaine abstinence. Of 130 cells recorded before abstinence, 82 (63%) displayed patterned discharges (increases or decreases in firing rate, termed phasic activity) relative to operant responding for sucrose or cocaine. As in previous reports, the majority of those cells displayed nonoverlapping patterns of activity during responding for sucrose vs. cocaine. Specifically, only 17 (21%) showed similar patterns of activity (i.e. overlapping activity) across the two reinforcer conditions. After abstinence, this pattern was largely maintained, 23 of 70 phasic cells (33%) were overlapping. However, cocaine abstinence altered the overall percentage of selectively active neurons across reinforcer conditions. Specifically, significantly more neurons became selectively activated during cocaine-directed behaviors than during sucrose-directed behaviors. The results indicate that, although the selective encoding of cocaine and natural rewards is maintained even with a highly palatable substance, 30 days of cocaine abstinence dynamically alters the overall population encoding of natural and drug rewards by NAc neurons. Cameron CM, Carelli RM. Cocaine abstinence alters nucleus accumbens firing dynamics during goal-directed behaviors for cocaine and sucrose. Eur J Neurosci. 2012 Mar; 35(6): 940-951. doi: 10.1111/j.1460-9568.2012.08024.x. Epub 2012 Feb 22.

**Quantitative Assessment Of Female Sexual Motivation In The Rat: Hormonal Control Of Motivation** While a good deal of information has been garnered in the last few decades regarding the neural and hormonal control of female sexual behavior, literature elucidating these mechanisms with respect to female sexual motivation has been scarce. The authors believe that one reason for this is the lack of a standardized paradigm that will quantify female sexual motivation while allowing for sexual interaction to occur. Here they describe a two-chambered apparatus that utilizes operant responding (nose poking) to quantify female sexual motivation.

During the test, the female exhibits nose pokes to gain access to a sexually active male, with whom she is allowed to mate. Therefore, this apparatus allows for examination of sexual behavior as well as quantification of sexual motivation by assessing the number of nose pokes the female will exhibit within a fixed interval to gain access to the male. The authors report that hormone priming significantly increases sexual motivation in the female as indicated by the number of nose pokes she will exhibit to gain access to the male. Additionally, hormone primed females enter the male compartment after a shorter period and spend more time in direct contact with the male compared to when they are not hormone primed. In contrast, when females are not hormone primed they spend more time in view, but out of reach, of the male. This paradigm will help to advance the study of female sexual motivation, providing a method for quantifiable assessment of female sexual motivation while allowing for sexual activity to occur. Cummings JA, Becker JB. Quantitative assessment of female sexual motivation in the rat: Hormonal control of motivation. J Neurosci Methods. 2012 Mar 15; 204(2): 227-233. Epub 2011 Nov 19.

**Cocaine Self-Administration In Rats: Discrete Trials Procedures** A discrete trials procedure involves splitting up a self-administration session so that there are multiple distinct trials and inter-trial-intervals. This schedule is well suited to be used over 24 h periods which allows insight into diurnal variability in self-administration behavior. DT is also well suited for investigations using pretreatments for increasing or decreasing both high and low probability behavior. Dobrin CV, Roberts DC. Cocaine self-administration in rats: discrete trials procedures. Methods Mol Biol. 2012; 829: 291-302.

**Corticostriatal-Limbic Gray Matter Morphology In Adolescents With Self-Reported Exposure To Childhood Maltreatment** The objective of this work was to study the relationship between self-reported exposure to childhood maltreatment (CM) and cerebral gray matter (GM) morphology in adolescents without psychiatric diagnoses. Associations were examined between regional GM morphology and exposure to CM (measured using a childhood trauma self-report questionnaire for physical, emotional, and sexual abuse and for physical and emotional neglect). The study setting was a University hospital. Forty-two adolescents without psychiatric diagnoses served as participants. Correlations between childhood trauma self-report questionnaire scores and regional GM volume were assessed in voxel-based analyses of structural magnetic resonance images. Relationships among GM volume, subtypes of exposure to CM, and sex were explored. Childhood trauma self-report questionnaire total scores correlated negatively ($P < .005$) with GM volume in prefrontal cortex, striatum, amygdala, sensory association cortices, and cerebellum. Physical abuse, physical neglect, and emotional neglect were associated with rostral prefrontal reductions. Decreases in dorsolateral and orbitofrontal cortices, insula, and ventral striatum were associated with physical abuse. Decreases in cerebellum were associated with physical neglect. Decreases in dorsolateral, orbitofrontal, and subgenual prefrontal cortices, striatum, amygdala, hippocampus, and cerebellum were associated with emotional neglect. Decreases in the latter emotion regulation regions were also associated with childhood trauma self-report questionnaire scores in girls, while caudate reductions (which may relate to impulse dyscontrol) were seen in boys. Exposure to CM was associated with corticostriatal-limbic GM reductions in adolescents. Even if adolescents reporting exposure to CM do not present with symptoms that meet full criteria for psychiatric disorders, they may have corticostriatal-limbic GM morphologic alterations that place them at risk for behavioral difficulties. Vulnerabilities may be moderated by sex and by subtypes of exposure to CM. Edmiston EE, Wang F, Mazure CM, Guiney J, Sinha

R, Mayes LC, Blumberg HP. Corticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. Arch Pediatr Adolesc Med. 2011 Dec; 165(12): 1069-1077.

**Experimental Psychiatric Illness And Drug Abuse Models: From Human To Animal, An Overview** Preclinical animal models have supported much of the recent rapid expansion of neuroscience research and have facilitated critical discoveries that undoubtedly benefit patients suffering from psychiatric disorders. This overview serves as an introduction for the following chapters describing both in vivo and in vitro preclinical models of psychiatric disease components and briefly describes models related to drug dependence and affective disorders. Although there are no perfect animal models of any psychiatric disorder, models do exist for many elements of each disease state or stage. In many cases, the development of certain models is essentially restricted to the human clinical laboratory domain for the purpose of maximizing validity, whereas the use of in vitro models may best represent an adjunctive, well-controlled means to model specific signaling mechanisms associated with psychiatric disease states. The data generated by preclinical models are only as valid as the model itself, and the development and refinement of animal models for human psychiatric disorders continues to be an important challenge. Collaborative relationships between basic neuroscience and clinical modeling could greatly benefit the development of new and better models, in addition to facilitating medications development. Edwards S, Koob GF. Experimental psychiatric illness and drug abuse models: from human to animal, an overview. Methods Mol Biol. 2012; 829: 31-48.

**Development Of Mechanical Hypersensitivity In Rats During Heroin And Ethanol Dependence: Alleviation By $CRF_1$ Receptor Antagonism** Animal models of drug dependence have described both reductions in brain reward processes and potentiation of stress-like (or anti-reward) mechanisms, including a recruitment of corticotropin-releasing factor (CRF) signaling. Accordingly, chronic exposure to opiates often leads to the development of mechanical hypersensitivity. The authors measured paw withdrawal thresholds (PWTs) in male Wistar rats allowed limited (short access group: ShA) or extended (long access group: LgA) access to heroin or cocaine self-administration, or in rats made dependent on ethanol via ethanol vapor exposure (ethanol-dependent group). In heroin self-administering animals, after transition to LgA conditions, thresholds were reduced to around 50% of levels observed at baseline, and were also significantly lower than thresholds measured in animals remaining on the ShA schedule. In contrast, thresholds in animals self-administering cocaine under either ShA (1 h) or LgA (6 h) conditions were unaltered. Similar to heroin LgA rats, ethanol-dependent rats also developed mechanical hypersensitivity after eight weeks of ethanol vapor exposure compared to non-dependent animals. Systemic administration of the CRF1R antagonist MPZP significantly alleviated the hypersensitivity observed in rats dependent on heroin or ethanol. The emergence of mechanical hypersensitivity with heroin and ethanol dependence may thus represent one critical drug-associated negative emotional state driving dependence on these substances. These results also suggest a recruitment of CRF-regulated nociceptive pathways associated with escalation of intake and dependence. A greater understanding of relationships between chronic drug exposure and pain-related states may provide insight into mechanisms underlying the transition to drug addiction, as well as reveal new treatment opportunities. This article is part of a Special Issue entitled 'Post-Traumatic Stress Disorder'. Edwards S, Vendruscolo LF, Schlosburg JE, Misra KK, Wee S, Park PE, Schulteis G, Koob GF. Development of mechanical hypersensitivity in rats

during heroin and ethanol dependence: alleviation by $CRF_1$ receptor antagonism. Neuropharmacology. 2012 Feb; 62(2): 1142-1151. Epub 2011 Nov 23.

**Exploratory Studies In Sensory Reinforcement In Male Rats: Effects Of Methamphetamine** Understanding sensory reinforcement and the effects of stimulant drugs on sensory reinforcers is potentially important for understanding their influence on addiction processes. Experiment 1 explored the reinforcing properties of a visual stimulus and the effects of methamphetamine (METH) on responding maintained by a visual reinforcer (VRF) in male rats. Snout poke responses to the active alternative produced the VRF according to variable interval (VI) schedules of reinforcement, and responses to an inactive alternative had no programmed effect. Experiment 2 explored the effects of METH on choice between the VRF and a water reinforcer (H2ORF) using concurrent VI schedules in male rats. In Experiment 1, response-contingent onset of the VRF produced an increase in both the relative frequency and absolute rate of active responding. The rate of both active and inactive responding declined across the 40-min test sessions. METH did not differentially enhance active responding for the VRF. Instead, METH nondifferentially increased the rate of responding and attenuated the within-session decline of responding. In Experiment 2, METH differentially increased the rate of responding for the VRF relative to the H2ORF. The results of these exploratory experiments indicate that the reinforcing effects of the VRF were weak and transient. In addition, METH treatment increased responding, and the specificity of the enhancement of METH was dependent upon the testing conditions. Potential explanations of these differences, such as novelty and reinforcer type, are discussed. Gancarz AM, Ashrafioun L, San George MA, Hausknecht KA, Hawk LW Jr, Richards JB. Exploratory studies in sensory reinforcement in male rats: effects of methamphetamine. Exp Clin Psychopharmacol. 2012 Feb; 20(1): 16-27. Epub 2011 Sep 26.

**Ventral Striatum Encodes Past And Predicted Value Independent Of Motor Contingencies** The ventral striatum (VS) is thought to signal the predicted value of expected outcomes. However, it is still unclear whether VS can encode value independently from variables often yoked to value such as response direction and latency. Expectations of high value reward are often associated with a particular action and faster latencies. To address this issue the authors trained rats to perform a task in which the size of the predicted reward was signaled before the instrumental response was instructed. Instrumental directional cues were presented briefly at a variable onset to reduce accuracy and increase reaction time. Rats were more accurate and slower when a large versus small reward was at stake. The authors found that activity in VS was high during odors that predicted large reward even though reaction times were slower under these conditions. In addition to these effects, they found that activity before the reward predicting cue reflected past and predicted reward. These results demonstrate that VS can encode value independent of motor contingencies and that the role of VS in goal-directed behavior is not just to increase vigor of specific actions when more is at stake. Goldstein BL, Barnett BR, Vasquez G, Tobia SC, Kashtelyan V, Burton AC, Bryden DW, Roesch MR. Ventral striatum encodes past and predicted value independent of motor contingencies. J Neurosci. 2012 Feb 8; 32(6): 2027-2036.

**Elevated Gray And White Matter Densities In Cocaine Abstainers Compared To Current Users** Numerous neuroimaging studies have demonstrated lower neural tissue density in chronic cocaine users, which may be linked to cognitive dysfunction. The goal of this study was to determine whether neural tissue density was also impaired in individuals abstinent from cocaine and whether any observed changes were associated with cognitive performance. A total of 73 participants were included: 24 active cocaine users, 24 abstainers (abstinent for at least 1 month), and 25 nondrug-abusing controls rigorously matched for age, gender, and IQ. All participants performed a cognitive assessment battery and received an MRI which was analyzed using voxel-based morphometry. The abstainers had significantly higher gray matter density than the current cocaine users in neocortical areas including the frontal and temporal cortex. In contrast to the users, there was no difference in white matter density in the abstainers relative to the controls. The abstainers performed better than current users on several behavioral tasks. Within users and abstainers, cortical density was correlated with performance on memory and reaction time tasks. Subcortical gray matter density was lower in both the users and abstainers relative to the controls. Within abstainers, subcortical tissue density was correlated with the ability to set-shift. These data suggest that individuals able to remain abstinent from cocaine for at least 1 month have elevated neocortical tissue density and perform better on multiple cognitive tests, relative to current cocaine users. Larger, longitudinal studies are needed to address this interaction between abstinence, cognition, and cortical tissue density directly. Hanlon CA, Dufault DL, Wesley MJ, Porrino LJ. Elevated gray and white matter densities in cocaine abstainers compared to current users. Psychopharmacology (Berl). 2011 Dec; 218(4): 681-692. Epub 2011 Jun 22.

**GABA(B) Receptor-Positive Modulators: Brain Region-Dependent Effects** This study examined the positive modulatory properties of 2,6-di-tert-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol (CGP7930) and (R,S)-5,7-di-tert-butyl-3-hydroxy-3-trifluoromethyl-3H-benzofuran-2-one (rac-BHFF) at γ-aminobutyric acid B (GABA(B)) receptors in different brain regions. Using quantitative autoradiography, the authors measured GABA(B) receptor-stimulated binding of guanosine 5'-O-(3-[$^{35}$S]thiotriphosphate) ([$^{35}$S]GTPγS) to G proteins in medial prefrontal cortex (mPFC), hippocampus, and cerebellum. CGP7930 and rac-BHFF enhanced baclofen-stimulated [$^{35}$S]GTPγS binding similarly in mPFC and hippocampus, but were more effective in cerebellum. CGP7930 (100 μM) increased [$^{35}$S]GTPγS binding stimulated by baclofen (30 μM) from 29 to 241% above basal in mPFC and from 13 to 1530% above basal in cerebellum. Likewise, rac-BHFF (10 μM) increased baclofen-stimulated [$^{35}$S]GTPγS binding more in cerebellum (from 13 to 1778% above basal) than in mPFC (from 29 to 514% above basal). rac-BHFF (10 μM) in combination with γ-hydroxybutyrate (20 mM) increased [$^{35}$S]GTPγS binding in cerebellum but not in mPFC. rac-BHFF also enhanced the effects of 3-aminopropyl(diethoxymethyl)phosphinic acid (CGP35348). Consistent with its partial agonist properties, CGP35348 stimulated [$^{35}$S]GTPγS binding in mPFC when given alone (to 18% above basal), but less extensively than baclofen (140% above basal), and antagonized baclofen when given together. CGP35348 (1 mM) in combination with rac-BHFF (100 μM) produced an increase in [$^{35}$S]GTPγS binding that was larger in cerebellum (from 61 to 1260% above basal) than in mPFC (from 18 to 118% above basal). Taken together, the results show that GABA(B) receptor-positive modulators enhance [$^{35}$S]GTPγS binding stimulated by GABA(B) receptor agonists in a brain region-dependent manner. This regionally selective enhancement is further evidence of pharmacologically distinct GABA(B) receptor populations, possibly allowing for more selective therapeutic targeting of the GABA(B) system. Hensler JG, Advani T, Burke

TF, Cheng K, Rice KC, Koek W. GABA(B) receptor-positive modulators: brain region-dependent effects. J Pharmacol Exp Ther. 2012 Jan; 340(1): 19-26. Epub 2011 Sep 27.

**Reinstatement Of Methamphetamine Seeking In Male And Female Rats Treated With Modafinil And Allopregnanolone** Sex differences in methamphetamine (METH) use (females>males) have been demonstrated in clinical and preclinical studies. This experiment investigated the effect of sex on the reinstatement of METH-seeking behavior in rats and determined whether pharmacological interventions for METH-seeking vary by sex. Treatment drugs were modafinil (MOD), an analeptic, and allopregnanolone (ALLO), a neuroactive steroid and progesterone metabolite. Male and female rats were trained to self-administer i.v. infusions of METH (0.05 mg/kg/infusion). Next, rats self-administered METH for a 10-day maintenance period. METH was then replaced with saline, and rats extinguished lever-pressing behavior over 18 days. A multi-component reinstatement procedure followed whereby priming injections of METH (1mg/kg) were administered at the start of each daily session, preceded 30 min by MOD (128 mg/kg, i.p.), ALLO (15 mg/kg, s.c.), or vehicle treatment. MOD was also administered at the onset of the session to determine if it would induce the reinstatement of METH-seeking behavior. Female rats had greater METH-induced reinstatement responding compared to male rats following control treatment injections. MOD (compared to the DMSO control) attenuated METH-seeking behavior in male and female rats; however, ALLO only reduced METH-primed responding in females. MOD alone did not induce the reinstatement of METH-seeking behavior. These results support previous findings that females are more susceptible to stimulant abuse compared to males, and ALLO effectively reduced METH-primed reinstatement in females. Further, results illustrate the utility of MOD as a potential agent for prevention of relapse to METH use in both males and females. Holtz NA, Lozama A, Prisinzano TE, Carroll ME. Reinstatement of methamphetamine seeking in male and female rats treated with modafinil and allopregnanolone. Drug Alcohol Depend. 2012 Jan 1; 120(1-3): 233-237.

**Basolateral Amygdala Encodes Upcoming Errors But Not Response Conflict** Adaptive behavior depends on the detection of potential errors so that ongoing behavior might be corrected. Here, the authors ask whether basolateral amygdala (ABL) might serve this function by examining activity in rats performing a task in which errors were induced by pitting two behavioral responses against each other. This response competition or conflict was created by forcing rats to respond away from the direction in which they were freely choosing on the majority of trials. Rats were slower and less accurate on these incongruent trial types. The authors found that activity in ABL fired more strongly prior to errant responses, but did not signal the potential for errors on correctly performed incongruent trials. These data support a role for ABL in processing errors prior to their occurrence and suggest that ABL is not involved in monitoring conflict so that ongoing behavior might be corrected. Kashtelyan V, Tobia SC, Burton AC, Bryden DW, Roesch MR. Basolateral amygdala encodes upcoming errors but not response conflict. Eur J Neurosci. 2012 Mar; 35(6): 952-959. doi: 10.1111/j.1460-9568.2012.08022.x. Epub 2012 Feb 22.

**Social Influences On Morphine-Conditioned Place Preference In Adolescent BALB/Cj And C57BL/6J Mice** Among human adolescents, drug use is substantially influenced by the attitudes and behaviors of peers. Social factors also affect the drug-seeking behaviors of laboratory animals. Conditioned place preference (CPP) experiments indicate that social context can

influence the degree to which rodents derive a rewarding experience from drugs of abuse. However, the precise manner by which social factors alter drug reward in adolescent rodents remains unknown. The authors employed the relatively asocial BALB/cJ (BALB) mouse strain and the more prosocial C57BL/6J (B6) strain to explore whether "low" or "high" motivation to be with peers influences the effects of social context on morphine CPP (MCPP). Adolescent mice were conditioned by subcutaneous injections of morphine sulfate (0.25, 1.0, or 5.0 mg/kg). During the MCPP procedure, mice were housed in either isolation (Ih) or within a social group (Sh). Similarly, following injection, mice were conditioned either alone (Ic) or within a social group (Sc). Adolescent B6 mice expressed a robust MCPP response except when subjected to Ih-Sc, which indicates that, following isolation, mice with high levels of social motivation are less susceptible to the rewarding properties of morphine when they are conditioned in a social group. By contrast, MCPP responses of BALB mice were most sensitive to morphine conditioning when subjects experienced a change in their social environment between housing and conditioning (Ih-Sc or Sh-Ic). These findings demonstrate that susceptibility to morphine-induced reward in adolescent mice is moderated by a complex interaction between social context and heritable differences in social motivation. Kennedy BC, Panksepp JB, Runckel PA, Lahvis GP. Social influences on morphine-conditioned place preference in adolescent BALB/cJ and C57BL/6J mice. Psychopharmacology (Berl). 2012 Feb; 219(3): 923-932.

**Morphine-Induced Motor Stimulation, Motor Incoordination, And Hypothermia In Adolescent And Adult Mice** Given evidence for age-related differences in the effects of drugs of abuse, surprisingly few preclinical studies have explored effects of opioids in adolescents (versus adults). This study compared the motor stimulating, ataxic, and hypothermic effects of morphine in adolescent, late adolescent, and adult mice. Plasma and brain levels of morphine were assessed to examine possible pharmacokinetic differences among the age groups. Locomotion was measured as occlusions of horizontal infrared light beams, ataxia as failing the horizontal wire test, body temperature by rectal probe, and morphine levels by HPLC-UV. Morphine (3.2-56 mg/kg, i.p.) increased locomotion along an inverted U-shaped dose-response curve in adolescent, late adolescent, and adult male C57BL/6J mice. Its potency to stimulate locomotion was similar in all age groups. However, maximal stimulation was higher in adolescents than in late adolescents, and higher in late adolescents than in adults. In contrast, adolescents showed less ataxia than adults when given morphine (5.6-100 mg/kg, i.p.). The hypothermic effects of morphine did not differ among the age groups. Morphine levels, which peaked in plasma at 15 min and in brain at 45 min after i.p. injection, did not show age-related differences. The finding that adolescents are not generally more sensitive to morphine than adults, but differ in their sensitivity to effects involving nigrostriatal/mesolimbic dopamine systems, is consistent with evidence of overactivity of these dopamine systems during adolescence relative to adulthood. The age-related differences observed here are unlikely due to pharmacokinetic factors. Koek W, France CP, Javors MA. Morphine-induced motor stimulation, motor incoordination, and hypothermia in adolescent and adult mice. Psychopharmacology (Berl). 2012 Feb; 219(4):1027-1037. Epub 2011 Aug 12.

**Effects Of Hallucinogenic Agents Mescaline And Phencyclidine On Zebrafish Behavior And Physiology** Mescaline and phencyclidine (PCP) are potent hallucinogenic agents affecting human and animal behavior. As their psychotropic effects remain poorly understood, further research is necessary to characterize phenotypes they evoke in various animal models. Zebrafish

(Danio rerio) are rapidly emerging as a new model organism for neuroscience research. Here, the authors examine the effects of mescaline (5-20mg/l) and PCP (0.5-3mg/l) in several zebrafish paradigms, including the novel tank, open field and shoaling tests. Mescaline and PCP dose-dependently increased top activity in the novel tank test, also reducing immobility and disrupting the patterning of zebrafish swimming, as assessed by ethograms. PCP, but not mescaline, evoked circling behavior in the open field test. At the highest doses tested, mescaline markedly increased, while PCP did not affect, zebrafish shoaling behavior. Finally, 20mg/l mescaline did not alter, and 3mg/l PCP elevated, whole-body cortisol levels. Overall, these studies indicate high sensitivity of zebrafish models to hallucinogenic compounds with complex behavioral and physiological effects. Kyzar EJ, Collins C, Gaikwad S, Green J, Roth A, Monnig L, El-Ounsi M, Davis A, Freeman A, Capezio N, Stewart AM, Kalueff AV. Effects of hallucinogenic agents mescaline and phencyclidine on zebrafish behavior and physiology. Prog Neuropsychopharmacol Biol Psychiatry. 2012 Apr 27; 37(1): 194-202. Epub 2012 Jan 9.

**Neural Circuit Competition In Cocaine-Seeking: Roles Of The Infralimbic Cortex And Nucleus Accumbens Shell** Following cocaine self-administration and extinction training, activity in the infralimbic cortex (IL) suppresses cocaine-seeking behavior. IL inactivation induces cocaine-seeking whereas activation suppresses cocaine-reinstated drug-seeking. The authors asked how the suppression of cocaine-seeking induced by IL activation integrates with the circuitry promoting reinstated cocaine-seeking. Following cocaine self-administration and extinction training, rats underwent cue-induced reinstatement. In order to activate IL projections, microinjections of PEPA, a positive allosteric modulator of AMPA receptors, were made into the IL in combination with microinjections into a variety of nuclei known to regulate cocaine-seeking. Intra-IL PEPA administration suppressed cue-induced reinstatement without affecting locomotor activity. The suppression of cocaine-seeking was reversed by activating dopamine neurons in the ventral tegmental area with microinjections of the μ-opioid receptor agonist DAMGO, and was partially reversed by dopamine microinjections into the prelimbic cortex or basolateral amygdala. Previous evidence suggests that the nucleus accumbens shell both promotes and suppresses cocaine-seeking. The suppression of cue-induced cocaine seeking by PEPA in the IL was reversed by intra-shell microinjections of either dopamine or the AMPA receptor antagonist CNQX, suggesting that the accumbens shell bidirectionally regulates cocaine-seeking depending on whether dopamine input is mimicked or glutamate input is inhibited. Together, these findings indicate that the IL acts 'upstream' from structures promoting cocaine-seeking, including from the mesolimbic dopamine projections to the prelimbic cortex and basolateral amygdala, and that the accumbens shell may be a crucial point of integration between the circuits that promote (ventral tegmental area) and inhibit (IL) reinstated cocaine-seeking. Lalumiere RT, Smith KC, Kalivas PW. Neural circuit competition in cocaine-seeking: roles of the infralimbic cortex and nucleus accumbens shell. Eur J Neurosci. 2012 Feb; 35(3-4): 614-622. doi: 10.1111/j.1460-9568.2012.07991.x. Epub 2012 Feb 9.

**Eating High Fat Chow Increases The Sensitivity Of Rats To 8-OH-DPAT-Induced Lower Lip Retraction** Eating high fat food can alter sensitivity to drugs acting on dopamine systems; this study examined whether eating high fat food alters sensitivity to a drug acting on serotonin (5-HT) systems. Sensitivity to (+)-8-hydroxy-2-(dipropylamino) tetralin hydrobromide (8-OH-DPAT; 5-HT1A receptor agonist)-induced lower lip retraction was examined in separate groups (n=8-9) of rats with free access to standard (5.7% fat) or high fat (34.3% fat) chow; sensitivity to

quinpirole (dopamine D3/D2 receptor agonist)-induced yawning was also examined. Rats eating high fat chow gained more body weight than rats eating standard chow and, after 6 weeks of eating high fat chow, they were more sensitive to 8-OH-DPAT (0.01-0.1 mg/kg)-induced lower lip retraction and quinpirole (0.0032-0.32 mg/kg)-induced yawning. These changes were not reversed when rats that previously ate high fat chow were switched to eating standard chow and sensitivity to 8-OH-DPAT and quinpirole increased when rats that previously ate standard chow ate high fat chow. These data extend previous results showing changes in sensitivity to drugs acting on dopamine systems in animals eating high fat chow to a drug acting at 5-HT1A receptors and they provide support for the notion that eating certain foods impacts sensitivity to drugs acting on monoamine systems. Li JX, Ju S, Baladi MG, Koek W, France CP. Eating high fat chow increases the sensitivity of rats to 8-OH-DPAT-induced lower lip retraction. Behav Pharmacol. 2011 Dec; 22(8): 751-757.

**Stress Modulation Of Drug Self-Administration: Implications For Addiction Comorbidity With Post-Traumatic Stress Disorder** Drug abuse and dependence present significant health burdens for our society, affecting roughly 10% of the population. Stress likely contributes to the development and persistence of drug use; for example, rates of substance dependence are elevated among individuals diagnosed with post-traumatic stress disorder (PTSD). Thus, understanding the interaction between stress and drug use, and associated neuroadaptations, is key for developing therapies to combat substance use disorders. For this purpose, many rodent models of the effects of stress exposure on substance use have been developed; the models can be classified according to three categories of stress exposure: developmental, adult nonsocial, and adult social. The present review addresses preclinical findings on the effect of each type of trauma on responses to and self-administration of drugs of abuse by focusing on a key exemplar for each category. In addition, the potential efficacy of targeting neuropeptide systems that have been implicated in stress responses and stress system neuroadaptation in order to treat comorbid PTSD and substance abuse will be discussed. This article is part of a Special Issue entitled 'Post-Traumatic Stress Disorder'. Logrip ML, Zorrilla EP, Koob GF. Stress modulation of drug self-administration: implications for addiction comorbidity with post-traumatic stress disorder. Neuropharmacology. 2012 Feb; 62(2): 552-564. Epub 2011 Jul 19.

**Regulation Of Cocaine-Induced Reinstatement By Group II Metabotropic Glutamate Receptors In The Ventral Tegmental Area** A high rate of relapse is a daunting challenge facing clinical treatment of cocaine addiction. Recent studies have shown that drugs of abuse enhance glutamate neurotransmission in dopamine neurons in the ventral tegmental area (VTA) and such enhancement may contribute to the risk of relapse. Given the important role of group II metabotropic glutamate receptors (mGluR2/3s) in regulating glutamate release from the glutamatergic terminals, this study aimed to test whether activation of mGluR2/3s in the VTA can inhibit cocaine-induced reinstatement of cocaine-seeking behavior, a model of relapse to drug-seeking behavior. Rats were trained to self-administer intravenous cocaine (0.25 mg/infusion) under a modified fixed-ratio 5 schedule. After rats reached the training criteria, they went through extinction training to extinguish cocaine-seeking behavior. Then the dose-response effects of a selective mGluR2/3 agonist LY 379268 microinjected into the VTA on cocaine-induced reinstatement of cocaine-seeking behavior were assessed. LY 379268 (0.032-0.1 μg/side) dose-dependently decreased cocaine-induced reinstatement. The effect could not be fully attributed to diffusion of the drug to the neighboring substantia nigra or to motor

impairment. Interestingly, LY 379268 has a less potent effect on cocaine-induced reinstatement than on sucrose-induced reinstatement of sucrose-seeking behavior. These data support the idea that glutamate release in the VTA is critically involved in cocaine-induced reinstatement and indicate that loss of mGluR2/3-mediated regulation of glutamate release in the VTA may critically contribute to the risk of relapse. Lu L, Xue Y, Steketee JD, Rebec GV, Sun W. Regulation of cocaine-induced reinstatement by group II metabotropic glutamate receptors in the ventral tegmental area. Psychopharmacology (Berl). 2012 Mar; 220(1): 75-85. Epub 2011 Sep 1.

**Sucrose-Predictive Cues Evoke Greater Phasic Dopamine Release Than Saccharin-Predictive Cues** Cues that have been paired with food evoke dopamine in nucleus accumbens (NAc) and drive approach behavior. This cue-evoked dopamine signaling could contribute to overconsumption of food. One manner in which individuals try to restrict caloric intake is through the consumption of foods containing artificial (non-nutritive) sweeteners. The authors were interested in whether cues paired with a non-nutritive sweetener (saccharin) would evoke similar dopamine release as cues paired with a nutritive sweetener (sucrose). The authors trained food-restricted rats to associate distinct cues with sucrose or saccharin pellets. In the first group of rats, training sessions with each pellet took place on different days, maximizing the opportunity for rats to detect nutritional differences. After training, voltammetry recordings in NAc core revealed that sucrose cues evoked greater phasic dopamine release than saccharin cues. In a second group of rats, on each training day, sucrose and saccharin pellets were presented in pseudorandom order within the same session, to mask nutritional differences. In this condition, the difference in dopamine between sucrose and saccharin cues was attenuated, but not abolished. These results suggest that sucrose-paired cues will more powerfully motivate behavior than saccharin-paired cues. The differing responses to each cue seem to be driven by overall preference with both the nutritional value that the pellets predict as well as other factors, such as taste, contributing. McCutcheon JE, Beeler JA, Roitman MF. Sucrose-predictive cues evoke greater phasic dopamine release than saccharin-predictive cues. Synapse. 2012 Apr; 66(4): 346-351. doi: 10.1002/syn.21519. Epub 2011 Dec 29.

**A Cocaine Cue Is More Preferred And Evokes More Frequency-Modulated 50-Khz Ultrasonic Vocalizations In Rats Prone To Attribute Incentive Salience To A Food Cue** Individuals vary considerably in the extent to which they attribute incentive salience to food-associated cues. The authors asked whether individuals prone to attribute incentive salience to a food cue are also prone to attribute incentive properties to a stimulus associated with a drug of abuse-cocaine. They first identified those rats that attributed incentive salience to a food cue by quantifying the extent to which they came to approach and engage a food cue. They then used a conditioned place preference procedure to pair an injection of 10 mg/kg cocaine (i.p.) with one distinct floor texture (grid or holes) and saline with another. Following 8 days of conditioning, each rat was given a saline injection and placed into a chamber that had both floors present. They measured the time spent on each floor, and also 50-kHz ultrasonic vocalizations, which have been associated with positive affective states. Rats that vigorously engaged the food cue ("sign trackers") expressed a preference for the cocaine-paired floor compared to those that did not ("goal trackers"). In addition, sign trackers made substantially more frequency-modulated 50-kHz vocalizations when injected with cocaine and when later exposed to the cocaine cue. Rats prone to attribute incentive salience to a food cue are also prone to attribute incentive motivational properties to a tactile cue associated with cocaine. The authors suggest that

individuals prone to attribute incentive salience to reward cues will have difficulty resisting them and, therefore, may be especially vulnerable to develop impulse control disorders, including addiction. Meyer PJ, Ma ST, Robinson TE. A cocaine cue is more preferred and evokes more frequency-modulated 50-kHz ultrasonic vocalizations in rats prone to attribute incentive salience to a food cue. Psychopharmacology (Berl). 2012 Feb; 219(4): 999-1009. Epub 2011 Aug 11.

**Endocannabinoids Shape Accumbal Encoding Of Cue-Motivated Behavior Via CB1 Receptor Activation In The Ventral Tegmentum** Transient increases in nucleus accumbens (NAc) dopamine concentration are observed when animals are presented with motivationally salient stimuli and are theorized to energize reward seeking. They arise from high-frequency firing of dopamine neurons in the ventral tegmental area (VTA), which also results in the release of endocannabinoids from dopamine cell bodies. In this context, endocannabinoids are thought to regulate reward seeking by modulating dopamine signaling, although a direct link has never been demonstrated. To test this, the authors pharmacologically manipulated endocannabinoid neurotransmission in the VTA while measuring transient changes in dopamine concentration in the NAc during reward seeking. Disrupting endocannabinoid signaling dramatically reduced, whereas augmenting levels of the endocannabinoid 2-arachidonoylglycerol (2AG) increased, cue-evoked dopamine concentrations and reward seeking. These data suggest that 2AG in the VTA regulates reward seeking by sculpting ethologically relevant patterns of dopamine release during reward-directed behavior. Oleson EB, Beckert MV, Morra JT, Lansink CS, Cachope R, Abdullah RA, Loriaux AL, Schetters D, Pattij T, Roitman MF, Lichtman AH, Cheer JF. Endocannabinoids shape accumbal encoding of cue-motivated behavior via CB1 receptor activation in the ventral tegmentum. Neuron. 2012 Jan 26; 73(2): 360-373.

**Enhancement Of The Behavioral Effects Of Endogenous And Exogenous Cannabinoid Agonists By Phenylmethyl Sulfonyl Fluoride** Marijuana's effects in humans are most often reported as intoxicating or therapeutic; yet, some humans report dysphoria or other negative affect. To evaluate whether differences in endocannabinoid levels might account for this variability, the present study examined whether sensitivity to cannabinoids changed when anandamide (AEA) metabolism was inhibited through administration of phenylmethyl sulfonyl fluoride (PMSF) a non-specific irreversible amidase inhibitor. Male Long Evans rats were trained to discriminate 3 mg/kg Delta(9)-tetrahydrocannabinol (THC) versus vehicle in 2-lever drug discrimination procedure. ED(50)s for THC and CP 55,940 were lower when administered with PMSF than alone. PMSF administration also potentiated characteristic cannabimimetic effects of THC in ICR mice. Potentiation of AEA's in vivo effects by PMSF were also observed, primarily as a consequence of PMSF inhibition of the enzyme fatty acid amide hydrolase. Enhancement of the effects of THC and CP 55,940 through this mechanism is unlikely, as these cannabinoids are predominantly metabolized through the P450 system. Mass spectrometry revealed that, in the presence of THC, endogenous AEA levels in the brain decreased and that this decrease was prevented by PMSF, suggesting that increased AEA levels may have acted additively with exogenously administered cannabinoids to increase cannabimimetic effects. These findings may account for the varying affect in response to marijuana in humans or cannabinoids in animals while also suggesting that metabolic inhibitors of AEA may potentiate marijuana's intoxicating effects in humans. Vann RE, Walentiny DM, Burston JJ, Tobey KM, Gamage TF, Wiley JL. Neuropharmacology 2012; 62(Feb) 2: 1019-1027.

**Selective Serotonin Receptor Stimulation Of The Medial Nucleus Accumbens Differentially Affects Appetitive Motivation For Food On A Progressive Ratio Schedule Of Reinforcement** Previously, the authors reported that stimulation of selective serotonin (5-HT) receptor subtypes in the nucleus accumbens shell differentially affected consumption of freely available food. Specifically, activation of 5-HT(6) receptors caused a dose-dependent increase in food intake, while the stimulation of 5-HT(1/7) receptor subtypes decreased feeding [34]. The current experiments tested whether similar pharmacological activation of nucleus accumbens serotonin receptors would also affect appetitive motivation, as measured by the amount of effort non-deprived rats exerted to earn sugar reinforcement. Rats were trained to lever press for sugar pellets on a progressive ratio 2 schedule of reinforcement. Across multiple treatment days, three separate groups (N=8-10) received bilateral infusions of the 5-HT(6) agonist EMD 386088 (at 0.0, 1.0 and 4.0µg/0.5µl/side), the 5-HT(1/7) agonist 5-CT (at 0, 0.5, 1.0, or 4.0µg/0.5µl/side), or the 5-HT(2C) agonist RO 60-0175 fumarate (at 0, 2.0, or 5.0µg/0.5µl/side) into the anterior medial nucleus accumbens prior to a 1-h progressive ratio session. Stimulation of 5-HT(6) receptors caused a dose-dependent increase in motivation as assessed by break point, reinforcers earned, and total active lever presses. Stimulation of 5-HT(1/7) receptors increased lever pressing at the 0.5µg dose of 5-CT, but inhibited lever presses and break point at 4.0µg/side. Injection of the 5-HT(2C) agonist had no effect on motivation within the task. Collectively, these experiments suggest that, in addition to their role in modulating food consumption, nucleus accumbens 5-HT(6) and 5-HT(1/7) receptors also differentially regulate the appetitive components of food-directed motivation. Pratt WE, Schall MA, Choi E. Selective serotonin receptor stimulation of the medial nucleus accumbens differentially affects appetitive motivation for food on a progressive ratio schedule of reinforcement. Neurosci Lett. 2012 Mar 9; 511(2): 84-88. Epub 2012 Jan 24.

**Environmental Enrichment Protects Against The Acquisition Of Cocaine Self-Administration In Adult Male Rats, But Does Not Eliminate Avoidance Of A Drug-Associated Saccharin Cue** One of the most menacing consequences of drug addiction is the devaluation of natural rewards (e.g. food, sex, work, money, caring for one's offspring). However, evidence also suggests that natural rewards, such as an enriched environment, can devalue drugs of abuse. Thus, this study used a rodent model to test whether exposure to an enriched environment could protect adult rats from acquiring cocaine self-administration and from the resultant drug-induced devaluation of a natural saccharin reward cue. Adult male Sprague-Dawley rats were implanted with intravenous jugular catheters. Rats were then separated into two housing conditions: an enriched condition, including social companions (four/cage) and novel objects (e.g. balls, polyethylene tubes, paper, etc.), and a nonenriched condition where the rats were singly housed with no novel objects. During testing, the rats were given 5-min access to 0.15% saccharin, followed by 1 h to self-administer saline or cocaine (0.167 mg/infusion) on fixed ratio and progressive ratio schedules of reinforcement. The results showed that rats that were singly housed in the nonenriched environment fell into two groups: low drug-takers (n=34) and high drug-takers (n=12). In comparison, only one out of the 22 rats housed in the enriched environment was a high drug-taker. Thus, all rats in the enriched environment, except one, behaved like low drug-takers under the nonenriched condition. As such, these rats self-administered almost no drug on either the fixed ratio or the progressive ratio schedule of reinforcement and were extremely slow to self-administer their first cocaine infusion. Interestingly, despite their very low levels of drug self-administration, low-drug-taking

rats housed in the enriched environment continued to avoid intake of the drug-associated saccharin cue. Taken together, these data suggest that the enriched environment itself served as a salient natural reward that reduced cocaine seeking and cocaine taking, but had little impact on avoidance of the cocaine-paired taste cue. The protective effects of the enriched environment were robust and, as such, have important implications for the methods used in the study of drug addiction in animal models and for the prevention, and possibly the treatment, of the disease in adult humans. Puhl MD, Blum JS, Acosta-Torres S, Grigson PS. Environmental enrichment protects against the acquisition of cocaine self-administration in adult male rats, but does not eliminate avoidance of a drug-associated saccharin cue. 13. Behav Pharmacol. 2012 Feb; 23(1): 43-53.

**Use Of Vivo-Morpholinos For Control Of Protein Expression In The Adult Rat Brain** Vivo-morpholinos are commercially available morpholino oligomers with a terminal octa-guanidinium dendrimer for enhanced cell-permeability. Existing evidence from systemically delivered vivo-morpholinos indicate that genetic suppression can last from days to weeks without evidence of cellular toxicity. However, intravenously delivered vivo-morpholinos are ineffective at protein suppression in the brain, and no evidence is available regarding whether intracranially delivered vivo-morpholinos effectively reduce target protein levels, or do so without inducing neurotoxicity. Here the authors report examples in which in vivo microinjection of antisense vivo-morpholinos directed against three different targets (xCT, GLT1, orexin) in two different brain regions resulted in significant suppression of protein expression without neurotoxicity. Expression was significantly suppressed at six to seven days post-administration, but returned to baseline levels within fourteen days. These results indicate that direct intracranial administration of vivo-morpholinos provides an effective means by which to suppress protein expression in the brain for one to two weeks. Reissner KJ, Sartor GC, Vazey EM, Dunn TE, Aston-Jones G, Kalivas PW. Use of vivo-morpholinos for control of protein expression in the adult rat brain. J Neurosci Methods. 2012 Jan 30; 203(2): 354-360. Epub 2011 Oct 17.

**Modeling Risky Decision Making In Rodents** Excessive risk taking is a hallmark of various psychopathological disorders. The authors have developed a task that models such risky decision making in rats. In this task, rats are given choices between small, safe rewards and large rewards accompanied by a risk of punishment (footshock). The risk of punishment increases throughout the test session, which allows the quantification of risky decision making at different degrees of risk for each subject. Importantly, this task yields a consistently wide degree of reliable individual variability, allowing the characterization of rats as "risk taking" or "risk averse." This task has been demonstrated to be effective for testing the effects of pharmacological agents on risk taking, and the individual variability (which mimics the human population) allows assessment of neurobiological distinctions between subjects based on risk-taking profile. Simon NW, Setlow B. Modeling risky decision making in rodents. Methods Mol Biol. 2012; 829: 165-175.

**Weakening Of Negative Relative To Positive Associations With Cocaine-Paired Cues Contributes To Cue-Induced Responding After Drug Removal** Cocaine has been shown to have initial positive (euphoric) and delayed negative (anxiogenic) effects in both humans and animals. Cocaine-paired cues are consequently imbued with mixed positive and negative

associations. The current study examines the relative roles of these dual associations in the enhanced drug-seeking observed upon presentation of cocaine-paired cues. Rats ran a straight alley once/day for a single i.v. injection of cocaine (1.0 mg/kg/inj) in the presence of a distinctive olfactory cue (scented cotton swabs placed under the apparatus). An alternate scent was presented in a separate cage 2-h prior to runway testing. After 15 trials/days, the scents and cocaine reinforcer were removed and a series of extinction trials (lasting for 1 or 3 weeks) was initiated. Immediately following extinction, runway responding was tested during a single trial in the presence of the cocaine-paired or non-paired cue. As previously reported, while subjects initiated responding faster over trials (reduced latencies to leave the start box), they exhibited a progressive increase in approach-avoidance conflict behavior ("retreats") regarding goal-box entry, reflecting cocaine's dual positive+negative effects. Once established, retreat behaviors persisted over the course of 1 or 3 weeks days of extinction. However, both run times and retreats decreased in response to presentation of the cocaine-paired but not the non-paired scent. These data suggest that, after reinforcer removal, cue-induced cocaine-seeking stems in part from a reduction in approach-avoidance conflict; i.e., a greater weakening of the negative relative to the positive associations that animals form with cocaine-paired stimuli. Su ZI, Kichaev G, Wenzel J, Ben-Shahar O, Ettenberg A. Weakening of negative relative to positive associations with cocaine-paired cues contributes to cue-induced responding after drug removal. Pharmacol Biochem Behav. 2012 Jan; 100(3): 458-463. Epub 2011 Oct 8.

**Individual Differences In Psychostimulant Responses Of Female Rats Are Associated With Ovarian Hormones And Dopamine Neuroanatomy** Ovarian hormones modulate the pharmacological effects of psychostimulants and may enhance vulnerability to drug addiction. Female rats have more midbrain dopamine neurons than males and greater dopamine uptake and release rates. Cocaine stimulates motor behavior and dopamine efflux more in female than male rats, but the mediating mechanisms are unknown. This study investigated individual differences in anatomic, neurochemical, and behavioral measures in female rats to understand how ovarian hormones affect the relatedness of these endpoints. Ovarian hormone effects were assessed by comparing individual responses in ovariectomized (OVX) and sham adult female rats. Locomotion was determined before and following 10mg/kg cocaine. Electrically-stimulated dopamine efflux was assessed using fast cyclic voltammetry in vivo. Dopamine neuron number and density in substantia nigra (SN) and ventral tegmental area (VTA) were determined in the same animals using tyrosine-hydroxylase immunohistochemistry and unbiased stereology. Locomotor behavior and dopamine efflux did not differ at baseline but were greater in sham than OVX following cocaine. Cocaine increased dopamine release rates in both groups but uptake inhibition (K(m)) was greater in sham than OVX. Dopamine neuron number and density in SN and VTA were greater in shams. Sham females with the largest uterine weights exhibited the highest density of dopamine neurons in the SN, and the most cocaine-stimulated behavior and dopamine efflux. Ovariectomy eliminated these relationships. The authors postulate that SN density could link ovarian hormones and high-psychostimulant responses in females. Similar mechanisms may be involved in individual differences in the addiction vulnerability of women. Walker QD, Johnson ML, Van Swearingen AE, Arrant AE, Caster JM, Kuhn CM. Individual differences in psychostimulant responses of female rats are associated with ovarian hormones and dopamine neuroanatomy. Neuropharmacology. 2012 Feb 8. [Epub ahead of print]

**Suppression Of Cocaine Self-Administration In Monkeys: Effects Of Delayed Punishment** Delaying presentation of a drug can decrease its effectiveness as a reinforcer, but the effect of delaying punishment of drug self-administration is unknown. This study examined whether a histamine injection could punish cocaine self-administration in a drug-drug choice, whether delaying histamine would decrease its effectiveness, and whether the effects of delay could be described within a delay discounting framework. Monkeys were implanted with double-lumen catheters to allow separate injection of cocaine and histamine. In discrete trials, subjects first chose between cocaine (50 or 100 μg/kg/inj) alone and an injection of the same dose of cocaine followed immediately by an injection of histamine (0.37-50 μg/kg). Next, they chose between cocaine followed immediately by histamine and cocaine followed by an equal but delayed dose of histamine. When choosing between cocaine alone and cocaine followed immediately by histamine, preference increased with histamine dose from indifference to >80% choice of cocaine alone. When choosing between cocaine followed by immediate histamine and cocaine followed by delayed histamine, monkeys showed strong position preferences. When delayed histamine was associated with the nonpreferred position, preference for that option increased with delay from ≤30% to >85%. The corresponding decrease in choice of the preferred position was well described by a hyperboloid discounting function. Histamine can function as a punisher in the choice between injections of cocaine and delay can decrease its effectiveness as a punisher. The effects of delaying punishment of drug self-administration can be conceptualized within the delay discounting framework. Woolverton WL, Freeman KB, Myerson J, Green L. Suppression of cocaine self-administration in monkeys: effects of delayed punishment. Psychopharmacology (Berl). 2012 Apr; 220(3): 509-517.

**Gβ5-RGS Complexes Are Gatekeepers Of Hyperactivity Involved In Control Of Multiple Neurotransmitter Systems** Knowledge about genes involved in the control of basal motor activity that may contribute to the pathology of the hyperactivity disorders, e.g., attention deficit hyperactivity disorder (ADHD), is limited. Disruption of monoamine neurotransmitter signaling through G protein-coupled receptors (GPCR) is considered to be a major contributing factor to the etiology of the ADHD. Genetic association evidence and functional data suggest that regulators of G protein signaling proteins of the R7 family (R7 RGS) that form obligatory complexes with type 5 G protein beta subunit (Gβ5) and negatively regulate signaling downstream from monoamine GPCRs may play a role in controlling hyperactivity. To test this hypothesis, the authors conducted behavioral, pharmacological, and neurochemical studies using a genetic mouse model that lacked Gβ5, a subunit essential for the expression of the entire R7 RGS family. Elimination of Gβ5-RGS complexes led to a striking level of hyperactivity that far exceeds activity levels previously observed in animal models. This hyperactivity was accompanied by motor learning deficits and paradoxical behavioral sensitization to a novel environment. Neurochemical studies indicated that Gβ5-RGS-deficient mice had higher sensitivity of inhibitory GPCR signaling and deficits in basal levels, release, and reuptake of dopamine. Surprisingly, pharmacological treatment with monoamine reuptake inhibitors failed to alter hyperactivity. In contrast, blockade of NMDA receptors reversed the expression of hyperactivity in Gβ5-RGS-deficient mice. These findings establish that Gβ5-RGS complexes are critical regulators of monoamine-NMDA receptor signaling cross-talk and link these complexes to disorders that manifest as hyperactivity, impaired learning, and motor dysfunctions. Xie K, Ge S, Collins VE, Haynes CL, Renner KJ, Meisel RL, Lujan R, Martemyanov KA. Gβ5-RGS complexes are gatekeepers of hyperactivity involved in control of

multiple neurotransmitter systems. Psychopharmacology (Berl). 2012 Feb; 219(3): 823-834. Epub 2011 Jul 16.

**Inactivation Of The Central Nucleus Of The Amygdala Reduces The Effect Of Punishment On Cocaine Self-Administration In Rats** Continued cocaine use despite the negative consequences is a hallmark of cocaine addiction. One such consequence is punishment, which is often used by society to curb cocaine use. Unfortunately, little is known about the mechanism involved in regulation by punishment of cocaine use. The fact that cocaine addicts continue to use cocaine despite potentially severe punishment suggests that the mechanism may be impaired. Such impairment is expected to critically contribute to compulsive cocaine use. This study was aimed at testing the hypothesis that the central nucleus of the amygdala (CeN) plays a critical role in such regulation. To this end, rats were trained to press a lever to self-administer cocaine under a chained schedule: a response on one lever (cocaine-seeking lever) led to access to the other lever (cocaine-taking lever), on which a response was reinforced by cocaine and cues. Thereafter, responses on the seeking lever were punished by footshock with a probability of 0.5. Cocaine self-administration (SA) was significantly suppressed by punishment in an intensity-dependent manner. Interestingly, rats trained with daily 6-h (extended access) but not 2-h (limited access) sessions showed resistance to the lower intensity of punishment. Inactivation of the CeN induced a robust anti-punishment effect in both groups. These data provided evidence that the CeN is a critical neural substrate involved in regulation by punishment of cocaine SA. Rats with a history of extended cocaine SA appeared to be less sensitive to punishment. The decreased sensitivity could result from the neuroplastic changes induced by extended cocaine SA in the CeN. Xue Y, Steketee JD, Sun W. Inactivation of the central nucleus of the amygdala reduces the effect of punishment on cocaine self-administration in rats. Eur J Neurosci. 2012 Mar; 35(5): 775-783. doi: 10.1111/j.1460-9568.2012.08000.x. Epub 2012 Feb 6.

**Brain-Cocaine Concentrations Determine The Dose Self-Administered By Rats On A Novel Behaviorally Dependent Dosing Schedule** A novel behaviorally dependent dosing (BDD) schedule was used to examine the relationship between doses of cocaine self-administered by rats and brain drug levels within a session. The BDD schedule used a hold-down response to activate a syringe pump. The length of time the lever was held down determined the duration that the syringe pump was activated. In the first experiment, rats self-administered cocaine for daily 3 h sessions and brain levels of cocaine were modeled using well-established parameters. Although analysis revealed that rats self-administered doses within a predicted range, one extremely large dose was consistently observed at the beginning of each session when brain levels of cocaine were low. In the second experiment, the authors introduced a range of timeout periods (10-25 min) in order to produce variability in brain-cocaine concentrations. Animals self-administered larger doses immediately following each timeout period and the dose size was inversely correlated with the length of the timeout. These results show that the dose of cocaine that rats self-administer within a session is inversely related to the amount of drug on board. Zimmer BA, Dobrin CV, Roberts DC. Brain-cocaine concentrations determine the dose self-administered by rats on a novel behaviorally dependent dosing schedule. Neuropsychopharmacology. 2011 Dec; 36(13): 2741-2749. doi: 10.1038/npp.2011.165.

**Cocaine Self-Administration In Rats: Hold-Down Procedures** For decades, researchers have used animal self-administration models to examine the effects drugs of abuse have on physiology and behavior. Sophisticated self-administration procedures have been developed to model many different aspects of drug addiction. The hold-down procedure provides animals with control over the amount of each injection. Holding the lever down turns the syringe pump on and subsequently releasing the lever turns the pump off. In this way, animals can hold the lever down for any duration of time thereby self-administering any dose on a continuous spectrum. This procedure eliminates some of the ambiguity in translating results from effects only observed at one unit dose and allows examination of which dose the animal "prefers" at different times. Zimmer BA, Roberts DC. Cocaine self-administration in rats: hold-down procedures. Methods Mol Biol. 2012; 829: 279-290.

**Withdrawal from THC During Adolescence: Sex Differences in Locomotor Activity and Anxiety** Research suggests that the use and abuse of marijuana can be especially harmful if it occurs during adolescence, a period of vast developmental changes throughout the brain. Due to the localization of cannabinoid receptors within the limbic system and the established effects of cannabinoids on emotional states and anxiety levels of rats and humans, the authors studied the sex- and dose-related effects of Δ(9)-tetrahydrocannabinol (THC, the main psychoactive component in marijuana) on behavior and anxiety during spontaneous withdrawal. Male and female Sprague Dawley rats were administered 2, 7.5 or 15mg/kg THC or vehicle from postnatal day 35-41 (approximating mid-adolescence in humans). Locomotor activity and anxiety-related behaviors were measured during drug administration and abstinence. THC caused significant dose-dependent locomotor depression during drug administration. Locomotor depression initially abated upon drug cessation, but re-emerged by the end of the abstinence period and was greater in female than male rats. The authors found sensitization to the locomotor-depressing effects of THC in middle- and high-dose rats and the subsequent development of tolerance in high-dose rats. The high dose of THC increased anxiety-like behaviors while the low dose decreased anxiety-like behaviors during drug administration, with females more sensitive to the anxiogenic effects of THC than males. During abstinence, females were again especially sensitive to the anxiogenic effects of THC. This study demonstrates sexually-dimorphic effects of THC on anxiety-related behaviors and locomotor activity during and after THC administration during adolescence. This information may be useful in the development of therapeutic approaches for the treatment of marijuana withdrawal in adolescents. Harte-Hargrove LC, Dow-Edwards DL. Withdrawal from THC during adolescence: Sex differences in locomotor activity and anxiety. Behav Brain Res. 2012 Mar 5. [Epub ahead of print]:

**Environmental Enrichment Reduces Attribution Of Incentive Salience To A Food-Associated Stimulus** Animals reared in an enriched environment are less vulnerable to abuse-like behavior and exhibit less persistent drug seeking, perhaps due to a decrease in the incentive value of stimuli associated with reward. The present study investigated the effects of environmental enrichment on Pavlovian conditioned approach (PCA) performance, a measure of incentive salience attribution. Rats were first reared from postnatal day 21 to postnatal day 51 in either an enriched environment with large cages, social cohorts and novel objects, or in an isolated environment with small, hanging cages, no social cohorts and no novel objects. Rats were then trained on a PCA task for 5 consecutive days, where a retractable lever was predictive of a food reward. Isolated rats predominantly exhibited sign-tracking responses directed toward

the reward-predicted lever (indicative of incentive salience attribution), while enriched rats predominantly exhibited goal-tracking responses directed toward the location of food delivery. Both groups learned their respective response type at equal rates. The results indicate that environmental enrichment reduces the readiness to attribute incentive value to reward-associated cues, which may explain the enrichment-induced protection against addiction-like behaviors. Beckmann JS, and Bardo MT. Environmental enrichment reduces attribution of incentive salience to a food-associated stimulus. Beh. Brain Res. 2012 Jan; 226(1): 331-334.

**Schizophrenia And Tobacco Smoking Comorbidity: NAChR Agonists In The Treatment Of Schizophrenia-Associated Cognitive Deficits** Tobacco smoking is a preventable cause of morbidity and mortality throughout the world. Very high rates of tobacco smoking are seen in patients with schizophrenia. Importantly, smokers with schizophrenia generally have higher nicotine dependence scores, experience more severe withdrawal symptoms upon smoking cessation, have lower cessation rates than healthy individuals, and suffer from significant smoking-related morbidity and premature mortality compared with the general population. Interestingly, significant disturbances in cholinergic function are reported in schizophrenia patients. The high smoking-schizophrenia comorbidity observed in schizophrenia patients may be an attempt to compensate for this cholinergic dysfunction. Cholinergic neurotransmission plays an important role in cognition and is hypothesized to play an important role in schizophrenia-associated cognitive deficits. In this review, preclinical evidence highlighting the beneficial effects of nicotine and subtype-selective nicotinic receptor agonists in schizophrenia-associated cognitive deficits, such as working memory and attention, is discussed. Furthermore, some of the challenges involved in the development of procognitive medications, particularly subtype-selective nicotinic receptor agonists, are also discussed. Amelioration of schizophrenia-associated cognitive deficits may help in the treatment of schizophrenia-smoking comorbidity by promoting smoking cessation and thus help in the better management of schizophrenia patients. D'Souza MS, Manoranjan S, Markou A. Schizophrenia and tobacco smoking comorbidity: nAChR agonists in the treatment of schizophrenia-associated cognitive deficits. J Neuropharm. 2012 Mar; 62(3): 1546-1573.

**Long-Term Effects Of Juvenile Nicotine Exposure On Abstinence-Related Social Anxiety-Like Behavior And Amygdalar Cannabinoid Receptor 1 (CB1R) mRNA Expression In The Novelty-Seeking Phenotype** A rat model of novelty-seeking phenotype predicts vulnerability to nicotine relapse where locomotor reactivity to novelty is used to rank high (HR) versus low (LR) responders. The present study investigates the implication of cannabinoid receptor 1 (CBI R) in the basolateral (BLA) and the central (CeA) nuclei of amygdala in behaviorally sensitizing effects of nicotine and accompanying social anxiety following juvenile nicotine training and a 1- or 3-wk injection-free period in the novelty-seeking phenotype. Sprague-Dawley rats were phenotype screened, and received four, saline (1 ml/kg; s.c) or nicotine (0.35 mg/kg; s.c) injections, followed by a 1- or 3-wk injection-free period. Subsequently, animals were challenged with a low dose of nicotine (0.1 mg/kg; s.c.), subjected to the social interaction test and sacrificed. In situ hybridization histochemistry was used to assess CBI R messenger RNA (mRNA) levels in the amygdala. Nicotine pre-trained HRs displayed expression of locomotor sensitization to nicotine challenge along with enhanced social anxiety compared to saline pre-trained controls following a 1- or 3-wk injection-free period. HR-specific behavioral effects were accompanied by decreased CB1R mRNA levels in the CeA and the BLA following a 1-wk

injection-free period. Decreased CB1R mRNA levels in both compartments of the amygdala were also observed following nicotine challenge in saline pre-trained HRs after a 3-wk injection-free period compared to HRs after a 1-wk injection-free period. These findings show robust, long-lasting expression of behavioral sensitization to nicotine in HRs associated with changes in amygdalar CB1R mRNA as a potential substrate for abstinence-related anxiety. Aydin C, Oztan O, Isgor C. Long-term effects of juvenile nicotine exposure on abstinence-related social anxiety-like behavior and amygdalar cannabinoid receptor 1 (CB1R) mRNA expression in the novelty-seeking phenotype. Beh Brain Res. 2012 Mar 1; 228(1): 236-239.

**Environmental Enrichment Counters Cocaine Abstinence-Induced Stress And Brain Reactivity To Cocaine Cues But Fails To Prevent The Incubation Effect** Environmental enrichment (EE) during a period of forced abstinence attenuates incentive motivational effects of cocaine-paired stimuli. Here the authors examined whether EE during forced abstinence from cocaine self-administration would prevent time-dependent increases in cue-elicited cocaine-seeking behavior (i.e. the incubation effect). Rats were trained to self-administer cocaine, which was paired with light/tone cues, for 15 days while living in isolated conditions (IC). Controls received yoked saline infusions. Subsequently, rats were assigned to live in either continued IC or EE for either 1 or 21 days of forced abstinence prior to a test for cocaine-seeking behavior. During testing, responding resulted only in presentation of the light/tone cues. Contrary to the authors' prediction, cocaine-seeking behavior increased over time regardless of living condition during abstinence; however, EE attenuated cocaine-seeking behavior relative to IC regardless of length of abstinence. Brains were harvested and trunk blood was collected immediately after the 60-minute test and later assayed. Results indicated that short-term EE elevated hippocampal brain-derived neurotrophic factor and reduced plasma corticosterone compared with IC. Furthermore, 21 days of EE during forced abstinence prevented increases in the cue-elicited amygdala phosphorylated extracellular signal-regulated kinase expression that was observed in IC rats. These findings suggest that EE attenuates incentive motivational effects of cocaine cues through a mechanism other than preventing the incubation effect, perhaps involving reduction of stress and neural activity in response to cocaine-paired cues during acute withdrawal. Thiel KJ, Painter MR, Pentkowski NS, Mitroi D, Crawford CA, Neisewander JL. Environmental enrichment counters cocaine abstinence-induced stress and brain reactivity to cocaine cues but fails to prevent the incubation effect. Addiction Bio. 2012 Mar; 17(2): 365-377.

**Varenicline Dose Dependently Enhances Responding for Nonpharmacological Reinforcers and Attenuates the Reinforcement-Enhancing Effects of Nicotine** Varenicline (VAR), a partial nicotinic agonist, is one of the most effective smoking cessation pharmacotherapies. The therapeutic efficacy of VAR could be partly the result of substituting for and/or blocking the reinforcement-enhancing effects of nicotine (NIC). The authors assessed the effects of VAR alone and in combination with NIC (0.4 mg/kg) while rats pressed the lever for a moderately reinforcing visual stimulus (VS). Rats were injected with placebo (0.9% saline), NIC, VAR (0.1-1 mg/kg), or NIC + VAR. A follow-up study was conducted with a broader dose range of VAR-alone dosages (0.01-3.0 mg/kg). All drug manipulations were conducted in a between-subjects design to prevent confounding effects of repeated exposure. There was a dose-dependent effect of VAR alone. Moderate doses of VAR (0.1 and 1.0 mg/kg) increased the number of VS presentations earned, while lower and higher VAR doses (0.01 and 3.0 mg/kg) did not change responding for the VS. VAR dose dependently attenuated the reinforcement-enhancing effects of

NIC, with the highest dose (1.0 mg/kg) exhibiting the greatest antagonist effect. The results of these studies support the assertion that the therapeutic efficacy of VAR may be due to the partial agonist characteristics of the drug, specifically, its ability to partially replace the reinforcement-enhancing effects of NIC as well as antagonize these effects. Levin ME, Weaver MT, Palmatier MI, Caggiula AR, Sved AF, Donny EC. Varenicline dose dependently enhances responding for nonpharmacological reinforcers and attenuates the reinforcement-enhancing effects of nicotine. Nic & Tob Res. 2012 Mar; 14(3): 229-305.

**GABA(A)-Positive Modulator Selective Discriminative Stimulus Effects Of 1,1,1-Trichloroethane Vapor** The abuse-related behavioral effects of inhalant vapors are poorly understood but probably involve multiple neurotransmitter receptor mechanisms. The present study examined the receptor systems responsible for transducing the discriminative stimulus of the abused chlorinated hydrocarbon 1,1,1-trichloroethane (TCE) in mice. Thirty mice were trained to discriminate 10 min of 12 000 ppm TCE vapor exposure from air using an operant procedure. Substitution tests were then conduced with positive GABA(A) receptor modulators and/or NMDA receptor antagonists. The nonselective benzodiazepines midazolam and diazepam produced 62% and 61% and the barbiturate pentobarbital produced 68% TCE-lever selection. Zaleplon, an alphal subunit-preferring positive GABA(A) receptor benzodiazepine-site positive modulator resulted in 29% ICE-lever selection. The direct extrasynaptic GABA(A) agonist gaboxodol (THIP) and the GABA reuptake inhibitor tiagabine failed to substitute for ICE. No substitution was elicited by a competitive (CGS-19755), noncompetitive (dizocilpine) or glycine-site (L701,324) NMDA antagonist. The mixed benzodiazepine/noncompetitive NMDA antagonist anesthetic Telazol and the anticonvulsant valproic acid exhibited low levels of partial substitution for ICE (38% and 39%, respectively). Ethanol and nitrous oxide failed to substitute for ICE. The results suggest that the discriminative stimulus effects of TCE are fairly selectively mediated by positive modulation of GABA(A) receptors. The failure of gaboxadol to substitute and the poor substitution by zaleplon suggests that extrasynaptic GABA(A) receptors as well as GABA(A) receptors containing alphal subunits and are not involved in transducing the discriminative stimulus of TCE. Studies with additional GABA(A) benzodiazepine-site positive modulators will be necessary to confirm and extend these findings. Shelton KL and Nicholson KL. GABA(A)-positive modulator selective discriminative stimulus effects of 1,1,1-trichloroethane vapor. Drug & Alc Depend. 2012 Feb 1; 121: 103-109.

**Delta(9)-Tetrahydrocannabinol Attenuates MDMA-Induced Hyperthermia In Rhesus Monkeys** Cannabis is commonly consumed by Ecstasy (3,4-methylenedioxymethamphetamine; MDMA) users, including as an intentional strategy to manipulate the drug experience. The most active psychoactive constituent in cannabis, Delta(9)-tetrahydrocannabinol (THC), and other drugs with partial or full agonist activity at the CB1 receptor, produces a reduction of body temperature in rodents. Reports show that administration of THC can attenuate temperature increases caused by MDMA in mice or rats; however, a recent study in humans shows that THC potentiates MDMA-induced temperature elevations. Relatively little scientific evidence on the thermoregulatory effects of THC in monkeys is available. The body temperature of male rhesus macaques was recorded after challenge with THC (0.1-0.3 mg/kg, i.m.) or combined challenge of THC with the CB1 receptor antagonist SR141716 (Rimonabant; 0.3 mg/kg, i.m.) or combined challenge of THC (0.1, 0.3 mg/kg, i.m.) with MDMA (1.78 mg/kg p.o.) using minimally-invasive, implanted radiotelemetry techniques. THC reduced the body temperature of monkeys

in a dose-dependent manner with the nadir observed 3-5 h post-injection; however, an attenuation of normal circadian cooling was also produced overnight following dosing. Hypothermia induced by THC (0.3 mg/kg, i.m.) was prevented by Rimonabant (0.3 mg/kg, i.m.). Finally, 0.3 mg/kg THC (i.m.) attenuated the elevation of body temperature produced by MDMA for about 4 h after oral dosing. As with rodents THC produces a robust and lasting decrement in the body temperature of rhesus monkeys; this effect is mediated by the CB1 receptor. THC also protects against the immediate hyperthermic effects of MDMA in monkeys in a dose-dependent manner. Nevertheless, a paradoxical attenuation of circadian cooling overnight after the THC/MDMA combination cautions that longer-term effects may be critical in assessing risks for the recreational user of cannabis in combination with MDMA. Taffe MA. Delta(9)-Tetrahydrocannabinol attenuates MDMA-induced hyperthermia in Rhesus monkeys. J Neurosci. 2012 Jan 10; 201: 125-133.

**Dissociable Effects Of Monoamine Reuptake Inhibitors On Distinct Forms Of Impulsive Behavior In Rats** High levels of impulsivity are a core symptom of psychiatric disorders such as ADHD, mania, personality disorders and drug addiction. The effectiveness of drugs targeting dopamine (DA), noradrenaline (NA) and/or serotonin (5-HT) in the treatment of impulse control disorders emphasizes the role of monoaminergic neurotransmission in impulsivity. However, impulsive behavior is behaviorally and neurally heterogeneous, and several caveats remain in our understanding of the role of monoamines in impulse control. This study aims to investigate the role of DA, NA and 5-HT in two main behavioral dimensions of impulsivity. The effects of selective DA (GBR12909; 2.5-10 mg/kg), NA (atomoxetine; 0.3-3.0 mg/kg) and 5-HT (citalopram; 0.3-3.0 mg/kg) reuptake inhibitors as well as amphetamine (0.25-1.0 mg/kg) were evaluated on impulsive action in the five-choice serial reaction time task (5-CSRTT) and impulsive choice in the delayed reward task (DRT). In the 5-CSRTT, neuropharmacological challenges were performed under baseline and long intertrial interval (ITI) conditions to enhance impulsive behavior in the task. Amphetamine and GBR12909 increased impulsive action and perseverative responding and decreased accuracy and response latency in the 5-CSRTT. Atomoxetine increased errors of omission and response latency under baseline conditions in the 5-CSRTT. Under a long ITI, atomoxetine also reduced premature and perseverative responding and increased accuracy. Citalopram improved impulse control in the 5-CSRTT. Amphetamine and GBR12909, but not citalopram or atomoxetine, reduced impulsive choice in the DRT. Elevation of DA neurotransmission increases impulsive action and reduces impulsive choice. Increasing NA or 5-HT neurotransmission reduces impulsive action. Baarendse PJJ, Vanderschuren LJMJ. Dissociable effects of monoamine reuptake inhibitors on distinct forms of impulsive behavior in rats. Psychopharm 2012 Jan; 219: 313-326.

**Access To A Running Wheel Decreases Cocaine-Primed And Cue-Induced Reinstatement In Male And Female Rats** Relapse to drug use after a period of abstinence is a persistent problem in the treatment of cocaine dependence. Physical activity decreases cocaine self-administration in laboratory animals and is associated with a positive prognosis in human substance-abusing populations. The purpose of this study was to examine the effects of long-term access to a running wheel on drug-primed and cueinduced reinstatement of cocaine-seeking behavior in male and female rats. Long-Evans rats were obtained at weaning and assigned to sedentary (no wheel) and exercising (access to wheel) groups for the duration of the study. After 6 weeks, rats were implanted with intravenous catheters and trained to self-administer cocaine

for 14 days. After training, saline was substituted for cocaine and responding was allowed to extinguish, after which cocaine-primed reinstatement was examined in both groups. Following this test, cocaine self-administration was re-established in both groups for a 5-day period. Next, a second period of abstinence occurred in which both cocaine and the cocaine-associated cues were withheld. After 5 days of abstinence, cue-induced reinstatement was examined in both groups. Sedentary and exercising rats exhibited similar levels of cocaine self-administration, but exercising rats responded less than sedentary rats during extinction. In tests of cocaine-primed and cue-induced reinstatement, exercising rats responded less than sedentary rats, and this effect was apparent in both males and females. These data indicate that long-term access to a running wheel decreases drug-primed and cue-induced reinstatement, and that physical activity may be effective at preventing relapse in substance-abusing populations. Smith MA, Pennock MM, Walker KL, Lang KC. Access to a running wheel decreases cocaine-primed and cue-induced reinstatement in male and female rats. Drug & Alc Depend 2012 Feb 1; 121: 54-61.

**Reciprocal Inhibitory Effects Of Intravenous D-Methamphetamine Self-Administration And Wheel Activity In Rats** Some epidemiological and cessation studies suggest physical exercise attenuates or prevents recreational drug use in humans. Preclinical studies indicate that wheel activity reduces cocaine self-administration in rats; this may, however, require the establishment of compulsive wheel activity. Effects of concurrent wheel activity on intravenous d-methamphetamine (METH) self-administration were examined in male Wistar and Sprague Dawley rats with negligible prior wheel experience. Wistar rats self-administered METH (0.05 mg/kg/inf) under a fixed-ratio 1 (FR1) schedule with concurrent access to an activity wheel during sessions 1-14, 8-21 or 15-21. Control rats which did not self-administer METH had access to an activity wheel during sessions 1-14,8-21 or 15-28. Sprague Dawley rats self-administered METH (0.1 mg/kg/inf) under FR1 for 14 sessions with either concurrent access to a locked or an unlocked activity wheel. METH self-administration was lower when the wheel was available concurrently from the start of self-administration training in both strains, even though Sprague Dawley rats self-administered twice as many METH infusions and ran one-sixth as much on the wheel compared to Wistar rats. Wheel access initiated after 7 or 14 days had no effect on METH self-administration in Wistar rats. Wheel activity was significantly reduced in these groups compared with the group with concurrent wheel and METH access for the first 14 sessions. These data show that METH self-administration is reduced by exercise if initiated from the start of self-administration and that prior METH self-administration experience interferes with the value of exercise as a reinforcer. Miller ML, Vaillancourt BD, Wright MJ, Aarde SM, Vandewater SA, Creehan KM, Taffe MA. Reciprocal inhibitory effects of intravenous d-methamphetamine self-administration and wheel activity in rats. Drug & Alc Depend 2012 Feb 1; 121: 90-96.

**Glutamatergic Medications For The Treatment Of Drug And Behavioral Addictions** Historically, most pharmacological approaches to the treatment of addictive disorders have utilized either substitution-based methods (i.e., nicotine replacement or opioid maintenance) or have targeted monoaminergic or endogenous opioidergic neurotransmitter systems. However, substantial evidence has accumulated indicating that ligands acting on glutamatergic transmission are also of potential utility in the treatment of drug addiction, as well as various behavioral addictions such as pathological gambling. The purpose of this review is to summarize the pharmacological mechanisms of action and general clinical efficacy of glutamatergic

medications that are currently approved or are being investigated for approval for the treatment of addictive disorders. Medications with effects on glutamatergic transmission that will be discussed include acamprosate, N-acetylcysteine, D-cycloserine, gabapentin, lamotrigine, memantine, modafinil, and topiramate. The authors conclude that manipulation of glutamatergic neurotransmission is a relatively young but promising avenue for the development of improved therapeutic agents for the treatment of drug and behavioral addictions. Olive MF, Cleva RM, Kalivas PW, Malcolm RJ. Glutamatergic medications for the treatment of drug and behavioral addictions Pharma Biochem & Beh. 2012 Feb; 100(4SI): 801-810.

**Exploratory Studies In Sensory Reinforcement In Male Rats: Effects Of Methamphetamine** Understanding sensory reinforcement and the effects of stimulant drugs on sensory reinforcers is potentially important for understanding their influence on addiction processes. Experiment 1 explored the reinforcing properties of a visual stimulus and the effects of methamphetamine (METH) on responding maintained by a visual reinforcer (VRF) in male rats. Snout poke responses to the active alternative produced the VRF according to variable interval (VI) schedules of reinforcement, and responses to an inactive alternative had no programmed effect. Experiment 2 explored the effects of METH on choice between the VRF and a water reinforcer (H2ORF) using concurrent VI schedules in male rats. In Experiment 1, response-contingent onset of the VRF produced an increase in both the relative frequency and absolute rate of active responding. The rate of both active and inactive responding declined across the 40-min test sessions. METH did not differentially enhance active responding for the VRF. Instead, METH nondifferentially increased the rate of responding and attenuated the within-session decline of responding. In Experiment 2, METH differentially increased the rate of responding for the VRF relative to the H2ORF. The results of these exploratory experiments indicate that the reinforcing effects of the VRF were weak and transient. In addition, METH treatment increased responding, and the specificity of the enhancement of METH was dependent upon the testing conditions. Potential explanations of these differences, such as novelty and reinforcer type, are discussed. Gancarz AM, Ashrafioun L, San George MA, Hausknecht KA, Hawk LW Jr, Richards JB. Exploratory studies in sensory reinforcement in male rats: effects of methamphetamine. Exp Clin Psychopharmacol. 2012 Feb; 20(1): 16-27.

**Attentional Bias To Drug Cues Is Elevated Before And During Temptations To Use Heroin And Cocaine** Relapse is an important problem in substance dependence treatment. When drug users try to abstain from drug use, they often report strong temptations to use drugs. Temptation episodes have commonalities with relapse episodes, and assessment of temptation episodes may help to identify individuals at risk of relapse. This study aims to examine affect and cognition prior to and during temptation episodes by administering self-report and implicit cognitive assessments on a handheld computer (PDA) using Ecological Momentary Assessment. Heroin-dependent patients (N = 68) attending a drug detoxification unit completed up to four random assessments (RAs) per day on a PDA for 1 week. They also completed an assessment when they experienced a temptation to use drugs (temptation assessment; TA). Participants completed 1,482 assessments (353 TAs, 1,129 RAs). The rate of TAs was maximal during the first 2 days. Participants reported higher levels of negative affect, anxiety, and difficulty concentrating, and more positive explicit attitudes to drugs, at TAs compared to RAs. In addition, they exhibited elevated attentional bias to drug cues (assessed using the modified Stroop task) at TAs compared to RAs. Implicit affective associations with drug cues (assessed using the Implicit Association

Test) were not different at TAs compared to RAs. Attentional bias was elevated in the 1 h prior to the entry of a temptation episode. Elevated attentional bias may be a harbinger of temptation episodes. Interventions that target cognitions prior to or during temptation episodes may reduce the probability or severity of a temptation episode. Waters AJ, Marhe R, Franken IHA. Attentional bias to drug cues is elevated before and during temptations to use heroin and cocaine Psychopharmacology 2012 Feb; 219(3): 909-921.

**Dopamine Receptor Blockade Attenuates The General Incentive Motivational Effects Of Noncontingently Delivered Rewards And Reward-Paired Cues Without Affecting Their Ability To Bias Action Selection** Environmental cues affect our behavior in a variety of ways. Despite playing an invaluable role in guiding our daily activities, such cues also appear to trigger the harmful, compulsive behaviors that characterize addiction and other disorders of behavioral control. In instrumental conditioning, rewards and reward-paired cues bias action selection and invigorate reward-seeking behaviors, and appear to do so through distinct neurobehavioral processes. Although reward-paired cues are known to invigorate performance through a dopamine-dependent incentive motivational process, it is not known if dopamine also mediates the influence of rewards and reward-paired cues over action selection. The current study contrasted the effects of systemic administration of the nonspecific dopamine receptor antagonist flupentixol on response invigoration and action bias in Pavlovian-instrumental transfer, a test of cue-elicited responding, and in instrumental reinstatement, a test of noncontingent reward-elicited responding. Hungry rats were trained on two different stimulus-outcome relationships (eg, tone-grain pellets and noise-sucrose solution) and two different action-outcome relationships (eg, left press-grain and right press-sucrose). At test, the authors found that flupentixol pretreatment blocked the response invigoration generated by the cues but spared their ability to bias action selection to favor the action whose outcome was signaled by the cue being presented. The response-biasing influence of noncontingent reward deliveries was also unaffected by flupentixol. Interestingly, although flupentixol had a modest effect on the immediate response invigoration produced by those rewards, it was particularly potent in countering the lingering enhancement of responding produced by multiple reward deliveries. These findings indicate that dopamine mediates the general incentive motivational effects of noncontingent rewards and reward-paired cues but does not support their ability to bias action selection. Ostlund SB, Maidment NT. Dopamine receptor blockade attenuates the general incentive motivational effects of noncontingently delivered rewards and reward-paired cues without affecting their ability to bias action selection. Neuropsychopharmacology. 2012 Jan; 37(2): 508-519. doi: 10.1038/npp.2011.217.

## BEHAVIORAL AND BRAIN DEVELOPMENT RESEARCH

**Longitudinal Effects of Prenatal Cocaine Use on Mother-Child Interactions at Ages 3 and 5 Years** The objective of this study was to assess the effect of maternal prenatal and past-year cocaine use on mother-child interactions across preschool years. The sample is drawn from the Miami Prenatal Cocaine Study, a longitudinal follow-up of prenatal cocaine exposure (PCE) in a large cohort of African-American infants prospectively enrolled at birth. Analyses are based on the 366 children (168 PCE and 198 non-cocaine-exposed) in the care of their biological mothers and with completed mother-child interaction measures at the 3- and/or 5-year assessments. Videotaped interactions were coded using a modified Egeland Teaching Task scheme. Generalized linear models with a generalized estimating equations approach were used to evaluate the effect of PCE on the overall quality of maternal-child interaction, measured by the Egeland total score at both study visits, and on the individual Egeland subscales at the 5-year visit, while adjusting for other suspected influences on interactions. PCE dyads demonstrated less optimal overall mother-child interactions compared with non-cocaine-exposed dyads. The estimated PCE-associated difference did not shift appreciably with statistical adjustment for child sex, child age at examination, or other birth covariates. PCE dyads with past-year maternal cocaine use had significantly lower Egeland summary scores compared with children with neither exposure. In subscale analyses, PCE was most strongly associated with greater maternal intrusiveness and boundary dissolution at the 5-year visit. Prenatal and past-year maternal cocaine use seems to be associated with poorer quality in mother-child interaction during early childhood. These dynamics should be considered when examining the association between PCE and child cognitive, behavioral, and academic outcomes. Mansoor E, Morrow CE, Accornero VH, Xue L, Johnson AL, Anthony JC, Bandstra ES. Longitudinal effects of prenatal cocaine use on mother-child interactions at ages 3 and 5 years. J Dev Behav Pediatr. 2012 Jan; 33(1): 32-41.

**Security of Attachment and Quality of Mother-Toddler Social Interaction in a High-Risk Sample** The quality of children's social interactions and their attachment security with a primary caregiver are two widely studied indices of socioemotional functioning in early childhood. Although both Bowlby and Ainsworth suggested that the parent-child interactions underlying the development of attachment security could be distinguished from other aspects of parent-child interaction (e.g., play), relatively little empirical research has examined this proposition. The aim of the current study was to explore this issue by examining concurrent relations between toddler's attachment security in the Strange Situation Procedure and quality of mother-child social interaction in a high-risk sample of toddlers characterized by prenatal cocaine exposure and low levels of maternal education. Analyses of variance suggested limited relations between attachment security and quality of social interaction. Further research examining the interrelations among various components of the parent-child relationship is needed. Haltigan JD, Lambert BL, Seifer R, Ekas NV, Bauer CR, Messinger DS. Security of attachment and quality of mother-toddler social interaction in a high-risk sample. Infant Behav Dev. 2012 Feb; 35(1): 83-93.

**Corticostriatal-Limbic Gray Matter Morphology in Adolescents with Self-Reported Exposure to Childhood Maltreatment** The objective of this study was to examine the relationship between self-reported exposure to childhood maltreatment (CM) and cerebral gray matter (GM) morphology in adolescents without psychiatric diagnoses. Associations were

examined between regional GM morphology and exposure to CM (measured using a childhood trauma self-report questionnaire for physical, emotional, and sexual abuse and for physical and emotional neglect).The setting is a University hospital. The participants are forty-two adolescents without psychiatric diagnoses. Correlations between childhood trauma self-report questionnaire scores and regional GM volume were assessed in voxel-based analyses of structural magnetic resonance images. Relationships among GM volume, subtypes of exposure to CM, and sex were explored. Childhood trauma self-report questionnaire total scores correlated negatively ($P < .005$) with GM volume in prefrontal cortex, striatum, amygdala, sensory association cortices, and cerebellum. Physical abuse, physical neglect, and emotional neglect were associated with rostral prefrontal reductions. Decreases in dorsolateral and orbitofrontal cortices, insula, and ventral striatum were associated with physical abuse. Decreases in cerebellum were associated with physical neglect. Decreases in dorsolateral, orbitofrontal, and subgenual prefrontal cortices, striatum, amygdala, hippocampus, and cerebellum were associated with emotional neglect. Decreases in the latter emotion regulation regions were also associated with childhood trauma self-report questionnaire scores in girls, while caudate reductions (which may relate to impulse dyscontrol) were seen in boys. Exposure to CM was associated with corticostriatal-limbic GM reductions in adolescents. Even if adolescents reporting exposure to CM do not present with symptoms that meet full criteria for psychiatric disorders, they may have corticostriatal-limbic GM morphologic alterations that place them at risk for behavioral difficulties. Vulnerabilities may be moderated by sex and by subtypes of exposure to CM. Edmiston EE, Wang F, Mazure CM, Guiney J, Sinha R, Mayes LC, Blumberg HP. Corticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. Arch Pediatr Adolesc Med. 2011 Dec; 165(12): 1069-1077.

**Adolescents' Depressive Symptoms Moderate Neural Responses to their Mothers' Positive Behavior** The way that parents express their emotions during interactions with their adolescent children is important for adolescent adjustment, and predicts adolescent emotional problems such as depression. In the current study, the authors assessed whether adolescent depressive symptoms were associated with neural activity during exposure to their mother's affective behavior. Thirty adolescents (18 females, mean age 17.35, s.d. 0.43) participated in an fMRI task that used digitized video segments of their own mother's, as well as an unfamiliar mother's affective behavior as stimuli. Exposure to one's own (compared to an unfamiliar) mother's positive (compared to neutral) behavior was associated with activation in the anterior and posterior cingulate, precuneus and ventrolateral prefrontal cortex. In contrast, exposure to positive behavior across own and an unfamiliar mother (controlling for neutral behavior) was associated with superior temporal sulcus, occipital pole, amygdala and striatum activity. Adolescent depressive symptoms were associated with reduced rostral anterior cingulate activity during exposure to one's own (compared to an unfamiliar) mother's positive behavior, and reduced striatal activity during exposure to positive behavior in general. This study represents an important step in furthering our understanding of the neural basis of affective processing in adolescents. Further, the results support a disruption of reward function in depression. Whittle S, Yücel M, Forbes EE, Davey CG, Harding IH, Sheeber L, Yap MB, Allen NB. Adolescents' depressive symptoms moderate neural responses to their mothers' positive behavior. Soc Cogn Affect Neurosci. 2012 Jan; 7(1): 23-34.

**An Assessment of the Individual and Collective Effects of Variants on Height using Twins and a Developmentally Informative Study Design** In a sample of 3,187 twins and 3,294 of their parents, the authors sought to investigate association of both individual variants and a genotype-based height score involving 176 of the 180 common genetic variants with adult height identified recently by the GIANT consortium. First, longitudinal observations on height spanning pre-adolescence through adulthood in the twin sample allowed us to investigate the separate effects of the previously identified SNPs on pre-pubertal height and pubertal growth spurt. The authors show that the effect of SNPs identified by the GIANT consortium is primarily on prepubertal height. Only one SNP, rs7759938 in LIN28B, approached a significant association with pubertal growth. Second, they show how using the twin data to control statistically for environmental variance can provide insight into the ultimate magnitude of SNP effects and consequently the genetic architecture of a phenotype. Specifically, the authors computed a genetic score by weighting SNPs according to their effects as assessed via meta-analysis. This weighted score accounted for 9.2% of the phenotypic variance in height, but 14.3% of the corresponding genetic variance. Longitudinal samples will be needed to understand the developmental context of common genetic variants identified through GWAS, while genetically informative designs will be helpful in accurately characterizing the extent to which these variants account for genetic, and not just phenotypic, variance. Vrieze SI, McGue M, Miller MB, Legrand LN, Schork NJ, Iacono WG. An assessment of the individual and collective effects of variants on height using twins and a developmentally informative study design. PLoS Genet. 2011 Dec; 7(12).

**Social-Environmental Factors Related to Prenatal Smoking** Cigarette smoking during pregnancy is a significant public health issue that has profound effects on maternal and fetal health. Although many women stop smoking upon pregnancy recognition, a large number continue. Given the higher burden of smoking among low-income women, the focus of this study is to examine the impact of pre-conception social-environmental influences on smoking cessation during the first trimester of pregnancy. Pregnant women who presented for prenatal were asked to complete a screening form at their first prenatal appointment. Women who agreed to participate were scheduled for a total of four interviews; a prenatal interview at the end of each trimester and a postnatal interview at 2 months of infant age. The sample for the current report consisted of pregnant women (first trimester) with a partner (N=316). After controlling for pre-conception heaviness of smoking, a number of social-environmental factors were associated with smoking during the first trimester. Women were more likely to smoke during the first trimester if their partner was a smoker; however, the presence of other household smokers was not associated with increased risk for smoking. Additionally, women with a greater proportion of friends (but not relatives) who smoked and more frequent exposure to environmental tobacco were more likely to smoke. This work found differential impacts of the social network on smoking suggesting that understanding relationship type, not simply number of smokers, may be important for smoking cessation efforts. Understanding differences in social network influences on smoking can help to inform interventions. Homish GG, Eiden RD, Leonard KE, Kozlowski LT. Social-environmental factors related to prenatal smoking. Addict Behav. 2012 Jan; 37(1): 73-77.

**Age and Sex Effects Levels of Choline Compounds in the Anterior Cingulate Cortex of Adolescent Methamphetamine Users** Methamphetamine can be neurotoxic to the adult brain; however, many individuals first use methamphetamine during adolescence, and the drug's impact on this period of brain development is unknown. Therefore, the authors evaluated young methamphetamine users for possible abnormalities in brain metabolite concentrations. Anterior cingulate cortex (ACC), frontal white matter (FWM), basal ganglia, and thalamus were studied with localized proton magnetic resonance spectroscopy in 54 periadolescent (ages 13-23 years) methamphetamine users and 53 comparison subjects. The concentrations of major brain metabolites and their associations with age, sex and cognition were assessed. FWM total-creatine correlated with age in methamphetamine-using males and comparison females, but not comparison males or methamphetamine-using females, leading to a drug by sex by age interaction (p=0.003) and ACC choline-containing compounds (CHO) correlated with age only in comparison males leading to a drug by sex by age interaction (p=0.03). Higher ACC CHO was associated with faster performance on the Stroop Interference task in the control males. Male methamphetamine users had slowest performance on the Stroop Interference task and did not show age-appropriate levels of ACC CHO. The altered age-appropriate levels of ACC CHO and poorer executive function in male methamphetamine users suggest methamphetamine abuse may interfere with brain maturation. These periadolescents did not have the abnormal neuronal markers previously reported in adult methamphetamine users, suggesting that neuronal abnormalities may be the result of long-term use or interference in normal cortical maturation, emphasizing the need for early intervention for young methamphetamine users. Cloak CC, Alicata D, Chang L, Andrews-Shigaki B, Ernst T. Age and sex effects levels of choline compounds in the anterior cingulate cortex of adolescent methamphetamine users. Drug Alcohol Depend. 2011 Dec 15; 119(3): 207-215.

**Fathering and Mothering in the Family System: Linking Marital Hostility and Aggression in Adopted Toddlers** Previous studies have linked marital conflict, parenting, and externalizing problems in early childhood. However, these studies have not examined whether genes account for these links nor have they examined whether contextual factors such as parental personality or financial distress might account for links between marital conflict and parenting. The authors used an adoption design to allow for a clear examination of environmental impact rather than shared genes of parents and children, and assessments of parental personality and financial strain to assess the effects of context on relationships between marriage and parenting of both mothers and fathers. Participants were 308 adoption-linked families comprised of an adopted child, her/his biological mother (BM), adoptive mother (AM) and adoptive father (AF). BMs were assessed 3-6 and 18 months postpartum and adoptive families were assessed when the child was 18 and 27 months old. Structural equations models were used to examine associations between marital hostility, fathers' and mothers' parenting hostility, and child aggressive behavior at 27 months of age. In addition, the contribution of financial strain and adoptive parent personality traits was examined to determine the associations with the spillover of marital hostility to hostile parenting. A hostile marital relationship was significantly associated with hostile parenting in fathers and mothers, which were associated with aggressive behavior in toddlers. Subjective financial strain was uniquely associated with marital hostility and child aggression. Antisocial personality traits were related to a more hostile/conflicted marital relationship and to hostile parenting. Results clarify mechanisms that may account for the success of early parent-child prevention programs that include a focus on parental economic strain and personality in addition

to parent training. Stover CS, Connell CM, Leve LD, Neiderhiser JM, Shaw DS, Scaramella LV, Conger R, Reiss D. Fathering and mothering in the family system: linking marital hostility and aggression in adopted toddlers. J Child Psychol Psychiatry. 2012 Apr; 53(4): 401-409.

**Negative Emotionality and Externalizing Problems in Toddlerhood: Overreactive Parenting as a Moderator of Genetic Influences** The current study examines the interplay between parental overreactivity and children's genetic backgrounds as inferred from birth parent characteristics on the development of negative emotionality during infancy, and in turn, to individual differences in externalizing problems in toddlerhood. The sample included 361 families linked through adoption (birth parents and adoptive families). Data were collected when the children were 9, 18, and 27 months old. Results indicated links between individual levels and changes in negative emotionality during infancy and toddlerhood to externalizing problems early in the third year of life. Findings also revealed an interaction between birth mother negative affect and adoptive mother overreactive parenting on children's negative emotionality. This Genotype × Environment interaction predicted externalizing problems indirectly through its association with negative emotionality and revealed stronger effects of genetic risk for children with less overreactive parenting from their mothers. Limitations of this study and directions for future research are discussed. Lipscomb ST, Leve LD, Shaw DS, Neiderhiser JM, Scaramella LV, Ge X, Conger RD, Reid JB, Reiss D. Negative emotionality and externalizing problems in toddlerhood: overreactive parenting as a moderator of genetic influences. Dev Psychopathol. 2012 Feb; 24(1): 167-179.

**Underpinnings of the Costs of Flexibility in Preschool Children: the Roles of Inhibition and Working Memory** This study addressed the respective contributions of inhibition and working memory to two underlying components of flexibility, goal representation (as assessed by mixing costs) and switch implementation (as assessed by local costs), across the preschool period. By later preschool age (4 years, 6 months and 5 years, 3 months), both inhibition and working-memory performance were associated with mixing costs, but not with local costs, whereas no relation was observed earlier (3 years, 9 months). The relations of inhibition and working memory to flexibility appear to emerge late in the preschool period and are mainly driven by goal representation. Chevalier N, Sheffield TD, Nelson JM, Clark CA, Wiebe SA, Espy KA. Underpinnings of the costs of flexibility in preschool children: the roles of inhibition and working memory. Dev Neuropsychol. 2012 Feb; 37(2): 99-118.

**Chronic Cocaine Exposure During Pregnancy Increases Postpartum Neuroendocrine Stress Responses** The cycle of chronic cocaine (CC) use and withdrawal results in increased anxiety, depression and disrupted stress-responsiveness. Oxytocin and corticosterone (CORT) interact to mediate hormonal stress responses and can be altered by cocaine use. These neuroendocrine signals play important regulatory roles in a variety of social behaviours, specifically during the postpartum period, and are sensitive to disruption by CC exposure in both clinical settings and preclinical models. To determine whether CC exposure during pregnancy affected behavioural and hormonal stress response in the early postpartum period in a rodent model, Sprague-Dawley rats were administered cocaine daily (30 mg/kg) throughout gestation (days 1-20). Open field test (OFT) and forced swim test (FST) behaviours were measured on postpartum day 5. Plasma CORT concentrations were measured prior to and following testing throughout the test day, while plasma and brain oxytocin concentrations were measured post-

testing only. Results indicated increased CORT response following the OFT in CC-treated dams ($p \leq 0.05$). CC-treated dams also exhibited altered FST behaviour ($p \leq 0.05$), suggesting abnormal stress responsiveness. Peripheral, but not central, oxytocin levels were increased by cocaine treatment ($p \leq 0.05$). Peripheral oxytocin and CORT increased following the FST regardless of treatment condition ($p \leq 0.05$). Changes in stress-responsiveness, both behaviourally and hormonally may underlie some deficits in maternal behaviour, thus a clearer understanding of CC's effect on the stress response system may potentially lead to treatment interventions which could be relevant to clinical populations. Additionally, these results indicate that CC treatment can have long-lasting effects on peripheral oxytocin regulation in rats, similar to changes observed in persistent social behaviour and stress-response deficits in clinical populations.
Williams SK, Barber JS, Jamieson-Drake AW, Enns JA, Townsend LB, Walker CH, Johns JM. Chronic cocaine exposure during pregnancy increases postpartum neuroendocrine stress responses. J Neuroendocrinol. Apr; 24(4): 701-711.

## EPIDEMIOLOGY RESEARCH

**Integrated HIV Testing, Malaria, and Diarrhea Prevention Campaign in Kenya: Modeled Health Impact and Cost-Effectiveness** A 2008 community integrated prevention campaign in Western Province, Kenya, reached 47,000 individuals over 7 days, providing HIV testing and counseling, water filters, insecticide-treated bed nets, condoms, and for HIV-infected individuals cotrimoxazole prophylaxis and referral for ongoing care. The authors modeled the potential cost-effectiveness of a scaled-up integrated prevention campaign. They estimated averted deaths and disability-adjusted life years (DALYs) based on published data on baseline mortality and morbidity and on the protective effect of interventions, including antiretroviral therapy. They incorporate a previously estimated scaled-up campaign cost. They used published costs of medical care to estimate savings from averted illness (for all three diseases) and the added costs of initiating treatment earlier in the course of HIV disease. Per 1000 participants, projected reductions in cases of diarrhea, malaria, and HIV infection avert an estimated 16.3 deaths, 359 DALYs and $85,113 in medical care costs. Earlier care for HIV-infected persons adds an estimated 82 DALYs averted (to a total of 442), at a cost of $37,097 (reducing total averted costs to $48,015). Accounting for the estimated campaign cost of $32,000, the campaign saves an estimated $16,015 per 1000 participants. In multivariate sensitivity analyses, 83% of simulations result in net savings, and 93% in a cost per DALY averted of less than $20. A mass, rapidly implemented campaign for HIV testing, safe water, and malaria control appears economically attractive. Kahn JG, Muraguri N, Harris B, Lugada E, Clasen T, Grabowsky M, Mermin J, Shariff S. PLoS One. 2012; 7(2): e31316. Epub 2012 Feb 8.

**Epigenetic and Inflammatory Marker Profiles Associated with Depression in a Community-Based Epidemiologic Sample** Recent work suggests that epigenetic differences may be associated with psychiatric disorders. Here the authors investigate, in a community-based sample, whether methylation profiles distinguish between individuals with and without lifetime depression. They also investigate the physiologic consequences that may be associated with these profiles. Using whole blood-derived genomic DNA from a subset of participants in the Detroit Neighborhood Health Study (DNHS), the authors applied methylation microarrays to assess genome-wide methylation profiles for over 14,000 genes in 33 persons who reported a lifetime history of depression and 67 non-depressed adults. Bioinformatic functional analyses were performed on the genes uniquely methylated and unmethylated in each group, and inflammatory biomarkers [interleukin (IL)-6 and C-reactive protein (CRP)] were measured to investigate the possible functional significance of the methylation profiles observed.Uniquely unmethylated gene sets distinguished between those with versus without lifetime depression. In particular, some processes (e.g. brain development, tryptophan metabolism) showed patterns suggestive of increased methylation among individuals with depression whereas others (e.g. lipoprotein) showed patterns suggestive of decreased methylation among individuals with depression. IL-6 and CRP levels were elevated among those with lifetime depression and, among those with depression only, IL-6 methylation showed an inverse correlation with circulating IL-6 and CRP.Genome-wide methylation profiles distinguish individuals with versus without lifetime depression in a community-based setting, and show coordinated signals with pathophysiological mechanisms previously implicated in the etiology of this disorder. Examining epigenetic mechanisms in concert with other dynamic markers of physiologic functioning should improve

our understanding of the neurobiology of depression. Uddin M, Koenen KC, Aiello AE, Wildman DE, de los Santos R, Galea S. Epigenetic and inflammatory marker profiles associated with depression in a community-based epidemiologic sample. Psychol Med. 2011; 41(5): 997-1007.

**Could A Continuous Measure Of Individual Transmissible Risk Be Useful In Clinical Assessment Of Substance Use Disorder? Findings from the National Epidemiological Survey on Alcohol and Related Conditions** Toward meeting the need for a measure of individual differences in substance use disorder (SUD) liability that is grounded in the multifactorial model of SUD transmission, this investigation tested to what degree transmissible SUD risk is better measured using the continuous Transmissible Liability Index (TLI) (young adult version) compared to alternative contemporary clinical methods. Data from 9,535 18- to 30-year-olds in the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions, a U.S. representative sample, were used to compute TLI scores and test hypotheses. Other variables were SUDs of each DSM-IV drug class, clinical predictors of SUD treatment outcomes, treatment seeking and usage, age of onset of SUDs and substance use (SU), and eligibility for SUD clinical trials.TLI scores account for variation in SUD risk over and above parental lifetime SUD, conduct and antisocial personality disorder criteria and frequency of SU. SUD risk increases two- to four-fold per standard deviation increment in TLI scores. The TLI is associated with SUD treatment seeking and usage, younger age of onset of SU and SUD, and exclusion from traditional clinical trials of SUD treatment. The TLI can identify persons with high versus low transmissible SUD risk, worse prognosis of SUD recovery and to whom extant SUD clinical trials results may not generalize. Recreating TLI scores in extant datasets facilitates etiology and applied research on the full range of transmissible SUD risk in development, treatment and recovery without obtaining new samples. Ridenour TA, Kirisci L, Tarter RE, Vanyukov MM. Could a continuous measure of individual transmissible risk be useful in clinical assessment of substance use disorder? Findings from the National Epidemiological Survey on Alcohol and Related Conditions. Drug Alcohol Depend. 2011; 119(1-2): 1-2.

**Racial/Ethnic Variations In Substance-Related Disorders Among Adolescents In The United States** While young racial/ethnic groups are the fastest growing population in the United States, data about substance-related disorders among adolescents of various racial/ethnic backgrounds are lacking. The objective of this study was to examine the magnitude of past-year DSM-IV substance-related disorders (alcohol, marijuana, cocaine, inhalants, hallucinogens, heroin, analgesic opioids, stimulants, sedatives, and tranquilizers) among adolescents of white, Hispanic, African American, Native American, Asian or Pacific Islander, and multiple race/ethnicity. The study design employed the 2005 to 2008 National Survey on Drug Use and Health. The setting was academic research. Study participants were noninstitutionalized household adolescents aged 12 to 17 years. Substance-related disorders were assessed by standardized survey questions administered using the audio computer-assisted self-interviewing method. Of 72,561 adolescents aged 12 to 17 years, 37.0% used alcohol or drugs in the past year; 7.9% met criteria for a substance-related disorder, with Native Americans having the highest prevalence of use (47.5%) and disorder (15.0%). Analgesic opioids were the second most commonly used illegal drugs, following marijuana, in all racial/ethnic groups; analgesic opioid use was comparatively prevalent among adolescents of Native American (9.7%) and multiple race/ethnicity (8.8%). Among 27,705 past-year alcohol or drug users, Native Americans

(31.5%), adolescents of multiple race/ethnicity (25.2%), adolescents of white race/ethnicity (22.9%), and Hispanics (21.0%) had the highest rates of substance-related disorders. Adolescents used marijuana more frequently than alcohol or other drugs, and 25.9% of marijuana users met criteria for marijuana abuse or dependence. After controlling for adolescents' age, socioeconomic variables, population density of residence, self-rated health, and survey year, adjusted analyses of adolescent substance users indicated elevated odds of substance-related disorders among Native Americans, adolescents of multiple race/ethnicity, adolescents of white race/ethnicity, and Hispanics compared with African Americans; African Americans did not differ from Asians or Pacific Islanders. Substance use is widespread among adolescents of Native American, white, Hispanic, and multiple race/ethnicity. These groups also are disproportionately affected by substance-related disorders. Wu L, Woody G, Yang C, Pan J, Blazer D. Racial/ethnic variations in substance-related disorders among adolescents in the United States. Arch Gen Psychiatry. 2011; 68(11): 1176-1185.

**Predicting Alcohol Consumption In Adolescence From Alcohol-Specific And General Externalizing Genetic Risk Factors, Key Environmental Exposures And Their Interaction** Alcohol consumption is influenced by specific genetic risk factors for alcohol use disorders (AUDs), non-specific genetic risk factors for externalizing behaviors and various environmental experiences. Knowledge of how these risk factors inter-relate through development is limited. Retrospective assessments in 1,796 adult male twins using a life history calendar of key environmental exposures and alcohol consumption from early adolescence to mid-adulthood. Analysis by linear mixed models.The importance of non-specific genetic risk factors on maximal alcohol consumption rose rapidly in early to mid-adolescence, peaked at ages 15-17 years and then declined slowly. Alcohol-specific genetic risk factors increased slowly in influence through mid-adulthood. The authors detected robust evidence for environmental moderation of genetic effects on alcohol consumption that was more pronounced in early and mid-adolescence than in later periods. Alcohol availability, peer deviance and low prosocial behaviors showing the strongest moderation effects. More interactions with environmental risk factors were seen for the non-specific externalizing disorder risk than for specific genetic risk for AUDs. The impact of specific and non-specific genetic influences on alcohol consumption have different development trajectories. Genetic effects on alcohol use are more pronounced when social constraints are minimized (e.g. low prosocial behaviors or parental monitoring) or when the environment permits easy access to alcohol and/or encourages its use (e.g. high alcohol availability or peer deviance). Gene-environment interactions influencing alcohol intake may be more robust at younger ages, indicating greater plasticity of genetic influences early in the development of drinking patterns. Kendler KS, Gardner C, Dick DM. Predicting alcohol consumption in adolescence from alcohol-specific and general externalizing genetic risk factors, key environmental exposures and their interaction. Psychol Med. 2011; 41(7): 1507-1516.

**Mental Health Service Use By Persons Of Asian Ancestry With DSM-IV Mental Disorders in the United States** This study compared the prevalence and odds of mental health service utilization among people of Asian ancestry with lifetime DSM-IV mood, anxiety, alcohol, and drug use disorders with utilization by members of other racial and ethnic groups with similar disorders. Between 2001 and 2002, a total of 43,093 non-institutionalized individuals were assessed by the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study of lifetime prevalence of DSM-IV psychiatric disorders and mental health service

utilization among various ethnic and racial groups. Among individuals with lifetime mood disorders, Asians had significantly lower mental health service utilization compared with whites (odds ratio [OR]=.31, 95% confidence interval [CI]=.21-.46), Hispanics (OR=.49, CI=.33-71), and Native Americans (OR=.27, CI=.15-.48) but similar utilization compared with blacks. There were no statistically significant differences in lifetime mental health service utilization for alcohol and drug use disorders among racial and ethnic groups. Asians with lifetime mood disorders underutilized mental health services even after adjustment was made for socioeconomic variables and years of residency in the United States. Future studies of culture-specific attitudes, correlates, and barriers to mental health service utilization are warranted. Lee S, Martins S, Keyes K, Lee H. Mental health service use by persons of Asian ancestry with DSM-IV mental disorders in the United States. Psychiatr Serv. 2011; 62 (10): 1180-1186.

**A Latent Class Analysis Of DSM-IV And Fagerström (FTND) Criteria For Nicotine Dependence** Nicotine dependence is associated with considerable morbidity and mortality. Two predominant classification systems, the Diagnostic and Statistical Manual (DSM-IV) and Fagerström Test for Nicotine Dependence (FTND), have been used to measure liability to nicotine dependence, yet few studies have attempted to simultaneously examine both sets of criteria. Using a sample of 624 regular smoking individuals who are offspring of Vietnam Era Twin fathers ascertained for an offspring of twin study, the authors applied latent class analysis to the 7 DSM-IV and the 6 FTND criteria to classify individuals by their nicotine dependence symptom profiles. Post-hoc across-class comparisons were conducted using a variety of smoking-related variables and aspects of psychopathology. Whether a single class identified offspring at high genetic and environmental vulnerability was also investigated. The cross-diagnosis kappa was .30. A 4-class solution fit these data best. The classes included a low DSM-low FTND class and a high DSM-high FTND class; a moderate DSM-moderate FTND class, which was distinguished by moderate levels of smoking and intermediate levels of comorbid psychopathology; and a light smoking-moderate FTND class consisting primarily of lighter smokers with a more recent onset of regular smoking. High genetic and environmental vulnerability to nicotine dependence was noted in all classes with no statistically significant across-class differences. In general, the DSM-IV and FTND criteria performed similarly to define a continuum of risk for nicotine dependence. The emerging class of light smokers should be further investigated to assess whether they transition to another class or remain as such. Agrawal A, Scherrer J, Pergadia M, Lynskey M, Madden P, Sartor C, Grant J, Duncan A, Haber J, Jacob T, Bucholz K, Xian H. A Latent class analysis of DSM-IV and Fagerström (FTND) criteria for nicotine dependence. Nicotine Tob Res. 2011; 13 (10): 972-981.

**Deviant Socialization Mediates Transmissible And Contextual Risk On Cannabis Use Disorder Development: A Prospective Study** This study examined the contribution of transmissible risk, in conjunction with family and peer contextual factors during childhood and adolescence, on the development of cannabis use disorder in adulthood. The family high-risk design was used to recruit proband fathers with, and without substance use disorder and track their sons longitudinally from late childhood to adulthood. The families were recruited under the aegis of the Center for Education and Drug Abuse Research in Pittsburgh, Pennsylvania. The oldest son in the family was studied at ages 10-12, 16, 19 and 22 years. The transmissible liability index (TLI), along with measures of quality of the parent-child relationship, cooperative behavior at home, social attitudes and peer milieu were administered to model the developmental

pathway to cannabis use disorder. Affiliation with socially deviant peers and harboring non-normative attitudes (age 16) mediate the association between transmissible risk for substance use disorder (SUD) (age 10-12) and use of illegal drugs (age 19), leading to cannabis use disorder (age 22). Deviant socialization resulting from transmissible risk and poor parent-child relationship is integral to development of cannabis use disorder in young adulthood. Tarter R, Fishbein D, Kirisci L, Mezzich A, Ridenour T, Vanyukov M. Deviant socialization mediates transmissible and contextual risk on cannabis use disorder development: a prospective study. Addiction. 2011; 106 (7): 1301-1308.

**Inactivation and Survival Of Hepatitis C Virus On Inanimate Surfaces** Hepatitis C virus (HCV) cross-contamination from inanimate surfaces or objects has been implicated in transmission of HCV in health-care settings and among injection drug users. The authors established HCV-based carrier and drug transmission assays that simulate practical conditions to study inactivation and survival of HCV on inanimate surfaces. Studies were performed with authentic cell culture derived viruses. HCV was dried on steel discs and biocides were tested for their virucidal efficacy against HCV. Infectivity was determined by a limiting dilution assay. HCV stability was analyzed in a carrier assay for several days or in a drug transmission assay using a spoon as cooker. HCV can be dried and recovered efficiently in the carrier assay. The most effective alcohol to inactivate the virus was 1-propanol, and commercially available disinfectants reduced infectivity of HCV to undetectable levels. Viral infectivity on inanimate surfaces was detectable in the presence of serum for up to 5 days, and temperatures of about 65-70°C were required to eliminate infectivity in the drug transmission assay. These findings are important for assessment of HCV transmission risks and should facilitate the definition of stringent public health interventions to prevent HCV infections. Doerrbecker J, Friesland M, Ciesek S, Erichsen T, Mateu-Gelabert P, Steinmann J, Steinmann J, Pietschmann T, Steinmann E. Inactivation and survival of Hepatitis C virus on inanimate surfaces. J Infect Dis. 2011; 204 (12): 1830-1838.

**Association of Childhood Adversities and Early-Onset Mental Disorders with Adult-Onset Chronic Physical Conditions** The physical health consequences of childhood psychosocial adversities may be as substantial as the mental health consequences, but whether this is the case remains unclear because much prior research has involved unrepresentative samples and a selective focus on particular adversities or physical outcomes. The association between early-onset mental disorders and subsequent poor physical health in adulthood has not been investigated. The objective of this study was to investigate whether childhood adversities and early-onset mental disorders are independently associated with increased risk of a range of adult-onset chronic physical conditions in culturally diverse samples spanning the full adult age range. The study design comprised cross-sectional community surveys of adults in 10 countries. The study was conducted in a general population setting. Participants were adults (ie, aged 18 years; N = 18,303), with diagnostic assessment and determination of age at onset of DSM-IV mental disorders, assessment of childhood familial adversities, and age of diagnosis or onset of chronic physical conditions. Main outcome measures comprised risk (ie, hazard ratios) of adult-onset (ie, at age >20 years) heart disease, asthma, diabetes mellitus, arthritis, chronic spinal pain, and chronic headache as a function of specific childhood adversities and early-onset (ie, at age <21 years) DSM-IV depressive and anxiety disorders, with mutual adjustment. A history of 3 or more childhood adversities was independently associated with onset of all 6 physical conditions

(hazard ratios, 1.44 to 2.19). Controlling for current mental disorder made little difference to these associations. Early-onset mental disorders were independently associated with onset of 5 physical conditions (hazard ratios, 1.43 to 1.66). These results are consistent with the hypothesis that childhood adversities and early-onset mental disorders have independent, broad-spectrum effects that increase the risk of diverse chronic physical conditions in later life. They require confirmation in a prospectively designed study. The long course of these associations has theoretical and research implications. Scott K, Von Korff M, Angermeyer M, Benjet C, Bruffaerts R, de Girolamo G, Haro J, Lépine J, Ormel J, Posada-Villa J, Tachimori H, Kessler R. Association of childhood adversities and early-onset mental disorders with adult-onset chronic physical conditions. Arch Gen Psychiatry. 2011; 68 (8): 838-844.

**SLC6A4 Methylation Modifies the Effect of the Number of Traumatic Events on Risk for Posttraumatic Stress Disorder** Posttraumatic stress disorder (PTSD) is a common and debilitating mental disorder that occurs following exposure to a traumatic event. However, most individuals do not develop PTSD following even a severe trauma, leading to a search for new variables, such as genetic and other molecular variation, associated with vulnerability and resilience in the face of trauma exposure. The authors examined whether serotonin transporter (SLC6A4) promoter genotype and methylation status modified the association between number of traumatic events experienced and PTSD in a subset of 100 individuals from the Detroit Neighborhood Health Study. Number of traumatic events was strongly associated with risk of PTSD. Neither SLC6A4 genotype nor methylation status was associated with PTSD in main effects models. However, SLC6A4 methylation levels modified the effect of the number of traumatic events on PTSD after controlling for SLC6A4 genotype. Persons with more traumatic events were at increased risk for PTSD, but only at lower methylation levels. At higher methylation levels, individuals with more traumatic events were protected from this disorder. This interaction was observed whether the outcome was PTSD diagnosis, symptom severity, or number of symptoms. Gene-specific methylation patterns may offer potential molecular signatures of increased risk for and resilience to PTSD. Koenen K, Uddin M, Chang S, Aiello A, Wildman D, Goldmann E, Galea S. SLC6A4 Methylation modifies the effect of the number of traumatic events on risk for posttraumatic stress disorder. Depress Anxiety. 2011; 28 (8): 639-647.

**Moderation of the Association between Childhood Maltreatment and Neuroticism by the Corticotropin-Releasing Hormone Receptor 1 Gene** Neuroticism is a personality trait reflecting the tendency to experience negative affect. It is a major risk for psychopathology, especially depression and anxiety disorders. Childhood maltreatment is another major risk factor for psychopathology and may influence personality. Maltreatment may interact with genotype to predict developmental outcomes. Variation in three polymorphisms of the CRHR1 gene has been found to moderate the association of childhood maltreatment with depression, and the authors hypothesized that it would also be linked to neuroticism. Variation in three CRHR1 SNPs (rs110402, rs242924, rs7209436) was assessed in 339 maltreated and 275 demographically similar nonmaltreated children, who participated in a day camp research program. Maltreated children were further categorized based on the number of types of maltreatment they had experienced and the most severe form of maltreatment experienced. Genotype and maltreatment status were used to predict the Big Five personality traits, as assessed by camp counselors following a week of interaction with children. CRHR1 genotype significantly moderated the

association of maltreatment with neuroticism but none of the other traits. Having two copies of the TAT haplotype of CRHR1 was associated with higher levels of neuroticism among maltreated children relative to nonmaltreated children, with the exception of sexually abused children and children who had experienced 3 or 4 types of abuse. Effects sizes of these interactions ranged from ·2=.01 (p=.02) to ·2=.03 (p=.006). Variation in CRHR1 moderates the association of maltreatment with neuroticism. The effects of specific types of maltreatment on neuroticism are differentially moderated by CRHR1 genotype, as are the effects of experiencing more or fewer types of maltreatment. DeYoung C, Cicchetti D, Rogosch F. Moderation of the association between childhood maltreatment and neuroticism by the corticotropin-releasing hormone receptor 1 gene. J Child Psychol Psychiatry. 2011; 52 (8): 898-906.

**Epidemiologic Trends And Geographic Patterns Of Fatal Opioid Intoxications in Connecticut, USA: 1997-2007** The leading cause of injury death among adults in Connecticut (CT), USA is drug poisonings. The authors analyzed the epidemiology and geographic distribution of opioid-involved accidental drug-involved intoxication deaths ("overdoses") in CT over an 11-year period. They reviewed data from 1997 to 2007 on all adult accidental/ undetermined drug intoxication deaths in CT that were referred to the Office of the Chief Medical Examiner (OCME). Regression analyses were conducted to uncover risk factors for fatal opioid-involved intoxications and to compare heroin- to prescription opioid- and methadone-involved deaths. Death locations were mapped to visualize differences in the geographic patterns of overdose by opioid type. Of the 2900 qualifying deaths, 2231 (77%) involved opioids. Trends over time revealed increases in total opioid-related deaths although heroin-related deaths remained constant. Methadone, oxycodone and fentanyl, the most frequently cited prescription opioids, exhibited significant increases in opioid deaths. Prescription opioid-only deaths were more likely to involve other medications (e.g., benzodiazepines) and to have occurred among residents of a suburban or small town location, compared to heroin-involved or methadone-involved deaths. Heroin-only deaths tended to occur among non-Whites, were more likely to involve alcohol or cocaine and to occur in public locations and large cities. The epidemiology of fatal opioid overdose in CT exhibits distinct longitudinal, risk factor, and geographic differences by opioid type. Each of these trends has implications for public health and prevention efforts. Green T, Grau L, Carver H, Kinzly M, Heimer R. Epidemiologic trends and geographic patterns of fatal opioid intoxications in Connecticut, USA: 1997-2007. Drug Alcohol Depend. 2011; 115 (3): 221-228.

**A Multinational Study of Mental Disorders, Marriage, and Divorce** The objective of this study was to estimate predictive associations of mental disorders with marriage and divorce in a cross-national sample. The method employed was population surveys of mental disorders which included assessment of age at first marriage in 19 countries (n = 46,128) and age at first divorce in a subset of 12 countries (n = 30,729). Associations between mental disorders and subsequent marriage and divorce were estimated in discrete time survival models. Fourteen of 18 premarital mental disorders are associated with lower likelihood of ever marrying (odds ratios ranging from 0.6 to 0.9), but these associations vary across ages of marriage. Associations between premarital mental disorders and marriage are generally null for early marriage (age 17 or younger), but negative associations come to predominate at later ages. All 18 mental disorders are positively associated with divorce (odds ratios ranging from 1.2 to 1.8). Three disorders, specific phobia, major depression, and alcohol abuse, are associated with the largest population attributable risk

proportions for both marriage and divorce. This evidence adds to research demonstrating adverse effects of mental disorders on life course altering events across a diverse range of socioeconomic and cultural settings. These effects should be included in considerations of public health investments in preventing and treating mental disorders. Breslau J, Miller E, Jin R, Sampson N, Alonso J, Andrade L, Bromet E, de Girolamo G, Demyttenaere K, Fayyad J, Fukao A, Glon M, Gureje O, He Y, Hinkov H, Hu C, Kovess-Masfety V, Matschinger H, Medina-Mora M, Ormel J, Posada-Villa J, Sagar R, Scott K, Kessler R. A multinational study of mental disorders, marriage, and divorce. Acta Psychiatr Scand. 2011; 124 (6): 474-486.

**Adverse Childhood Experiences and Risk of Physical Violence in Adolescent Dating Relationships** This study evaluates associations of commonly co-occurring childhood adversities with physical violence in dating relationships to identify potential strategies for refining and targeting dating violence prevention programmes. Data on 5,130 adult respondents to a nationally representative survey with at least one dating relationship before the age of 21 years were analysed. Logistic regression models assessed associations between 12 childhood adversities and physical dating violence (PDV). Adjusting for the number of co-occurring adversities, 10 of the 12 childhood adversities were significantly associated with PDV perpetration or victimisation (OR 1.5-2.8). The population attributable risk proportion of PDV due to all 12 childhood adversities was 53.4%. Childhood adversities with the highest attributable risk proportions were sexual abuse (13.8%), interparental violence (11.6%) and parent mental illness (10.7%). Multivariate prediction equations ranked respondents by their childhood adversity risk profiles; 46.4% of PDV cases occurred in the top two risk deciles. Assessment of a broad range of childhood exposures to familial adversities may help to identify adolescents at particularly high risk of PDV and to guide prevention efforts. Miller E, Breslau J, Chung W, McLaughlin KA, Kessler RC, Green JG. Adverse childhood experiences and risk of physical violence in adolescent dating relationships. J Epidemiol Community Health. 2011; 65 (11): 1006-1013.

**Building Conditions, 5-HTTLPR Genotype, and Depressive Symptoms in Adolescent Males and Females** Emerging work suggests that both environmental and genetic factors contribute to risk of depression in adolescents, and that these factors may differ between genders. The authors assessed whether features of the social environment (SE), measured at varying levels, and genetic factors jointly contribute to the risk of depression in adolescent males and females. Using data from a national survey of U.S. adolescents, they applied cross-sectional, multilevel mixed models to assess the contribution of: (i) 5-HTTLPR genotype and respondent-level building conditions to depressive symptom score (DSS); and (ii) 5-HTTLPR genotype and neighborhood-level building conditions to DSS. Models testing potential gene-SE interactions were also conducted. All models were stratified by gender and adjusted for age, race/ethnicity, family structure, parental education, and social support. Among females, adjusted analyses indicated that sl genotype carriers enjoyed a marginally significant ($p = .07$) protective effect against higher DSS in models assessing respondent-level building conditions. In contrast, among males, adjusted analyses predicted significantly higher DSS for residents of neighborhoods with relatively poor building conditions ($p < .01$). No significant gene-SE interactions were detected for either gender. These results suggest that adverse, macro-level SE factors increase risk of depression to a greater extent in adolescent males than in females. Intervention strategies designed to improve mental health in adolescent populations should consider a growing body of

work suggesting that the contextual factors conferring increased risk of depression differ among males and females. Uddin M, de los Santos R, Bakshis E, Cheng C, Aiello A. Building conditions, 5-HTTLPR genotype, and depressive symptoms in adolescent males and females. J Adolesc Health. 2011; 49 (4): 379-385.

**Childhood Socio-Economic Status and the Onset, Persistence, and Severity of DSM-IV Mental Disorders in a US National Sample** Although significant associations between childhood socio-economic status (SES) and adult mental disorders have been widely documented, SES has been defined using several different indicators often considered alone. Little research has examined the relative importance of these different indicators in accounting for the overall associations of childhood SES with adult outcomes. Nor has previous research distinguished associations of childhood SES with first onsets of mental disorders in childhood, adolescence, and adulthood from those with persistence of these disorders into adulthood in accounting for the overall associations between childhood SES and adult mental disorders. Disaggregated data of this sort are presented here for the associations of childhood SES with a wide range of adult DSM-IV mental disorders in the US National Comorbidity Survey Replication (NCS-R), a nationally-representative sample of 5692 adults. Childhood SES was assessed retrospectively with information about parental education and occupation and childhood family financial adversity. Associations of these indicators with first onset of 20 DSM-IV disorders that included anxiety, mood, behavioral, and substance disorders at different life-course stages (childhood, adolescence, early adulthood, and mid-later adulthood) and the persistence/severity of these disorders were examined using discrete-time survival analysis. Lifetime disorders and their ages-of-onset were assessed retrospectively with the WHO Composite International Diagnostic Interview. Different aspects of childhood SES predicted onset, persistence, and severity of mental disorders. Childhood financial hardship predicted onset of all classes of disorders at every life-course stage with odds-ratios (ORs) of 1.7-2.3. Childhood financial hardship was unrelated, in comparison, to disorder persistence or severity. Low parental education, although unrelated to disorder onset, significantly predicted disorder persistence and severity, whereas parental occupation was unrelated to onset, persistence, or severity. Some, but not all, of these associations were explained by other co-occurring childhood adversities. These specifications have important implications for mental health interventions targeting low-SES children. McLaughlin K, Breslau J, Green J, Lakoma M, Sampson N, Zaslavsky A, Kessler R. Childhood socio-economic status and the onset, persistence, and severity of DSM-IV mental disorders in a US National Sample. Soc Sci Med. 2011; 73(7): 1088-1096.

**Interactive Effects of Corticotropin Releasing Hormone Receptor 1, Serotonin Transporter Linked Polymorphic Region, and Child Maltreatment on Diurnal Cortisol Regulation and Internalizing Symptoms** Within an allostatic load framework, the effect of Gene by Environment (G x E) interactions on diurnal cortisol regulation and internalizing symptomatology were investigated. Variation in the corticotropin releasing hormone receptor 1 (CRHR1) TAT haplotype and serotonin transporter linked polymorphic region (5-HTTLPR) was determined in a sample of maltreated (n = 238, 21.4% with early physical and sexual abuse) and nonmaltreated (n = 255) children (M age = 10.08) participating in a summer research camp. Internalizing and depressive symptoms were assessed by other and self-report. G x E effects for CRHR1 and maltreatment and early abuse on diurnal cortisol regulation were observed; CRHR1 variation was related to cortisol dysregulation only among maltreated children. Early abuse and

high internalizing symptoms also interacted to predict atypical diurnal cortisol regulation. The interaction of CRHR1, 5-HTTLPR, and child maltreatment (G x G x E) identified a subgroup of maltreated children with high internalizing symptoms who shared the same combination of the two genes. The findings support an allostatic load perspective on the effects of the chronic stress associated with child maltreatment on cortisol regulation and internalizing symptomatology as moderated by genetic variation. Cicchetti, D, Oshri A, Rogosch FA. Interactive effects of corticotropin releasing hormone receptor 1, serotonin transporter linked polymorphic region, and child maltreatment on diurnal cortisol regulation and internalizing symptomatology. Dev Psychopathol. 2011; 23 (4): 1125-1138.

**Premarital Mental Disorders and Physical Violence in Marriage: Cross-National Study of Married Couples** Mental disorders may increase the risk of physical violence among married couples. The aim of the study was to estimate associations between premarital mental disorders and marital violence in a cross-national sample of married couples. A total of 1,821 married couples (3642 individuals) from 11 countries were interviewed as part of the World Health Organization's World Mental Health Survey Initiative. Sixteen mental disorders with onset prior to marriage were examined as predictors of marital violence reported by either spouse. Any physical violence was reported by one or both spouses in 20% of couples, and was associated with husbands ' externalising disorders (OR = 1.7, 95% CI 1.2-2.3). Overall, the population attributable risk for marital violence related to premarital mental disorders was estimated to be 17.2%. Husbands' externalising disorders had a modest but consistent association with marital violence across diverse countries. This finding has implications for the development of targeted interventions to reduce risk of marital violence. Miller E, Breslau J, Petukhova M, Fayyad J, Green J, Kola L, Seedat S, Stein D, Tsang A, Viana M, Andrade L, Demyttenaere K, de Girolamo G, Haro J, Hu C, Karam E, Kovess-Masfety V, Tomov T, Kessler R. Premarital mental disorders and physical violence in marriage: Cross-national study of married couples. Br J Psychiatry. 2011; 199 (4): 330-337.

**The Role of Smoking Expectancies in the Relationship between PTSD Symptoms and Smoking Behavior among Women Exposed to Intimate Partner Violence** Intimate partner violence (IPV) is a public health problem associated with negative health consequences, including higher rates of tobacco smoking. Smoking expectancies are related to motivation to quit and relapse. IPV-exposed women endorse higher rates of PTSD symptoms, which are related to smoking and smoking expectancies. The present study sought to examine the relationship among smoking behavior, smoking expectancies, and PTSD symptoms among IPV-exposed women. Participants were 83 women who reported experiencing IPV within the last month, smoked an average of 12 cigarettes per day, and reported moderate levels of nicotine dependence (FTND mean=4.4). Participants completed baseline and follow-up interviews. Multiple regression analyses assessed the relationships among smoking expectancies and PTSD symptoms to cigarettes smoked per day and nicotine dependence. Findings demonstrated that Stimulation/State Enhancement expectancies were positively related to cigarettes per day, whereas PTSD arousal symptoms were negatively related to cigarettes per day, p 's<.05. Neither smoking expectancies nor PTSD symptoms were significantly related to nicotine dependence. Supplemental analyses revealed that PTSD re-experiencing symptoms were negatively related and PTSD avoidance/numbing symptoms were positively related to Stimulation/State Enhancement expectancies, p 's<.05. This study extends findings regarding the association

between PTSD symptoms and smoking among an understudied population - IPV-exposed women. The relationship between PTSD symptoms and smoking differed across PTSD symptom clusters and expectancy scales, which may have implications for treatment development. The fact that expectancies and PTSD symptoms are related to smoking behavior among IPV-exposed women may be important for enhancing prevention and intervention efforts. Ashare R, Weinberger A, McKee S, Sullivan T. The role of smoking expectancies in the relationship between PTSD symptoms and smoking behavior among women exposed to intimate partner violence. Addict Behav. 2011; 36 (12): 1333-1336.

**Risky Health Environments: Women Sex Workers' Struggles To Find Safe, Secure And Non-Exploitative Housing In Canada's Poorest Postal Code** This study explored low-income and transitional housing environments of women sex workers and their role in shaping agency and power in negotiating safety and sexual risk reduction in Vancouver, Canada. A series of 12 focus group discussions were conducted with 73 women currently involved in street-based sex work. These women were purposively sampled for a range of experiences living in low-income housing environments, including homeless shelters, transitional housing, and co-ed and women-only single-room occupancy (SRO) hotels. Drawing on the risk environment framework and theoretical constructs of gender, agency and power, analyses demonstrate that women continue to be vulnerable to violence and sexual and economic exploitation and have reduced ability to negotiate risk reduction resulting from the physical, structural and social environments of current dominant male-centred housing models. Within the physical environment, women described inhabitable housing conditions in SROs with infestations of bedbugs and rats, leading women to even more transitional housing options such as shelters and couch-surfing. In many cases, this resulted in their economic exploitation and increased sexual risk. Within the structural environment, enforcement of curfews and guest policies forced women to accept risky clients to meet curfew, or work outdoors where their ability to negotiate safety and condom use were limited. Certain policies promoted women's agency and mitigated their ability to reduce risks when selling sex. These included flexible curfews and being able to bring clients home. The social environments of co-ed single-room occupancy hotels resulted in repeated violence by male residents and discrimination by male building staff. Women-only shelters and SROs facilitated 'enabling environments ' where women developed support systems with other working women that resulted in safer work practices. The narratives expressed in this study reveal the critical need for public health interventions and safer supportive housing to account for the daily lived experiences of women sex workers. Lazarus L, Chettiar J, Deering K, Nabess R, Shannon K. Risky health environments: Women sex workers ' struggles to find safe, secure and non-exploitative housing in Canada's poorest postal code. Soc Sci Med. 2011; 73(11): 1600-1607.

**Severe Food Insecurity Is Associated With Elevated Unprotected Sex Among HIV-Seropositive Injection Drug Users Independent Of HAART Use** Despite emerging evidence of a significant adverse relationship between food insecurity and sexual risk-taking, data have been primarily derived from resource-constrained settings and HIV-negative populations. To the authors' knowledge, this study is the first to longitudinally evaluate the relationship between food insecurity and unprotected sex among HIV-seropositive people who inject drugs [injection drug users (IDUs)] both on and not on HAART. Longitudinal analyses were restricted to HIV-positive IDUs who completed baseline and at least one follow-up visit in a prospective cohort (AIDS Care Cohort to evaluate Exposure to Survival Services, 2005-2009). The authors

constructed a multivariate logistic model using generalized estimating equations (GEEs) to assess an independent relationship between severe food insecurity (e.g., hunger due to lack of access or means to acquire food) and unprotected vaginal/anal sex. Among 470 HIV-positive IDUs, the median age was 42 years (interquartile range 36-47) with 61% men and 39% women. The prevalence of severe food insecurity was 71%, with no differences by HAART use. Severe food insecure IDUs were marginally less likely to have a suppressed HIV-1 RNA viral load (31 vs. 39%, P = 0.099). In multivariate GEE analyses, severe food insecurity [adjusted odds ratio = 2.68, 95% confidence interval 1.49-4.82] remained independently correlated with unprotected sex among HIV-positive IDUs, controlling for age, sex/gender, married/cohabitating partner, binge drug use, homelessness, and HAART use. These findings highlight a crucial need for structural HIV interventions that incorporate targeted food assistance strategies for IDUs. Given recent evidence of poor virological response among food insecure individuals on HAART, innovative HIV care models should integrate targeted food security programs and early access to HAART. Shannon K, Kerr T, Milloy M, Anema A, Zhang R, Montaner J, Wood E. Severe food insecurity is associated with elevated unprotected sex among HIV-seropositive injection drug users independent of HAART use. AIDS. 2011; 25(16): 2037-2042.

**Controlled HIV Viral Replication, Not Liver Disease Severity Associated With Low Bone Mineral Density In HIV/HCV Co-Infection** The objectivwe of this study was to evaluate the prevalence and risk factors for low bone mineral density (BMD) in persons co-infected with HIV and Hepatitis C. HIV/HCV co-infected study participants (n=179) were recruited into a prospective cohort and underwent dual-energy X-ray absorptiometry (DXA) within 1 year of a liver biopsy. Fibrosis staging was evaluated according to the METAVIR system. Osteoporosis was defined as a T-score ýýý-2.5. Z-scores at the total hip, femoral neck, and lumbar spine were used as the primary outcome variables to assess the association between degree of liver disease, HIV-related variables, and BMD. The population was 65% male, 85% Black with mean age 50.3 years. The prevalence of osteoporosis either at the total hip, femoral neck, or lumbar spine was 28%, with 5% having osteoporosis of the total hip, 6% at the femoral neck, 25% at the spine. The mean Z-scores (standard deviation) were -0.42 (1.01) at the total hip, -0.16 (1.05) at the femoral neck, and -0.82 (1.55) at the lumbar spine. In multivariable models, controlled HIV replication (HIV RNA <400 copies/ml vs. ýýý400 copies/ml) was associated with lower Z-scores (mean ýý standard error) at the total hip (-0.44 ýý 0.17, p = 0.01), femoral neck (-0.59 ýý 0.18, p = 0.001), and the spine (-0.98 ýý 0.27, p = 0.0005). There was no association between degree of liver fibrosis and Z-score. Osteoporosis was very common in this population of predominately African-American HIV/HCV co-infected patients, particularly at the spine. Lower BMD was associated with controlled HIV replication, but not liver disease severity. El-Maouche D, Mehta SH, Sutcliffe C, Higgins Y, Torbenson MS, Moore RD, Thomas DL, Sulkowski MS, Brown TT. Controlled HIV viral replication, not liver disease severity associated with low bone mineral density in HIV/HCV co-infection. J Hepatol. 2011; 55(4): 770-776.

**Correlates of Non-Medical Prescription Drug Use Among A Cohort Of Injection Drug Users in Baltimore City** Despite reports of increasing non-medical prescription drug use, relatively few studies have systematically evaluated the prevalence and correlates of non-medical prescription drug use, particularly in populations that might be especially vulnerable (e.g., injection drug users [IDUs]). The authors examined factors associated with non-medical prescription drug use among a community-based cohort of current and former IDUs in Baltimore

(The ALIVE Study). They conducted a cross-sectional analysis of data from cohort participants that responded to a survey that included questions on non-medical prescription drug use between 2005-06 (n=1320). Non-medical prescription drug use was considered to be use of any of the following: Opiates (Oxycontin, Percocet), Benzodiazepines or Clonidine, purchased on the street and taken orally within the last six months. Data on other covariates of interest (e.g., demographics, substance use, general health) was obtained through a standardized interview. The median age was 46 years; 66% were male, 85% were African-American. Twenty one percent reported any non-medical prescription drug use; 12% reported using more than one drug. Non-medical use of opiates was most common (17%). In multivariate analysis, non-medical prescription drug use was significantly associated with Caucasian race (prevalence ratio [PR]: 1.79), self-reported bodily pain (PR: 1.58), hazardous alcohol use (PR: 1.47), marijuana use (PR: 1.65), non-injection cocaine/heroin use (PR: 1.70), diverted use of buprenorphine (PR: 1.51) or methadone (PR: 2.51), and active injection drug use (PR: 3.50; $p<0.05$ for all). The association between bodily pain and non-medical prescription drug use was stronger among persons that were not using substances (marijuana, injecting drugs, snorting/smoking heroin, cocaine, using crack) as compared to those using these substances. The high prevalence of non-medical prescription drug use among this population warrants further research and action. Information on the risks of nonmedical prescription drug use especially overdose, should be incorporated into interventions targeted at IDUs. Khosla N, Juon H, Kirk G, Astemborski J, Mehta S. Correlates of non-medical prescription drug use among a cohort of injection drug users in Baltimore City. Addict Behav. 2011; 36(12): 1282-1287.

**Differential Gender Effects Of Depression On Use Of HIV Medications Among HIV-Positive Puerto Rican Drug Users** Many barriers to the use of HIV medications have been identified. Research findings have also shown a gender disparity in HIV care behaviors. However, interaction effects of gender with the potential barriers to use of HIV medications among HIV-positive minority drug users remain under-studied. This study examined interaction effects of gender with potential moderating factors (i.e., individual and network characteristics) on the use of HIV medications. Analyses were based on 260 HIV-positive Puerto Rican heroin and cocaine users, recruited in New York (N=178) and Puerto Rico (N=82) in 1998-2003. HIV status was assessed using OraSure, and heroin or cocaine use was verified by urinalysis. All participants were tested and interviewed at baseline and six-month follow-up (183 males; 77 females). In predicting use of HIV medications at follow-up (HIVMEDF), use of HIV medications at baseline (HIVMED), individual characteristics (e.g., depression), network characteristics (e.g., having an intravenous drug user [IDU] sex partner), recruitment site, and interaction effects of these variables with gender, were examined in multiple logistic regression analysis. Use of HIV medications was low (29% at baseline; 40% at follow-up). HIVMED, recruitment site, gender, and depression had significant main effects on HIVMEDF. Depression also had a significant interaction effect with gender on HIVMEDF. Unlike men, women with depression were less likely than women without depression to use the medications. The findings indicate that gender-specific issues should be addressed by treatment programs for HIV-positive drug users, with particular efforts needed to enhance use of medications for depressed women. Kang S, Deren S, Colón H. Differential gender effects of depression on use of HIV medications among HIV-positive Puerto Rican drug users. AIDS Care. 2011; 23(11): 1467-1471.

**Difficulty Accessing Syringes Mediates The Relationship Between Methamphetamine Use And Syringe Sharing Among Young Injection Drug Users** Injection drug users (IDU) who use methamphetamine (MA) are at an increased risk of HIV infection due to engagement in injection-related risk behavior including syringe sharing. In this cohort study of young IDU aged 18-30, the authors investigated the relationship between injection MA use and syringe sharing, and whether difficulty accessing sterile syringes mediated this association. Behavioral questionnaires were completed by 384 IDU in Vancouver, Canada between October 2005 and May 2008. Generalized estimating equations were used to estimate direct and indirect effects. The median age of participants was 24 (IQR: 22-27) and 214 (55.7%) were male. Injecting MA was independently associated with syringe sharing. Mediation analyses revealed that difficulty accessing sterile syringes partially mediated the association between injecting MA and syringe sharing. Interventions to reduce syringe sharing among young methamphetamine injectors must address social and structural barriers to accessing HIV prevention programs. Marshall BD, Shoveller JA, Wood E, Patterson T, Kerr T. Difficulty accessing syringes mediates the relationship between methamphetamine use and syringe sharing among young injection drug users. AIDS Behav. 2011; 15(7): 1546-1553.

**Drug Dealing Cessation Among A Cohort Of Drug Users in Vancouver, Canada** Drug dealing among drug users has been associated with elevated risk-taking and negative health outcomes. However, little is known about the cessation of drug dealing among this population. The authors assessed time to cessation of drug dealing using Cox regression. They also used generalized estimating equation (GEE) analysis and chi-square analysis to examine factors associated with willingness to cease drug dealing. In total, 868 participants reported drug dealing between November 2005 and March 2009. Among 381 participants dealing drugs at baseline, 194 (51%) ceased dealing. Incidence of dealing cessation was positively associated with spending less than $50 per day on drugs (Adjusted Hazard Ratio [AHR]=1.88, 95% confidence interval [CI]: 1.14-3.10) and negatively associated with buying drugs from the same source (AHR=0.60, 95% CI: 0.37-0.98). In a GEE analysis, willingness to cease dealing was positively associated with older age (Adjusted Odds Ratio [AOR]=1.02, 95% CI: 1.01-1.03), crack use (AOR=2.00, 95% CI: 1.44-2.79), public injecting (AOR=1.95, 95% CI: 1.55-2.43), and reporting that police presence affects drug purchases (AOR=1.53, 95% CI: 1.22-1.91), and negatively associated with crystal methamphetamine injection (AOR=0.62, 95% CI: 0.47-0.83). Intensity of drug use and acquisition method were predictive of dealing cessation. Willingness to cease dealing was associated with a range of risky drug-related activities. Interventions to reduce drug dealing should be conceived in tandem with addiction treatment strategies. Werb D, Bouchard M, Kerr T, Shoveller J, Qi J, Montaner J, Wood E. Drug dealing cessation among a cohort of drug users in Vancouver, Canada. Drug Alcohol Depend. 2011; 118(2-3): 459-463.

**HIV Infection, Immune Suppression, And Uncontrolled Viremia Are Associated With Increased Multimorbidity Among Aging Injection Drug Users** Despite an increasing burden of age-associated non-AIDS outcomes, few studies have investigated the prevalence or correlates of multimorbidity among aging human immunodeficiency virus (HIV)-infected and epidemiologically comparable at-risk populations. Among 1,262 AIDS Linked to the IntraVenous Experience (ALIVE) study participants followed in a community-based observational cohort, the authors defined the prevalence of 7 non-AIDS-defining chronic conditions (diabetes, obstructive lung disease, liver disease, anemia, obesity, kidney dysfunction,

and hypertension) using clinical and laboratory criteria. Ordinal logistic regression was used to model the odds of increased multimorbidity associated with demographic, behavioral, and clinical factors. Self-reported prevalence was compared with clinically defined prevalence. Participants were a median of 48.9 years of age; 65.1% were male, 87.5% were African-American, and 28.7% were HIV infected. In multivariable analysis, HIV infection (odds ratio [OR], 1.50; 95% confidence interval [CI], 1.13-1.99) was positively associated with increased multimorbidity. Among HIV-infected participants, multimorbidity was increased with lower nadir CD4 T-cell count (OR, 1.14 per 100-cell decrease; 95% CI, 1.00-1.29) and higher current HIV RNA (OR, 1.32 per log(10) increase; 95% CI, 1.08-1.60). Older age, being female, not using cigarettes or drugs, and having depressive symptoms were also associated with increased multimorbidity. A substantial proportion of multimorbid conditions in HIV-infected and HIV-uninfected participants were unrecognized and untreated. HIV-infected participants experienced increased numbers of multimorbid conditions; risk increased with advanced immunosuppression and higher viremia. These results underscore the heavy burden of multimorbidity associated with HIV and highlight the need for incorporating routine assessment and integrated management of chronic diseases as part of comprehensive healthcare for aging, HIV-infected persons. Salter M, Lau B, Go V, Mehta S, Kirk G. HIV infection, immune suppression, and uncontrolled viremia are associated with increased multimorbidity among aging injection drug users. Clin Infect Dis. 2011; 53(12): 1256-1264.

**Increased Gonorrhoea And Chlamydia Testing Did Not Increase Case Detection In An HIV Clinical Cohort 1999-2007** Since 2003, US organizations have recommended universal screening, rather than targeted screening, of HIV-infected persons for gonorrhoea and chlamydia. The objective of this study was to determine whether wider testing resulting from these guidelines would produce an increase in gonorrhoea/chlamydia diagnoses. 3,283 patients receiving HIV care in 1999-2007 in the Johns Hopkins Hospital HIV clinic were studied. The two primary outcomes were the occurrence of any gonorrhoea/chlamydia testing in each year of care and the occurrence of any positive result(s) in years of testing. The proportion of all patients in care who were diagnosed with gonorrhoea/chlamydia was defined as the number of patients with positive results divided by the number of patients in care. Trends were analysed with repeated measures logistic regression. The proportion of patients tested for gonorrhoea/ chlamydia increased steadily from 0.12 in 1999 to 0.33 in 2007 (OR per year for being tested 1.17, 95% CI 1.15 to 1.19). The proportion positive among those tested decreased significantly after 2003 (OR per year 0.67, 95% CI 0.55 to 0.81). The proportion of all patients in care diagnosed with gonorrhoea/chlamydia therefore remained generally stable in 1999-2007 (OR per year 0.97, 95% CI 0.91 to 1.04). Universal annual screening, as implemented, did not increase the proportion of all patients in care who were diagnosed with gonorrhoea/chlamydia. Similarly low implementation rates have been reported in cross-sectional studies. If future efforts to enhance implementation do not yield increases in diagnoses, then guidelines focusing on targeted screening of high-risk groups rather than universal screening may be warranted. Berry S, Ghanem K, Page K, Gange S, Thio C, Moore R, Gebo K. Increased gonorrhoea and chlamydia testing did not increase case detection in an HIV clinical cohort 1999-2007. Sex Transm Infect. 2011; 87(6): 469-475.

**Injection Methamphetamine Use Is Associated With An Increased Risk Of Attempted Suicide: A Prospective Cohort Study** Methamphetamine (MA) use is a growing public health concern in many settings around the world. While some physical and mental health effects associated with injection MA use have been well described, little is known about the relationship between injecting MA and suicidal behavior. The authors sought to determine whether MA injection was associated with an increased risk of attempting suicide among a prospective cohort of injection drug users (IDUs) in Vancouver, Canada. Between 2001 and 2008, eligible participants enrolled in the Vancouver Injection Drug Users Study (VIDUS) completed semi-annual questionnaires that elicited information regarding sociodemographics, drug use patterns, and mental health problems including suicidal behavior. The authors used Cox proportional hazards models with time-dependent covariates to determine whether self-reported MA injection was an independent predictor of attempting suicide at subsequent time points. Of 1873 eligible participants, 149 (8.0%) reported a suicide attempt, resulting in an incidence density of 2.5 per 100 person-years. Participants who attempted suicide were more likely to be younger (median: 35 vs. 40, $p<0.01$), female (48.3% vs. 35.1%, $p<0.01$), and of Aboriginal ancestry (43.6% vs. 31.3%, $p<0.01$). In a Cox proportional hazards model, MA injection was associated with an 80% increase in the risk of attempting suicide (adjusted hazard ratio=1.80, 95% CI: 1.08-2.99, $p=0.02$). These findings suggest that IDUs who inject MA should be monitored for suicidal behavior. Improved integration of mental health and suicide prevention interventions within harm reduction and drug treatment programs may be fruitful. Marshall B, Galea S, Wood E, Kerr T. Injection methamphetamine use is associated with an increased risk of attempted suicide: A prospective cohort study. Drug Alcohol Depend. 2011; 119(1-2): 134-137.

**KIR2DL2 Enhances Protective And Detrimental HLA Class I-Mediated Immunity In Chronic Viral Infection** Killer cell immunoglobulin-like receptors (KIRs) influence both innate and adaptive immunity. But while the role of KIRs in NK-mediated innate immunity is well-documented, the impact of KIRs on the T cell response in human disease is not known. Here the authors test the hypothesis that an individual's KIR genotype affects the efficiency of their HLA class I-mediated antiviral immune response and the outcome of viral infection. They show that, in two unrelated viral infections, hepatitis C virus and human T lymphotropic virus type 1, possession of the KIR2DL2 gene enhanced both protective and detrimental HLA class I-restricted anti-viral immunity. These results reveal a novel role for inhibitory KIRs. They conclude that inhibitory KIRs, in synergy with T cells, are a major determinant of the outcome of persistent viral infection. Seich Al Basatena N, Macnamara A, Vine A, Thio C, Astemborski J, Usuku K, Osame M, Kirk G, Donfield S, Goedert J, Bangham C, Carrington M, Khakoo S, Asquith B. KIR2DL2 enhances protective and detrimental HLA class I-mediated immunity in chronic viral infection. PLoS Pathog. 2011; 7(10): e1002270-e1002270.

**Social Network Influences Of Alcohol And Marijuana Cognitive Associations** Decision-making is a social process whereby behaviors are often driven by social influences and social consequences. Research shows that social context also plays an integral role in decision-making processes. In particular, evidence suggests that implicit or non-conscious cognitions are linked to social information in memory and that implicit attitudes can be communicated and assimilated between people on an unconscious level. This study assesses social contagion of implicit cognitions regarding alcohol and marijuana among high school friend networks. Data are from an evidence-based drug education program delivered by either a health educator or by nominated

class leaders over a 3-month period. Implicit attitudes were found to be susceptible to social influences, particularly for alcohol. Surprisingly, social contagion was stronger for cognitions than for behaviors. In addition, results support prior research that has found that implicit attitudes are not entirely stable and may be more susceptible to change than are behaviors. Public health initiatives to engender behavioral change could be facilitated by targeting flexible cognitive associations within existing social network structures. Coronges K, Stacy A, Valente T. Social network influences of alcohol and marijuana cognitive associations. Addict Behav. 2011; 36(12): 1305-1308.

**Patterns of Use, Sequence Of Onsets And Correlates Of Tobacco And Cannabis** While most individuals initiate their use of tobacco prior to onset of cannabis use, recent reports have identified a smaller subset of youth who report onset of cannabis use prior to tobacco use. In this study, the authors characterize patterns of cannabis and tobacco use (tobacco but not cannabis, cannabis but not tobacco or both) and compare the factors associated with onset of tobacco before cannabis and cannabis before tobacco. Data on 1,812 offspring aged 12-32 years, drawn from two related offspring of Vietnam Era twin studies, were used. Individuals were divided into tobacco but not cannabis (T), cannabis but not tobacco (C) and users of both substances (CT). Those who used both could be further classified by the timing of onset of tobacco and cannabis use. Multinomial logistic regression was used to characterize the groups using socio-demographic and psychiatric covariates. Furthermore, data on parental smoking and drug use was used to identify whether certain groups represented greater genetic or environmental vulnerability. 22% (N=398) reported T, 3% (N=55) reported C and 44% reported CT (N=801). Of the 801 CT individuals, 72.8% (N=583), 9.9% (N=77) and 17.3% (N=139) reported onset of tobacco before cannabis, cannabis before tobacco and onsets at the same age. C users were as likely as CT users to report peer drug use and psychopathology, such as conduct problems while CT was associated with increased tobacco use relative to T. Onset of tobacco prior to cannabis, when compared onset of cannabis before tobacco or reporting initiation at the same age was associated with greater cigarettes smoked per day, however no distinct factors distinguished the group with onset of cannabis before tobacco from those with initiation at the same age. A small subset of individuals report cannabis without tobacco use. Of those who use both cannabis and tobacco, a small group report cannabis use prior to tobacco use. Follow-up analyses that chart the trajectories of these individuals will be required to delineate their course of substance involvement. Agrawal A, Scherrer J, Lynskey M, Sartor C, Grant J, Haber J, Madden P, Jacob T, Bucholz K, Xian H. Patterns of use, sequence of onsets and correlates of tobacco and cannabis. Addict Behav. 2011; 36(12): 1141-1147.

**A Comparison Of Syringe Disposal Practices Among Injection Drug Users In A City With Versus A City Without Needle And Syringe Programs** The United States (U.S.) approved use of federal funds for needle and syringe programs (NSPs) in December 2009. This study compares syringe disposal practices in a U.S. city with NSPs to a U.S. city without NSPs by examining the prevalence of improperly discarded syringes in public places and the self-reported syringe disposal practices of injection drug users (IDUs) in the two cities. The authors conducted visual inspection walkthroughs in a random sample of the top-quartile of drug-affected neighborhoods in San Francisco, California (a city with NSPs) and Miami, Florida (a city without NSPs). They also conducted quantitative interviews with adult IDUs in San Francisco (N=602) and Miami (N=448). In the visual inspections, the authors found 44 syringes/1000

census blocks in San Francisco, and 371 syringes/1000 census blocks in Miami. Survey results showed that in San Francisco 13% of syringes IDUs reported using in the 30 days preceding the study interviews were disposed of improperly versus 95% of syringes by IDUs in Miami. In multivariable logistic regression analysis, IDUs in Miami had over 34 times the adjusted odds of public syringe disposal relative to IDUs in San Francisco (adjusted odds ratio=34.2, 95% CI=21.92, 53.47). The authors found eight-fold more improperly disposed syringes on walkthroughs in the city without NSPs compared to the city with NSPs, which was corroborated by survey data. NSPs may help IDUs dispose of their syringes safely in cities with large numbers of IDUs. Tookes H, Kral A, Wenger L, Cardenas G, Martinez A, Sherman R, Pereyra M, Forrest D, Lalota M, Metsch L. A comparison of syringe disposal practices among injection drug users in a city with versus a city without needle and syringe programs. Drug Alcohol Depend. 2011; 1-5.

**Assessing Geographic And Individual Level Factors Associated With Arrests Among Injection Drug Users In California** Law enforcement strategies to reduce street-based drug activity are often concentrated in neighborhoods with high levels of social and economic disadvantage. Intensive street-level policing is associated with fear and reluctance on the part of injection drug users (IDUs) to utilize syringe exchange programs (SEPs). The authors aim to build on previous research by analyzing the influence of zip code and individual level factors on the probability of arrest among IDUs in California. Individual characteristics and behaviors were more strongly associated with arrest than zip code characteristics. However, living in a disadvantaged zip code exerted a protective effect against arrest after adjusting for individual level factors (AOR 0.7, 95% 0.5, 0.9). Further efforts to contextualize the circumstances surrounding an arrest, including the characteristics of the geographic setting, may be useful for understanding how law enforcement practices impact the success of SEPs and the health of injection drug users. Martinez A, Bluthenthal R, Neilands T, Kral A. Assessing geographic and individual level factors associated with arrests among injection drug users in California. Health Place. 2011; 17(6): 1258-1265.

**Population-Level Effects Of Uninterrupted Health Insurance On Services Use Among HIV-Positive Unstably Housed Adults** Health services research consistently confirms the benefit of insurance coverage on the use of health services sought in the USA. However, few studies have simultaneously addressed the multitude of competing and unmet needs specifically among unstably housed persons. Moreover, few have accounted for the fact that hospitalization may lead to obtaining insurance coverage, rather than the other way around. This study used marginal structural models to determine the longitudinal impact of insurance coverage on the use of health services and antiretroviral therapy (ART) among HIV-positive unstably housed adults. The impact of insurance status on the use of health services and ART was adjusted for a broad range of confounders specific to this population. Among 330 HIV-positive study participants, both intermittent and continuous insurance coverage during the prior 3-12 months had strong and positive effects on the use of ambulatory care and ART, with stronger associations for continuous insurance coverage. Longer durations of continuous coverage were less robust in affecting emergency and inpatient care. Race and ethnicity had no significant influence on health services use in this low-income population when confounding due to competing needs was considered in adjusted analyses. Given that ambulatory care and ART are factors with substantial potential impact on the course of HIV disease, these data suggest that securing uninterrupted

insurance coverage would result in large reductions in morbidity and mortality. Health care policy efforts aimed at increasing consistent insurance coverage in vulnerable populations are warranted. Riley ED, Moore KL, Haber S, Neilands TB, Cohen J, Kral AH. Population-level effects of uninterrupted health insurance on services use among HIV-positive unstably housed adults. AIDS Care. 2011; 10: 1-9.

**Temporal Changes In HCV Genotype Distribution In Three Different High Risk Populations In San Francisco, California** Hepatitis C virus (HCV) genotype (GT) has become an important measure in the diagnosis and monitoring of HCV infection treatment. In the United States (U.S.) HCV GT 1 is reported as the most common infecting GT among chronically infected patients. In Europe, however, recent studies have suggested that the epidemiology of HCV GTs is changing. The authors assessed HCV GT distribution in 460 patients from three HCV-infected high risk populations in San Francisco, and examined patterns by birth cohort to assess temporal trends. Multiple logistic regression was used to assess factors independently associated with GT 1 infection compared to other GTs (2, 3, and 4). Overall, GT 1 was predominant (72.4%), however younger injection drug users (IDU) had a lower proportion of GT 1 infections (54.7%) compared to older IDU and HIV-infected patients (80.5% and 76.6%, respectively). Analysis by birth cohort showed increasing proportions of non-GT 1 infections associated with year of birth: birth before 1970 was independently associated with higher adjusted odds of GT 1: AOR 2.03 (95% CI: 1.23, 3.34). African-Americans as compared to whites also had higher adjusted odds of GT 1 infection (AOR: 3.37; 95% CI: 1.89, 5.99). Although, HCV GT 1 remains the most prevalent GT, especially among older groups, changes in GT distribution could have significant implications for how HCV might be controlled on a population level and treated on an individual level. Dias P, Hahn J, Delwart E, Edlin B, Martin J, Lum P, Evans J, Kral A, Deeks S, Busch M, Page K. Temporal changes in HCV genotype distribution in three different high risk populations in San Francisco, California. BMC Infect Dis. 2011; 11: 208-208.

**Comparing Injection And Non-Injection Routes Of Administration For Heroin, Methamphetamine, And Cocaine Users in the United States** Research examining the demographic and substance use characteristics of illicit drug use in the United States has typically failed to consider differences in routes of administration or has exclusively focused on a single route of administration-injection drug use. Data from National Survey on Drug Use and Health were used to compare past-year injection drug users and non-injection drug users' routes of administration of those who use the three drugs most commonly injected in the United States: heroin, methamphetamine, and cocaine. Injection drug users were more likely than those using drugs via other routes to be older (aged 35 and older), unemployed, possess less than a high school education, and reside in rural areas. IDUs also exhibited higher rates of abuse/ dependence, perceived need for substance abuse treatment, and co-occurring physical and psychological problems. Fewer differences between IDUs and non-IDUs were observed for heroin users compared with methamphetamine or cocaine users. Novak SP, Kral AH. Comparing injection and non-injection routes of administration for heroin, methamphetamine, and cocaine users in the United States. J Addict Dis. 2011; 30(3): 248-257.

**Variations in Patterns of Sexual Risk Behavior among Seattle-Area MSM Based on their HIV Status, the HIV Status of their Partner and Partner Type** The authors evaluated sexual risk behavior in 368 Seattle-area MSM recruited in the 2008 National HIV Behavioral Surveillance survey. They found significant concordance between participants' self-reported HIV status and that of their sexual partners. Persons unaware of partners' HIV status were more likely to report only oral sex. Those aware were less likely to report non-concordant unprotected anal intercourse (UAI). Participants reporting themselves HIV-positive were more likely than those self-reporting HIV-negative status to report non-concordant UAI and several other sexual risk behaviors. The level of non-concordant UAI did not materially differ by whether their partner was a main or casual partner. Burt R, Thiede H. Variations in patterns of sexual risk behavior among Seattle-Area MSM based on their HIV status, the HIV status of their partner and partner type. AIDS Behav. 2011: 1-1.

**Personality And Alcohol Use: The Role Of Impulsivity** Research has shown that personality traits associated with impulsivity influence alcohol use during emerging adulthood, yet relatively few studies have examined how distinct facets of impulsivity are associated with alcohol use and abuse. The authors examine the influence of impulsivity traits on four patterns of alcohol use including frequency of alcohol use, alcohol-related problems, binge drinking, and alcohol use disorders (AUDs) in a community sample of young individuals (N=190). In multivariate regression analyses that controlled for peer and parental alcohol use, psychological distress, and developmental correlates (i.e., college, marriage, employment) in emerging adulthood, the authors found that urgency and sensation seeking were consistently related to all four constructs of alcohol use. The present study suggests that distinct impulsivity traits may play different roles in escalation of alcohol use and development of AUDs during emerging adulthood. Shin S, Hong H, Jeon S. Personality and alcohol use: The role of impulsivity. Addict Behav. 2012; 37(1): 102-107.

**Reconciling Incongruous Qualitative And Quantitative Findings In Mixed Methods Research: Exemplars From Research With Drug Using Populations** Mixed methods research is increasingly being promoted in the health sciences as a way to gain more comprehensive understandings of how social processes and individual behaviours shape human health. Mixed methods research most commonly combines qualitative and quantitative data collection and analysis strategies. Often, integrating findings from multiple methods is assumed to confirm or validate the findings from one method with the findings from another, seeking convergence or agreement between methods. Cases in which findings from different methods are congruous are generally thought of as ideal, whilst conflicting findings may, at first glance, appear problematic. However, the latter situation provides the opportunity for a process through which apparently discordant results are reconciled, potentially leading to new emergent understandings of complex social phenomena. This paper presents three case studies drawn from the authors' research on HIV risk amongst injection drug users in which mixed methods studies yielded apparently discrepant results. The authors use these case studies (involving injection drug users [IDUs] using a Needle/Syringe Exchange Program in Los Angeles, CA, USA; IDUs seeking to purchase needle/syringes at pharmacies in Tijuana, Mexico; and young street-based IDUs in San Francisco, CA, USA) to identify challenges associated with integrating findings from mixed methods projects, summarize lessons learned, and make recommendations for how to more successfully anticipate and manage the integration of findings. Despite the challenges

inherent in reconciling apparently conflicting findings from qualitative and quantitative approaches, in keeping with others who have argued in favour of integrating mixed methods findings, the authors contend that such an undertaking has the potential to yield benefits that emerge only through the struggle to reconcile discrepant results and may provide a sum that is greater than the individual qualitative and quantitative parts. Wagner K, Davidson P, Pollini R, Strathdee S, Washburn R, Palinkas L. Reconciling incongruous qualitative and quantitative findings in mixed methods research: exemplars from research with drug using populations. Int J Drug Policy. 2012; 23(1): 54-61.

**Beyond Income: Material Resources Among Drug Users In Economically-Disadvantaged New York City Neighborhoods** Little is known about material resources among drug users beyond income. Income measures can be insensitive to variation among the poor, do not account for variation in cost-of-living, and are subject to non-response bias and underreporting. Further, most do not include illegal income sources that may be relevant to drug-using populations. The authors explored the reliability and validity of an 18-item material resource scale and describe correlates of adequate resources among 1593 current, former and non-drug users recruited in New York City. Reliability was determined using coefficient $\alpha$, $\omega_h$, and factor analysis. Criterion validity was explored by comparing item and mean scores by income and income source using ANOVA; content validity analyses compared scores by drug use. Multiple linear regression was used to describe correlates of adequate resources. The coefficient $\alpha$, and $\omega_h$, for the overall scale were 0.91 and 0.68, respectively, suggesting reliability was at least adequate. Legal income >$5000 (vs. d$5000) and formal (vs. informal) income sources were associated with more resources, supporting criterion validity. The authors observed decreasing resources with increasing drug use severity, supporting construct validity. Three factors were identified: basic needs, economic resources and services. Many did not have their basic needs met and few had adequate economic resources. Correlates of adequate material resources included race/ethnicity, income, income source, and homelessness. The 18-item material resource scale demonstrated reliability and validity among drug users. These data provide a different view of poverty, one that details specific challenges faced by low-income communities. Ompad D, Nandi V, Cerdá M, Crawford N, Galea S, Vlahov D. Beyond income: material resources among drug users in economically-disadvantaged New York City neighborhoods. Drug Alcohol Depend. 2012; 120(1-3): 127-134.

**Socializing In An Open Drug Scene: The Relationship Between Access To Private Space And Drug-Related Street Disorder** Limited attention has been given to the potential role that the structure of housing available to people who are entrenched in street-based drug scenes may play in influencing the amount of time injection drug users (IDU) spend on public streets. The authors sought to examine the relationship between time spent socializing in Vancouver's drug scene and access to private space. Using multivariate logistic regression the authors evaluated factors associated with socializing (three+ hours each day) in Vancouver's open drug scene among a prospective cohort of IDU. They also assessed attitudes towards relocating socializing activities if greater access to private indoor space was provided. Among our sample of 1,114 IDU, 43% fit our criteria for socializing in the open drug scene. In multivariate analysis, having limited access to private space was independently associated with socializing (adjusted odds ratio: 1.80, 95% confidence interval: 1.28-2.55). In further analysis, 65% of socializers' reported positive attitudes towards relocating socializing if they had greater access to private space. These

findings suggest that providing IDU with greater access to private indoor space may reduce one component of drug-related street disorder. Low-threshold supportive housing based on the 'housing first' model that include safeguards to manage behaviors associated with illicit drug use appear to offer important opportunities to create the types of private spaces that could support a reduction in street disorder. Debeck K, Wood E, Qi J, Fu E, McArthur D, Montaner J, Kerr T. Socializing In An Open Drug Scene: The relationship between access to private space and drug-related street disorder. Drug Alcohol Depend. 2012; 120(1-3): 28-34.

**Expanding ART for Treatment and Prevention of HIV in South Africa: Estimated Cost and Cost-Effectiveness 2011-2050** Antiretroviral Treatment (ART) significantly reduces HIV transmission. The authors conducted a cost-effectiveness analysis of the impact of expanded ART in South Africa. They model a best case scenario of 90% annual HIV testing coverage in adults 15-49 years old and four ART eligibility scenarios: CD4 count <200 cells/mm(3) (current practice), CD4 count <350, CD4 count <500, all CD4 levels. 2011-2050 outcomes include deaths, disability adjusted life years (DALYs), HIV infections, cost, and cost per DALY averted. Service and ART costs reflect South African data and international generic prices. ART reduces transmission by 92%. They conducted sensitivity analyses. RESULTS: Expanding ART to CD4 count <350 cells/mm(3) prevents an estimated 265,000 (17%) and 1.3 million (15%) new HIV infections over 5 and 40 years, respectively. Cumulative deaths decline 15%, from 12.5 to 10.6 million; DALYs by 14% from 109 to 93 million over 40 years. Costs drop $504 million over 5 years and $3.9 billion over 40 years with breakeven by 2013. Compared with the current scenario, expanding to <500 prevents an additional 585,000 and 3 million new HIV infections over 5 and 40 years, respectively. Expanding to all CD4 levels decreases HIV infections by 3.3 million (45%) and costs by $10 billion over 40 years, with breakeven by 2023. By 2050, using higher ART and monitoring costs, all CD4 levels saves $0.6 billion versus current; other ART scenarios cost $9-194 per DALY averted. If ART reduces transmission by 99%, savings from all CD4 levels reach $17.5 billion. Sensitivity analyses suggest that poor retention and predominant acute phase transmission reduce DALYs averted by 26% and savings by 7%. Increasing the provision of ART to <350 cells/mm3 may significantly reduce costs while reducing the HIV burden. Feasibility including HIV testing and ART uptake, retention, and adherence should be evaluated. Granich R, Kahn JG, Bennett R, Holmes CB, et al. Expanding ART for treatment and prevention of HIV in South Africa: estimated cost and cost-effectiveness 2011-2050. PLoS One 2012; 7(2): e30216.

**Homelessness As A Structural Barrier To Effective Antiretroviral Therapy Among HIV-Seropositive Illicit Drug Users In A Canadian Setting** Despite the advent of effective antiretroviral therapy (ART), HIV-seropositive injection drug users (IDU) continue to suffer from elevated levels of morbidity and mortality. Evidence is needed to identify social- and structural-level barriers to effective ART. The authors investigated the impact of homelessness on plasma HIV RNA response among illicit drug users initiating ART in a setting with free and universal access to HIV care. They accessed data from a long-running prospective cohort of community-recruited IDU linked to comprehensive HIV clinical monitoring and ART dispensation records. Using Cox proportional hazards with recurrent events modeling, they estimated the independent effect of homelessness on time to plasma HIV viral load suppression. Between May 1996 and September 2009, 247 antiretroviral naïve individuals initiated ART and contributed 1755 person-years of follow-up. Among these individuals, the incidence density of

plasma HIV RNA suppression less than 500 copies/mm(3) was 56.7 (95% confidence interval [CI]: 46.9-66.0) per 100 person-years. In unadjusted analyses, homelessness was strongly associated with lower rates suppression (hazard ratio = 0.56, 95% CI: 0.40-0.78, p = 0.001), however, after adjustment for adherence this association was no longer significant (adjusted hazard ratio = 0.79, 95% CI: 0.56-1.11, p = 0.177). Homelessness poses a significant structural barrier to effective HIV treatment. However, since this relationship appears to be mediated by lower levels of ART adherence, interventions to improve adherence among members of this vulnerable population are needed. Milloy M, Kerr T, Bangsberg D, Buxton J, Parashar S, Guillemi S, Montaner J, Wood E. Homelessness as a structural barrier to effective antiretroviral therapy among HIV-seropositive illicit drug users in a Canadian setting. AIDS Patient Care STDS. 2012; 26(1): 60-67.

**The Moderating Effects of Ethnic Identification on the Relationship between Parental Monitoring and Substance Use in Mexican Heritage Adolescents in the Southwest United States** The purpose of this study was to assess the combined effects of ethnic identification and perceived parental monitoring on the substance use of a sample of 162 male and 192 female Mexican heritage seventh grade adolescents. Parental monitoring predicted lower risk for substance use. An interaction of ethnic identification by parental monitoring was observed with parental monitoring exhibiting stronger effects in decreasing use of alcohol use among boys who scored low on ethnic identification. For girls, decreased substance use was predicted by stronger parental monitoring coupled with high ethnic identification. Results are discussed in terms of how the youth's ethnic identification is a distinct process from acculturation, and how ethnic identification may operate as an added protective factor in conjunction with parental monitoring, as protective factors against adolescent substance abuse. Nagoshi J, Marsiglia F, Parsai M, Castro F. The moderating effects of ethnic identification on the relationship between parental monitoring and substance use in Mexican heritage adolescents in the Southwest United States. J Community Psychol. 2011; 39(5): 520-533.

**Substance Use and Mental Health Disparities among Sexual Minority Girls: Results from the Pittsburgh Girls Study** The purpose of this study was to examine substance use and mental health disparities between sexual minority girls and heterosexual girls. Data from the Pittsburgh Girls Study were analyzed. All girls were 17 years old. Girls were included if they were not missing self-reported sexual orientation and mental health data (N = 527). Thirty-one girls (6%) endorsed same-sex romantic orientation/identity or current same-sex attraction. Bivariate analyses were conducted to test group differences in the prevalence of substance use and suicidal behavior, and group differences in depression, anxiety, borderline personality disorder (BPD), oppositional defiant disorder (ODD), and conduct disorder (CD) symptoms. Compared with heterosexual girls, sexual minority girls reported higher past-year rates of cigarette, alcohol, and heavy alcohol use, higher rates of suicidal ideation and self-harm, and higher average depression, anxiety, BPD, ODD, and CD symptoms. Sexual minority girls are an underrepresented group in the health disparities literature, and compared with heterosexual girls, they are at higher risk for mental health problems, most likely because of minority stress experiences such as discrimination and victimization. The disparities found in this report highlight the importance of discussing sexual orientation as part of a comprehensive preventive care visit. Marshal M, Sucato G, Stepp S, Hipwell A, Smith H, Friedman M, Chung T, Markovic N. Substance use and

mental health disparities among sexual minority girls: Results from the Pittsburgh Girls Study. J Pediatr Adolesc Gynecol. 2012; 25(1): 15-18.

**The Insults of Recreational Drug Abuse on Male Fertility** One-third of infertile couples may have a male factor present. Illicit drug use can be an important cause of male factor infertility and includes use of anabolic-androgenic steroids (AAS), marijuana, opioid narcotics, cocaine, and methamphetamines. The use of these illicit drugs is common in the US with a yearly prevalence rate for any drug consistently higher in males compared to females. The authors aim to provide a review of recent literature on the prevalence and effects of illicit drug use on male fertility and to aid health professionals when counseling infertile men whose social history suggests illicit drug use. Anabolic-androgenic steroids, marijuana, cocaine, methamphetamines, and opioid narcotics all negatively impact male fertility and adverse effects have been reported on the hypothalamic-pituitary-testicular axis, sperm function, and testicular structure. The use of illicit drugs is prevalent in our society and likely adversely impacting the fertility of men who abuse drugs. There is evidence in the literature to support a potential negative impact of illicit drug use on fertility in men. However, the current evidence-based data is limited. Future well-powered and designed studies are needed to better elucidate this relationship and its impact on this prevalent medical condition. Fronczak C, Kim E, Barqawi A. The insults of recreational drug abuse on male fertility. J Androl. 2011; 1-2.

**Rejuvenating Harm Reduction Projects For Injection Drug Users: Ukraine's Nationwide Introduction Of Peer-Driven Interventions** A peer-driven intervention (PDI) for injecting drug users (IDUs) was implemented in five Ukrainian city-sites to pilot-test its effectiveness in rejuvenating harm reduction (HR) projects that had become moribund. A PDI relies on drug users in a unique way to educate their peers in the community and recruit them for HIV prevention services. The goal of the PDI was to recruit in six months 500 IDUs who had never been respondents before to each of the five HR projects, especially stimulant- and women-injectors, and IDUs<25 years of age. The authors standardized the PDI's structure and operations across all five sites. All five PDIs were started in May 2007 using a carefully selected handful of "seed" IDU-recruiters who were trained to educate three peers who had never received HR services. They also accessed the database of all five projects and analysed the new respondents they recruited six-months prior to the start-up of the PDIs with the new recruits generated by the PDIs. Whilst the HR projects in the five city-sites recruited 72 new respondents on average during the six months prior to the PDIs' start-up, the PDIs recruited 455 new respondents on average in each city during their six months of operation, indicating that the PDI was 6.3 times more powerful as a recruitment mechanism. Compared to traditional outreach the PDIs resulted in significant increases in the recruitment of women- and young-injectors, and IDUs who injected a more diverse variety of drugs. The PDI can have a rejuvenating effect when added to HR projects that had become stagnate over time, resulting in an increase in the number and diversity of new IDU-respondents. Smyrnov P, Broadhead RS, Datsenko O, Matiyash O. Int J Drug Policy. 2012 Mar; 23(2): 141-147. Epub 2012 Feb 14.

## PREVENTION RESEARCH

**Social and Environmental Predictors of Plasma HIV RNA Rebound among Injection Drug Users Treated with Antiretroviral Therapy** Evidence is needed to improve HIV treatment outcomes for individuals who use injection drugs (IDU). Although studies have suggested higher rates of plasma viral load (PVL) rebound among IDU on antiretroviral therapy (ART), risk factors for rebound have not been thoroughly investigated. The authors used data from a long-running community-recruited prospective cohort of IDU in Vancouver, Canada, linked to comprehensive ART and clinical monitoring records. Using proportional hazards methods, they modeled the time to confirmed PVL rebound above 1000 copies/mL among IDU on ART with sustained viral suppression, defined as two consecutive undetectable PVL measures. Between 1996 and 2009, 277 individuals had sustained viral suppression. Over a median follow-up of 32 months, 125 participants (45.1%) experienced at least one episode of virologic failure for an incidence of 12.6 (95% Confidence Interval [CI]: 10.5 - 15.0) per 100 person years. In a multivariate model, PVL rebound was independently associated with sex trade involvement (Adjusted Hazard Ratio [AHR] = 1.40, 95% CI: 1.08-1.82) and recent incarceration (AHR = 1.83, 95% CI: 1.33-2.52). Methadone maintenance therapy (AHR = 0.79, 95% CI: 0.66 - 0.94) was protective. No measure of illicit drug use was predictive. In this setting of free ART, several social and environmental factors predicted higher risks of viral rebound among IDU, including sex trade involvement and incarceration. These findings should help inform efforts to identify individuals at risk of viral rebound as well as targeted interventions to treat and retain individuals in effective ART. Milloy M, Kerr T, Buxton J, Rhodes T, Krusi A, Guillemi S, Hogg R, Montaner J, Wood E. Social and environmental predictors of plasma hiv rna rebound among injection drug users treated with antiretroviral therapy. J Acquir Immune Defic Syndr. 2011; Epub Nov 2011: Epub.

**Cost-Benefit Analysis of Communities That Care Outcomes at Eighth Grade** This paper presents a cost-benefit analysis of the Communities That Care (CTC) prevention system, a public health approach to reducing risk, enhancing protection, and reducing the prevalence of adolescent health and behavior problems community wide. The analysis is based on outcomes from a panel of students followed from Grade 5 through Grade 8 in a randomized controlled trial involving 24 communities in 7 states. Previous analyses have shown that CTC prevented the initiation of cigarette smoking, alcohol use, and delinquency by the end of 8th grade in CTC communities compared to controls. This paper estimates long-term monetary benefits associated with significant intervention effects on cigarette smoking and delinquency as compared to the cost of conducting the intervention. Under conservative cost assumptions, the net present benefit is $5,250 per youth, including $812 from the prevention of cigarette smoking and $4,438 from the prevention of delinquency. The benefit-cost ratio indicates a return of $5.30 per $1.00 invested. Under less conservative but still viable cost assumptions, the benefit-cost ratio due to prevention of cigarette smoking and delinquency increases to $10.23 per $1.00 invested. Benefits from CTC's reduction in alcohol initiation as well as broader inclusion of quality-of-life gains would further increase CTC's benefit-cost ratio. Results provide evidence that CTC is a cost-beneficial preventive intervention and a good investment of public dollars, even under very conservative cost and benefit assumptions. Kuklinski M, Briney J, Hawkins J, Catalano R. Cost-benefit analysis of Communities That Care outcomes at eighth grade. Prev Sci. 2011; epub ahead of print.

**CHRM2, Parental Monitoring, and Adolescent Externalizing Behavior: Evidence for Gene-Environment Interaction** Psychologists, with their long-standing tradition of studying mechanistic processes, can make important contributions to further characterizing the risk associated with genes identified as influencing risk for psychiatric disorders. The authors report one such effort with respect to CHRM2, which codes for the cholinergic muscarinic 2 receptor and was of interest originally for its association with alcohol dependence. They tested for association between CHRM2 and prospectively measured externalizing behavior in a longitudinal, community-based sample of adolescents, as well as for moderation of this association by parental monitoring. They found evidence for an interaction in which the association between the genotype and externalizing behavior was stronger in environments with lower parental monitoring. There was also suggestion of a crossover effect, in which the genotype associated with the highest levels of externalizing behavior under low parental monitoring had the lowest levels of externalizing behavior at the extreme high end of parental monitoring. The difficulties involved in distinguishing mechanisms of gene-environment interaction are discussed. Dick DM, Meyers JL, Latendresse SJ, Creemers HE, Lansford JE, Pettit GS, Bates JE, Dodge KA, Budde J, Goate A, Buitelaar JK, Ormel J, Verhulst FC, Huizink AC. CHRM2, parental monitoring, and adolescent externalizing behavior: Evidence for gene-environment interaction. Psychol Sci. 2011; 22(4): 481-489.

**Differential Susceptibility to Adolescent Externalizing Trajectories: Examining the Interplay between CHRM2 and Peer Group Antisocial Behavior** The present study characterized prototypical patterns of development in self-reported externalizing behavior, between 12 and 22 years of age, within a community sample of 452 genotyped individuals. A Caucasian subset (n = 378) was then examined to determine whether their probabilities of displaying discrete trajectories were differentially associated with CHRM2, a gene implicated in self-regulatory processes across a range of externalizing behaviors, and if affiliating with antisocial peers moderated these associations. Findings indicate that relative to a normative "lower risk" externalizing trajectory, likelihood of membership in two "higher risk" trajectories increased with each additional copy of the minor allelic variant at CHRM2, and that this association was exacerbated among those exposed to higher levels of peer group antisocial behavior. Latendresse S, Bates J, Goodnight J, Lansford J, Budde J, Goate A, Dodge K, Pettit G, Dick D. Differential susceptibility to adolescent externalizing trajectories: Examining the interplay between CHRM2 and peer group antisocial behavior. Child Dev. 2011; 82 (6): 1797-1814.

**Non-medical Use of Prescription Drugs among Youth in an Appalachian Population: Prevalence, Predictors, and Implications for Prevention** This article examines prevalence of non-medical use of prescription drugs (NMUPD) in a sample of elementary and high school students in an Appalachian Tennessee county. The authors found that lifetime prevalence of NMUPD (35%) was higher than prevalence of cigarette use (28%) and marijuana use (17%), but lower than lifetime prevalence of alcohol use (46%). They examined characteristics, as well as risk and protective factors in several domains, as predictors of NMUPD. For comparison, they also examined these characteristics and factors as predictors of alcohol, cigarette, and marijuana use. Using survey data from a sample of late elementary school and high school students (grades 5, 7, 9, and 11), logistic regression analyses showed that the risk factors of friends' non-medical use and perceived availability, and the protective factors of perceived risk, parents' disapproval,

school commitment, and community norms against youth NMUPD were significant predictors of lifetime prevalence of NMUPD. Implications for prevention are discussed. Collins D, Abad M, Johnson K, Shamblen S, Thompson K. Non-medical use of prescription drugs among youth in an Appalachian population: Prevalence, predictors, and implications for prevention. J Drug Educ. 2011; 41(3): 309-326.

**HIV Treatment as Prevention among Injection Drug Users** The use of highly active antiretroviral therapy (HAART) as a strategy to prevent the transmission of HIV infection is of substantial international interest. Injection drug users (IDUs) are an important population with respect to HIV treatment as prevention because they are often less likely to access HAART in comparison with other risk groups. A recent multicentre randomized clinical trial demonstrated a 96% reduction in HIV transmission among heterosexual serodiscordant couples prescribed early HAART. Consistent with these results, independent observational studies from Baltimore and Vancouver have demonstrated that population level rates of HAART use among IDUs are associated with reduced rates of HIV incidence. In addition, impact assessments of HAART delivery to IDUs have generally demonstrated no negative effects of HAART use on rates of unsafe sex or syringe sharing. HAART prevents HIV transmission because it dramatically decreases HIV-1 RNA levels in biological fluids. This is relevant to vertical and sexual HIV transmission and also to blood-borne HIV transmission, as it is often the case among IDUs. Efforts to expand HAART to IDUs should be redoubled in an effort to realize both the individual and public health benefits of HAART. Wood E, Milloy M, Montaner J. HIV treatment as prevention among injection drug users. Curr Opin HIV AIDS. 2012; Epub Jan 2012.

**Behavioral Components of Impulsivity Predict Alcohol Consumption in Adults with ADHD and Healthy Controls** The degree to which distinct behavioral components of impulsivity predict alcohol consumption is as yet not well-understood. Further, the possibility that this relation might be more pronounced in groups characterized by heightened impulsivity (i.e., individuals with ADHD) has not been tested. The current study examined the degree to which three specific behavioral components of impulsivity (i.e., poor response inhibition, poor attentional inhibition, and increased risk-taking) were associated with quantity and frequency of alcohol consumption in a group of young adult social drinkers with ADHD (n = 33) and in a comparison control group (n = 21). Participants performed the delayed ocular return task (attentional inhibition), the cued go/no-go task (behavioral inhibition), and the balloon analogue risk task (risk-taking). Both poor behavioral inhibition and greater risk-taking were related to greater quantity of consumption in the entire sample, whereas poor attentional inhibition was related to greater quantity specifically among those with ADHD. By contrast, only risk-taking was associated with frequency of consumption, and this was found specifically in the control group. These findings provide important information regarding the potential role of distinct behavioral components of impulsivity in drinking behavior, and highlight unique relevance of attentional impairments to drinking behavior in those with ADHD. Weafer, J., Milich, R., Fillmore, MT. Behavioral components of impulsivity predict alcohol consumption in adults with adhd and healthy controls. Drug Alcohol Depend. 2011; 113(2-3): 139-146.

**Methylphenidate and Fluphenazine, but Not Amphetamine, Differentially Affect Impulsive Choice in Spontaneously Hypertensive, Wistar-Kyoto and Sprague-Dawley Rats**
Impulsivity is one of the core symptoms of attention-deficit/hyperactivity disorder (ADHD). The spontaneously hypertensive rat (SHR), a putative animal model of ADHD, has been used to investigate the neurobiology of impulsivity, although this model has been questioned over concerns that use of Wistar-Kyoto rats (WKY) as a comparison strain may exaggerate effects. The present study compared SHR, WKY and standard, outbred Sprague-Dawley (SD) rats on a delay discounting task where the primary measure was mean adjusted delay (MAD), or the indifference point (in sec) between choice of an immediate delivery of 1 grain-based pellet versus 3 pellets delivered after varying delays. The acute dose effects of the ADHD medications amphetamine (0.1-1.0 mg/kg) and methylphenidate (1.0-10 mg/kg) were then determined; in addition, the effect of the dopamine receptor antagonist fluphenazine (0.1-1.0 mg/kg) was also assessed for comparison with the indirect agonists. While there were no strain differences in the rate of task acquisition or stabilization of baseline MAD scores, SHR had significantly lower MAD scores than WKY but not SD due to the greater individual variability of MAD scores in SD. Although amphetamine did not alter MAD scores in any strain, methylphenidate selectively increased MAD scores in WKY and fluphenazine selectively increased MAD scores in SHR. WKY were also more sensitive than SHR and SD to the response-impairing effects of each drug. The finding that SHR showed a decrease in impulsivity following fluphenazine, but not following either amphetamine or methylphenidate, suggests that delay discounting in SHR may not represent a valid predictive model for screening effective ADHD medications in humans. Wooters T, Bardo M. Methylphenidate and fluphenazine, but not amphetamine, differentially affect impulsive choice in spontaneously hypertensive, Wistar-Kyoto and Sprague-Dawley Rats. Brain Res. 2011; 1396: 45-53.

**Internalizing Symptoms: Effects of a Preventive Intervention on Developmental Pathways from Early Adolescence to Young Adulthood** This study examined the mediated and moderated effects of a universal family-focused preventive intervention, delivered during young adolescence, on internalizing symptoms assessed in young adulthood. Sixth grade students (N = 446; 52% female; 98% White) and their families from 22 rural Midwestern school districts were randomly assigned to the experimental conditions in 1993. Self-report questionnaires were administered at seven time points (pre-test to young adulthood-age 21) to those receiving the Iowa Strengthening Families Program (ISFP) and to the control group. Results showed that growth factors of adolescent internalizing symptoms (grades 6-12) were predicted by ISFP condition and risk status (defined as early substance initiation). Moderation of the condition effect by risk status was found, with higher-risk adolescents benefitting more from the ISFP. Results also supported the hypothesis that the ISFP 's effect on internalizing symptoms in young adulthood was mediated through growth factors of adolescents' internalizing symptoms; risk moderation, however, was only marginally significant in young adulthood. The relative reduction rate on clinical or subclinical levels of young adult internalizing symptoms was 28%, indicating that for every 100 young adults displaying clinical or subclinical levels of internalizing symptoms from school districts not offering an intervention, there could be as few as 72 displaying those levels of symptoms in school districts that offered middle school prevention programming. These findings highlight how the positive effects of family-focused universal interventions can extend to non-targeted outcomes and the related potential public-health impact of scaling up these interventions. Trudeau L, Spoth R, Randall G, Mason W, Shin C.

Internalizing symptoms: Effects of a preventive intervention on developmental pathways from early adolescence to young adulthood. J Youth Adolesc. 2011; Published online Dec 10, 2011.

**Sustaining Fidelity following the Nationwide PMTO** This report describes three studies from the nationwide Norwegian implementation of Parent Management Training-Oregon Model (PMTO), an empirically supported treatment for families of children with behavior problems (Forgatch and Patterson 2010). Separate stages of the implementation were evaluated using a fidelity measure based on direct observation of intervention sessions. Study 1 assessed growth in fidelity observed early, mid, and late in the training of a group of practitioners. The authors hypothesized increased fidelity and decreased variability in practice. Study 2 evaluated method fidelity over the course of three generations of practitioners trained in PMTO. Generation 1 (G1) was trained by the PMTO developer/purveyors; Generation 2 (G2) was trained by selected G1 Norwegian trainers; and Generation 3 (G3) was trained by G1 and G2 trainers. The authors hypothesized decrease in fidelity with each generation. Study 3 tested the predictive validity of fidelity in a cross-cultural replication, hypothesizing that higher fidelity scores would correlate with improved parenting practices observed in parent-child interactions before and after treatment. In Study 1, trainees' performance improved and became more homogeneous as predicted. In Study 2, a small decline in fidelity followed the transfer from the purveyor trainers to Norwegian trainers in G2, but G3 scores were equivalent to those attained by G1. Thus, the hypothesis was not fully supported. Finally, the FIMP validity model replicated; PMTO fidelity significantly contributed to improvements in parenting practices from pre- to post-treatment. The data indicate that PMTO was transferred successfully to Norwegian implementation with sustained fidelity and cross-cultural generalization. Forgatch MS, DeGarmo DS. Sustaining fidelity following the nationwide PMTO. Prev Sci. 2011; 12(3): 235-246.

**Allostasis Model Facilitates Understanding Race Differences in the Diurnal Cortisol Rhythm** The concept of allostasis suggests that greater cumulative stress burden can influence stress-responsive physiology. Dysregulation of allostatic mediators, including the hypothalamic-pituitary-adrenal (HPA) axis, is thought to precede many other signs of age-related pathology as the persistent burden of stressors accumulates over the individual's life span. The authors predicted that even in young adulthood, HPA regulation would differ between Blacks and Whites, reflecting, in part, higher rates of stressor exposure and greater potential for stressors to "get under the skin." They examined whether stressor exposure, including experiences with racism and discrimination, explained race differences in waking cortisol and the diurnal rhythm. They also examined whether HPA functioning was associated with mental health outcomes previously linked to cortisol. Salivary cortisol was assayed in 275 young adults (127 Blacks, 148 Whites, 19 to 22 years old), four times a day across 3 days. Hierarchical linear models revealed flatter slopes for Blacks, reflecting significantly lower waking and higher bedtime cortisol levels compared to Whites. Associations of HPA functioning with stressors were typically more robust for Whites such that more stress exposure created an HPA profile that resembled that of Black young adults. For Blacks, greater stressor exposure did not further impact HPA functioning, or, when significant, was often associated with higher cortisol levels. Across both races, flatter slopes generally indicated greater HPA dysregulation and were associated with poor mental health outcomes. These differential effects were more robust for Whites. These findings support an allostatic model in which social contextual factors influence normal biorhythms, even as early as young adulthood. Skinner M, Shirtcliff E, Haggerty K, Coe C, Catalano R. Allostasis model

facilitates understanding race differences in the diurnal cortisol rhythm. Dev Psychopathol. 2011; 23(4): 1167-1186.

**The Effects of No Child Left Behind on the Prevalence of Evidence-Based Drug Prevention Curricula in the Nation's Middle Schools** Concerns have been expressed that No Child Left Behind (NCLB) may be reducing the amount of classroom time devoted to subjects other than those for which students are tested. The purpose of this article is to explore whether NCLB legislation has affected the provision of evidence-based drug prevention curricula (EBC) in the nation's middle schools, a subject area that is not assessed by standardized tests. Data were collected in spring 2005 and spring 2008 from a nationally representative sample of middle schools. Respondents completed a survey regarding their provision of EBC (2005 response rate: 78.1%). The authors also collected data on schools ' adequate yearly progress (AYP) status as of 2005 as a measure of their compliance with NCLB targets. The authors restricted their sample to schools that responded to our survey in both waves (n = 1324, or 76.9% of those schools responding in 2005) and conducted logistic regression analyses to determine whether those schools not making AYP in 2005 were less likely to be using an EBC in 2008. The results revealed no relationship between AYP status in 2005 and EBC use in 2008. Analyses of demographic characteristics showed that schools making AYP were more likely to be small and rural, and to serve majority White student populations whose families were characterized by lower levels of poverty. The authors' failure to find any relationship between AYP status and the provision of EBC suggests that concerns about the potential adverse effects of NCLB on drug use prevention have yet to be validated. Implications of our results are discussed. Ringwalt C, Hanley S, Ennett S, Vincus A, Bowling J, Haws S, Rohrbach L. The effects of no child left behind on the prevalence of evidence-based drug prevention curricula in the nation's middle schools. J Sch Health. 2011; 81(5): 265-272.

**The Mental Health, Substance Use, and Delinquency among Truant Youths in a Brief Intervention Project: A Longitudinal Study** The relationship between substance use, mental health disorders, and delinquency among youth is well documented. What has received far less attention from researchers is the relationship between these issues among truant youth, in spite of studies that document truants are a population at-risk for negative outcomes. The present study bridges this gap by (1) examining psychosocial functioning and delinquency among truants, and (2) assessing the efficacy of a Brief Intervention (BI) in reducing delinquent behavior over time. To meet these objectives, data were collected from 183 truant youth enrolled in an ongoing NIDA-funded BI project. Informed by a developmental damage perspective, a structural equation model was formulated and estimated. Interim results provide overall support for the model, and suggest the BI may be a promising, innovative intervention for truant youth. Service delivery implications and directions for future analyses are discussed. Dembo R, Briones-Robinson R, Barrett K, Winters KC, Schmeidler J, Ungaro R, Karas LM, Belenko S, Gulledge L. The mental health, substance use, and delinquency among truant youths in a brief intervention project: A longitudinal study. J Emot Behav Disord. Published online December 27, 2011.

**Preventing Early Child Maltreatment: Implications from a Longitudinal Study of Maternal Abuse History, Substance Use Problems, and Offspring Victimization** In the interest of improving child maltreatment prevention science, this longitudinal, community based study of 499 mothers and their infants tested the hypothesis that mothers' childhood history of

maltreatment would predict maternal substance use problems, which in turn would predict offspring victimization. Mothers (35% White/non-Latina, 34% Black/non-Latina, 23% Latina, 7% other) were recruited and interviewed during pregnancy, and child protective services records were reviewed for the presence of the participants' target infants between birth and age 26 months. Mediating pathways were examined through structural equation modeling and tested using the products of the coefficients approach. The mediated pathway from maternal history of sexual abuse to substance use problems to offspring victimization was significant (standardized mediated path [ab] = .07, 95% CI [.02, .14]; effect size = .26), as was the mediated pathway from maternal history of physical abuse to substance use problems to offspring victimization (standardized mediated path [ab] = .05, 95% CI [.01, .11]; effect size = .19). There was no significant mediated pathway from maternal history of neglect. Findings are discussed in terms of specific implications for child maltreatment prevention, including the importance of assessment and early intervention for maternal history of maltreatment and substance use problems, targeting women with maltreatment histories for substance use services, and integrating child welfare and parenting programs with substance use treatment. Appleyard K, Berlin LJ, Rosanbalm KD, Dodge KA. Preventing early child maltreatment: Implications. Prev Sci. 2011; 12: 139-149.

**Perceived Discrimination as a Risk Factor for Latina/o Youth's Substance Use: Do Parent- and Peer-based Communication and Relationship Resources Act as Protective Factors?** Based on general strain theory, it was hypothesized that as Latina/o youth experience perceived discrimination, they are more likely to develop acculturation stress and, in turn, more likely to use substances. Two additional hypotheses were set forth to examine how parent- and peer-based communication, relationship, and norm resources may function as buffers, thereby decreasing the likelihood that strained youth will use substances. Latina/o youth (N = 728) from 23 schools in Phoenix, AZ, completed surveys at three waves over 2 years. Structural equation modeling (SEM) results supported the first hypothesis. Yet, contrary to the second hypothesis, neither parent nor peer resources were significant moderators. Implications are discussed for theory and parent- and peer-based prevention research directed at perceived discrimination, acculturation stress, and substance use. Kam J, Cleveland M. Perceived discrimination as a risk factor for latina/o youth's substance use: do parent- and peer-based communication and relationship resources act as protective factors? Health Commun. 2011; 26(2): 111-124.

**Reciprocal Relations between Parents' Physical Discipline and Children's Externalizing Behavior during Middle Childhood and Adolescence** Using data from two long-term longitudinal projects, the authors investigated reciprocal relations between maternal reports of physical discipline and teacher and self-ratings of child externalizing behavior, accounting for continuity in both discipline and externalizing over time. In Study 1, which followed a community sample of 562 boys and girls from age 6 to 9, high levels of physical discipline in a given year predicted high levels of externalizing behavior in the next year, and externalizing behavior in a given year predicted high levels of physical discipline in the next year. In Study 2, which followed an independent sample of 290 lower income, higher risk boys from age 10 to 15, mother-reported physical discipline in a given year predicted child ratings of antisocial behavior in the next year, but child antisocial behavior in a given year did not predict parents' use of physical discipline in the next year. In neither sample was there evidence that associations

between physical discipline and child externalizing changed as the child aged, and findings were not moderated by gender, race, socioeconomic status, or the severity of the physical discipline. Implications for the reciprocal nature of the socialization process and the risks associated with physical discipline are discussed. Lansford JE, Criss MM, Laird RD, Shaw DS, Pettit GS, Bates JE, Dodge KA. Reciprocal relations between parents' physical discipline and children's externalizing behavior during middle childhood and adolescence. Dev Psychopathol. 2011; 23(1): 225-238.

**Adolescent Health-Risk Sexual Behaviors: Effects of Drug Abuse** Adolescents who abuse substances are more likely to engage in health-risking sexual behavior (HRSB) and are at particularly high risk for HIV/AIDS. Thus, substance abuse treatment presents a prime opportunity to target HIV-risk behaviors. The present study evaluated a one-session HIV-risk intervention embedded in a controlled clinical trial for drug-abusing adolescents. The trial was conducted in New Mexico and Oregon with Hispanic and Anglo adolescents. Youths were randomly assigned to individual cognitive behavior therapy (CBT) or to an integrated behavioral and family therapy (IBFT) condition, involving individual and family sessions. The HIV-specific intervention was not associated with change. IBFT and CBT were both efficacious in reducing HIV-risk behaviors from intake to the 18-month follow-up for high-risk adolescents. For low-risk adolescents, CBT (versus IBFT) was more efficacious in suppressing HRSB. These data suggest that drug abuse treatments can have both preventative and intervention effects for adolescents, depending on their relative HIV-risk. Hops H, Ozechowski TJ, Waldron HB, Davis B, Turner CW, Brody JL, Barrera M. Adolescent health-risk sexual behaviors: Effects of drug abuse. AIDS Behav. 2011; 15: 1664-1676.

**Increasing Discussions of Intimate Partner Violence in Prenatal Care Using Video Doctor Plus Provider Cueing** This study reports on the effectiveness of a prenatal intervention and to provide evidence that prenatal visits provide an opportune time for health assessment and counseling with abused women. Fifty ethnically diverse pregnant women who presented for routine prenatal care and who also reported being at risk for intimate partner violence (IPV) were recruited to the study. Participants were assigned to either usual care or the Video Doctor plus Provider Cueing intervention. At baseline and 1 month later at another routine prenatal visit, intervention group participants received a 15-minute Video Doctor assessment and interactive tailored counseling. Their providers received a printed Cue Sheet alert and suggested counseling statements. Participants in the intervention group were significantly more likely to report provider–patient discussions of IPV compared with participants receiving usual care at baseline (81.8% vs. 16.7%; $p < .001$) and at the 1-month follow-up (70.0% vs. 23.5%; $p < .005$). Summing the number of patient–provider discussions across the two visits at baseline and 1 month later, intervention participants were significantly more likely to have IPV risk discussion with their providers at one or both visits (90.0% vs. 23.6%; $p < .001$) compared with the participants who received usual care. When specifically asked about the helpfulness of these IPV-related discussions, 20 out of 22 (90.9%) participants rated the discussion as helpful or very helpful at baseline and all 18 (100%) participants rated the discussion as helpful or very helpful at the 1-month follow-up. Thus, Video Doctor plus Provider Cueing intervention significantly increases the likelihood of provider–patient IPV discussion with pregnant women with a history of abuse. Humphreys J, Tsoh JY, Kohn MA, Gerbert B. Increasing discussions of intimate

partner violence in prenatal care using video docgtor plus provider cueing: A Randomized, controlled trial. Womens Health Issues. 2011; 21(2): 136-144.

**Sexual Risk Behaviors and Acceptability of HIV Pre-exposure Prophylaxis among HIV-Negative Gay and Bisexual Men in Serodiscordant Relationships: A Mixed Methods Study** The objective of this mixed methods study was to examine current sexual risk behaviors, acceptability and potential adoption of pre-exposure prophylaxis (PrEP) for HIV prevention, and sexual behavior intentions with PrEP adoption among HIV-negative gay and bisexual men (GBM) in HIV serodiscordant relationships. A multiracial/ethnic sample of 25 HIV-negative GBM in serodiscordant relationships completed a qualitative interview and a brief interviewer-administered survey. A modified grounded theory approach was used to identify key themes relating to acceptability and future adoption of PrEP. Participants reported engaging in sexual risk behaviors that place them at risk for HIV infection. Participants also reported a high level of acceptability for PrEP and willingness to adopt PrEP for HIV prevention. Qualitative themes explaining future PrEP adoption included: (1) the opportunity to engage in sex using a noncondom HIV prevention method, (2) protection from HIV infection, and (3) less anxiety when engaging in sex with an HIV-positive partner. Associated with the future adoption of PrEP, a majority (64%) of participants indicated the likelihood for an increase in sexual risk behaviors and a majority (60%) of participants also indicated the likelihood for a decrease or abandonment of condom use, both of which are in contrast to the findings from the large iPrEx study. These findings suggest that the use of PrEP by HIV-negative GBM in serodiscordant relationships carries with it the potential for risk compensation. The findings suggest that PrEP only be offered as part of a comprehensive HIV prevention strategy that includes ongoing risk reduction counseling in the delivery of PrEP to help moderate risk compensation. Brooks R, Landovitz R, Kaplan R, Lieber E, Lee S, Barkley T. Sexual risk behaviors and acceptability of HIV pre-exposure prophylaxis among HIV-negative gay and bisexual men in serodiscordant relationships: A mixed methods study. AIDS Patient Care STDS. 2011; Epub Dec 2011.

**Exploring the Impact of Underage Sex Work among Female Sex Workers in Two Mexico-U.S. Border Cities** Although sex work and younger age increase HIV vulnerability, empirical data regarding the impacts of underage sex work are lacking. The authors explored associations between features of the risk environment, sex work, and drug use history, and underage sex work entry among 624 female sex workers (FSWs) in Tijuana and Ciudad Juarez, Mexico. Forty-one percent (n = 253) of women began sex work as minors, among whom HIV and any STI/HIV prevalence were 5.2 and 60.7%. Factors independently associated with increased odds of underage sex work were inhalants as the first drug used, forced first injection, number of drug treatment attempts, and recent receptive syringe sharing. Number of recent condom negotiation attempts with steady partners and depression as a reason for first injecting were negatively associated with underage entry. These results underscore the importance of efforts to prevent underage sex work and the wider factors contributing to HIV risk among vulnerable youth and underage FSWs. Goldenberg S, Rangel G, Vera A, Patterson T, Abramovitz D, Silverman J, Raj A, Strathdee S. Exploring the impact of underage sex work among female sex workers in two Mexico-US border cities. AIDS Behav. 2011; Epub Oct 2011.

**Injection Drug Users' Perspectives on Placing HIV Prevention and Other Clinical Services in Pharmacy Settings** In their role as a source of sterile syringes, pharmacies are ideally situated to provide additional services to injection drug users (IDUs). Expanding pharmacy services to IDUs may address the low utilization rates of healthcare services among this population. This qualitative study of active IDUs in San Francisco explored perspectives on proposed health services and interventions offered in pharmacy settings, as well as facilitators and barriers to service delivery. Eleven active IDUs participated in one-on-one semi-structured interviews at a community field site and at a local syringe exchange site between February and May 2010. Results revealed that most had reservations about expanding services to pharmacy settings, with reasons ranging from concerns about anonymity to feeling that San Francisco already offers the proposed services in other venues. Of the proposed health services, this group of IDUs prioritized syringe access and disposal, clinical testing and vaccinations, and provision of methadone. Pharmacists' and pharmacy staffs' attitudes were identified as a major barrier to IDUs' comfort with accessing services. The findings suggest that although IDUs would like to see some additional services offered within pharmacy settings, this is contingent upon pharmacists and their staff receiving professional development trainings that cultivate sensitivity towards the needs and experiences of IDUs. Lutnick A, Case P, Kral A. injection drug users' perspectives on placing HIV prevention and other clinical services in pharmacy settings. J Urban Health. 2012; Epub Jan 2012.

**The Good Behavior Game and the Future of Prevention and Treatment** The Good Behavior Game (GBG), a universal classroom behavior management method, was tested in first- and second-grade classrooms in Baltimore beginning in the 1985-1986 school year. Follow-up at ages 19-21 found significantly lower rates of drug and alcohol use disorders, regular smoking, antisocial personality disorder, delinquency and incarceration for violent crimes, suicide ideation, and use of school-based services among students who had played the GBG. Several replications with shorter follow-up periods have provided similar early results. The authors discuss the role of the GBG and possibly other universal prevention programs in the design of more effective systems for promoting children's development and problem prevention and treatment services. Kellam S, Mackenzie A, Brown C, Poduska J, Wang W, Petras H, Wilcox H. The Good Behavior Game and the future of prevention and treatment. Addict Sci Clin Pract. 2011; 6(1): 73-84.

**Effects of 24 Hours of Tobacco Withdrawal and Subsequent Tobacco Smoking among Low and High Sensation Seekers** Previous studies have indicated that high sensation seekers are more sensitive to the reinforcing effects of nicotine, initiate smoking at an earlier age, and smoke greater amounts of cigarettes. This study examined the influence of sensation-seeking status on tobacco smoking following deprivation in regular tobacco users. Twenty healthy tobacco-smoking volunteers with low or high impulsive sensation-seeking subscale scores completed 2 consecutive test days per week for 3 consecutive weeks. Each week, a range of self-report, performance, and cardiovascular assessments were completed during ad libitum smoking on Day 1 and before and after the paced smoking of a tobacco cigarette containing 0.05, 0.6, or 0.9 mg of nicotine following 24 hr of tobacco deprivation on Day 2. In addition, self-administration behavior was analyzed during a 2-hr free access period after the initial tobacco administration. In high sensation seekers, tobacco smoking independent of nicotine yield ameliorated deprivation effects, whereas amelioration of deprivation effects was dependent on nicotine yield among low

sensation seekers. However, this effect was limited to a small subset of measures. Subsequent cigarette self-administration increased in a nicotine-dependent manner for high sensation seekers only. Compared with low sensation seekers, high sensation seekers were more sensitive to the withdrawal relieving effects of non-nicotine components of smoking following 24 hr of deprivation on selective measures and more sensitive to nicotine yield during subsequent tobacco self-administration. These results are consistent with studies suggesting that factors driving tobacco dependence may vary as a function of sensation-seeking status. Lee D, Perkins K, Zimmerman E, Robbins G, Kelly T. Effects of 24 hours of tobacco withdrawal and subsequent tobacco smoking among low and high sensation seekers. Nicotine Tob Res. 2011; 13(10): 943-954.

**Individual Differences in Cognition, Affect, and Performance: Behavioral, Neuroimaging, and Molecular Genetic Approaches** The authors describe the use of behavioral, neuroimaging, and genetic methods to examine individual differences in cognition and affect, guided by three criteria: (1) relevance to human performance in work and everyday settings; (2) interactions between working memory, decision-making, and affective processing; and (3) examination of individual differences. The results of behavioral, functional MRI (fMRI), event-related potential (ERP), and molecular genetic studies show that analyses at the group level often mask important findings associated with sub-groups of individuals. Dopaminergic/noradrenergic genes influencing prefrontal cortex activity contribute to inter-individual variation in working memory and decision behavior, including performance in complex simulations of military decision-making. The interactive influences of individual differences in anxiety, sensation seeking, and boredom susceptibility on evaluative decision-making can be systematically described using ERP and fMRI methods. The authors conclude that a multi-modal neuroergonomic approach to examining brain function (using both neuroimaging and molecular genetics) can be usefully applied to understanding individual differences in cognition and affect and has implications for human performance at work. Parasuraman R, Jiang Y. Individual differences in cognition, affect, and performance: behavioral, neuroimaging, and molecular genetic approaches. Neuroimage. 2012; 59 (1): 70-82.

**Separating Automatic and Intentional Inhibitory Mechanisms of Attention in Adults with Attention-Deficit/Hyperactivity Disorder** Researchers in the cognitive sciences recognize a fundamental distinction between automatic and intentional mechanisms of inhibitory control. The use of eye-tracking tasks to assess selective attention has led to a better understanding of this distinction in specific populations such as children with attention-deficit/hyperactivity disorder (ADHD). This study examined automatic and intentional inhibitory control mechanisms in adults with ADHD using a saccadic interference (SI) task and a delayed ocular response (DOR) task. Thirty adults with ADHD were compared to 27 comparison adults on measures of inhibitory control. The DOR task showed that adults with ADHD were less able than comparison adults to inhibit a reflexive saccade towards the sudden appearance of a stimulus in the periphery. However, SI task performance showed that the ADHD group did not differ significantly from the comparison group on a measure of automatic inhibitory control. These findings suggest a dissociation between automatic and intentional inhibitory deficits in adults with ADHD. Roberts W, Fillmore MT, Milich R. Separating automatic and intentional inhibitory mechanisms of attention in adults with Attention-Deficit/Hyperactivity Disorder. J Abnorm Child Psychol. 2011; 120(1): 223-233.

**A Translational Behavioral Model of Mood-based Impulsivity: Implications for Substance Abuse** Laboratory tasks that measure various facets of impulsivity derived from self-report questionnaires are important for elucidating the behavioral consequences of impulsivity in humans and for back-translating these facets to non-human species. Negative urgency, or mood-based rash action, is a self-report facet of impulsivity linked to problem substance use; however, a valid behavioral task is lacking. The current studies were designed to bridge self-report questionnaire and behavioral measures of negative urgency in humans and to determine if this could be back-translated to rats. Humans scoring high in negative urgency showed greater behavioral responding and increased frustration following unexpected reward omission on a monetary-based task compared to subjects low in negative urgency. Rats also showed elevated responding for either sucrose pellets or intravenous amphetamine following unexpected reward omission. These results suggest that impulsive behavior engendered by unexpected reward omission may represent a valid behavioral model of negative urgency linked to substance abuse. Gipson C, Beckmann J, Adams Z, Marusich J, Nesland T, Yates J, Kelly T, Bardo M. A translational behavioral model of mood-based impulsivity: Implications for substance abuse. Drug Alcohol Depend. Published online October 5, 2011.

**High Impulsivity in Rats Predicts Amphetamine Conditioned Place Preference** Stimulants such as d-amphetamine (AMPH) are used commonly to treat attention-deficit hyperactivity disorder (ADHD), but concerns have been raised regarding the use of AMPH due to its reinforcing and potentially addictive properties. The current study examined if individual differences in impulsive choice predict AMPH-induced hyperactivity and conditioned place preference (CPP). Rats were first tested in delay discounting using an adjusting delay procedure to measure impulsive choice and then were subsequently tested for AMPH CPP. High impulsive (HiI) and low impulsive (LoI) rats were conditioned across four sessions with 0.1, 0.5, or 1.5 mg/kg of AMPH. AMPH increased locomotor activity for HiI and LoI rats following 0.5 mg/kg but failed to increase activity following 0.1 and 1.5 mg/kg. CPP was established for HiI rats with both 0.5 and 1.5 mg/kg of AMPH, whereas LoI rats did not develop CPP following any dose of AMPH; HiI and LoI groups differed significantly following 0.5 mg/kg of AMPH. These results indicate that HiI rats are more sensitive to the rewarding effects of AMPH compared to LoI rats, which is consistent with research showing that high impulsive individuals may be more vulnerable to stimulant abuse. Yates J, Marusich J, Gipson C, Beckmann J, Bardo M. High impulsivity in rats predicts amphetamine conditioned place preference. Pharmacol Biochem Behav. 2012; 100(3): 370-376.

**Social Facilitation of d-amphetamine Self-administration in Rats** The link between social influence and drug abuse has long been established in humans. However, preclinical animal models of drug abuse have only recently begun to consider the role of social influence. Since social factors influence the initiation and maintenance of drug use in humans, it is important to include these factors in preclinical animal models. The current study examined the effects of the presence of a social partner on responding for sucrose pellets under various motivational conditions, as well as on d-amphetamine (AMPH) self-administration. Rats were trained to lever press for either sucrose or AMPH (0.01 or 0.1 mg/kg/infusion unit dose). Following response stability, a novel same-sex conspecific was presented in an adjacent compartment separated by a clear divider, and responding for sucrose or AMPH reward was measured. Rats were allowed to restabilize, and subsequently given an additional partner presentation. Presence of the social

partner increased responding only during the first pairing with the AMPH 0.1 mg/kg/infusion unit dose, whereas inhibition of responding was observed during the first pairing during access to the 0.01 mg/kg/infusion unit dose. Under free feed conditions, inhibition of sucrose pellet responding was observed in the presence of the social partner, but this effect was attenuated under food restriction. In contrast, the results demonstrate social facilitation of AMPH self-administration at a high unit dose, thus extending the influence of social factors to an operant conditioning task. This model of social facilitation may have important implications as a preclinical model of social influence on drug abuse. Gipson C, Yates J, Beckmann J, Marusich J, Zentall T, Bardo M. Social facilitation of d-amphetamine self-administration in rats. Exp Clin Psychopharmacol. 2011; 19(6): 409-419.

**An Examination of the Validity of Retrospective Measures of Suicide Attempts in Youth**
This study used prospective data to investigate the validity of a retrospective measure of suicide attempts from four different perspectives. Data were retrieved from 883 participants in the Raising Healthy Children project, a longitudinal study of youth recruited from a Pacific Northwest school district. The retrospective measure was collected when participants were 18-19 years of age and results were compared with measures of depressive symptoms collected prospectively. Results showed strong corroboration between retrospective reports of first suicide attempt and prospective measures of depression, with attempters experiencing significantly more depression than their nonattempting peers, $t (df = 853) = 10.26$, $p < .001$. In addition, within the attempter group, depression scores during the year of their reported first attempt were significantly higher than the average depression score across previous years, $t (df = 67) = 3.01$, $p < .01$. Results from this study suggest that the reports of older adolescents regarding their suicide attempts are corroborated by their prospective reports of depression in childhood and earlier adolescence. Thus, there is support that retrospective measures of suicidal behavior, namely suicide attempts, may be a valid method of assessment. Mazza J, Catalano R, Abbott R, Haggerty K. An examination of the validity of retrospective measures of suicide attempts in youth. J Adolesc Health. 2011; 49(5): 532-537.

**A Community Prevention Model to Prevent Children from Inhaling and Ingesting Harmful Legal Products** Children's misuse of harmful legal products (HLPs), including inhaling or ingesting everyday household products, prescription drugs, and over-the-counter drugs, constitutes a serious health problem for American society. This article presents a community prevention model (CPM) focusing on this problem among pre and early adolescents. The model, consisting of a community mobilization strategy and environmental strategies targeting homes, schools, and retail outlets, is designed to increase community readiness and reduce the availability of HLPs, which is hypothesized to reduce HLPs use among children. The CPM is being tested in Alaskan rural communities as part of an inprogress eight-year National Institute on Drug Abuse randomized-controlled trial. This paper presents the CPM conceptual framework, describes the model, and highlights community participation, challenges, and lessons learned from implementation of the model over a 21-month period. Johnson K, Grube J, Ogilvie K, Collins D, Courser M, Dirks L, Ogilvie D, Driscoll D. A community prevention model to prevent children from inhaling and ingesting harmful legal products. Eval Program Plann. 2012; 35(1): 113-123.

**Mediation of a Preventive Intervention's 6-year Effects on Health Risk Behaviors** Using data from a 6-year longitudinal follow-up sample of 240 youth who participated in a randomized experimental trial of a preventive intervention for divorced families with children ages 9 to 12, the current study tested mechanisms by which the intervention reduced substance use and risky sexual behavior in mid to late adolescence (15-19 years old). Mechanisms tested included parental monitoring, adaptive coping, and negative errors. Parental monitoring at 6-year follow-up mediated program effects to reduce alcohol and marijuana use, polydrug use, and other drug use for those with high pretest risk for maladjustment. In the condition that included a program for mothers only, increases in youth adaptive coping at 6-year follow-up mediated program effects on risky sexual behavior for those with high pretest risk for maladjustment. Contrary to expectation, program participation increased negative errors and decreased adaptive coping among low-risk youth in some of the analyses. Ways in which this study furthers our understanding of pathways through which evidence-based preventive interventions affect health risk behaviors are discussed. Soper A, Wolchik S, Tein J, Sandler I. Mediation of a preventive intervention's 6-year effects on health risk behaviors. Psychol Addict Behav. 2010; 24(2): 300-310.

**Estimating Causal Effects in Mediation Analysis using Propensity Scores** Mediation is usually assessed by a regression-based or structural equation modeling (SEM) approach that we will refer to as the classical approach. This approach relies on the assumption that there are no confounders that influence both the mediator, M, and the outcome, Y. This assumption holds if individuals are randomly assigned to levels of M but generally random assignment is not possible. The authors propose the use of propensity scores to help remove the selection bias that may result when individuals are not randomly assigned to levels of M. The propensity score is the probability that an individual receives a particular level of M. Results from a simulation study are presented to demonstrate this approach, referred to as Classical + Propensity Model (C+PM), confirming that the population parameters are recovered and that selection bias is successfully dealt with. Comparisons are made to the classical approach that does not include propensity scores. Propensity scores were estimated by a logistic regression model. If all confounders are included in the propensity model, then the C+PM is unbiased. If some, but not all, of the confounders are included in the propensity model, then the C+PM estimates are biased although not as severely as the classical approach (i.e. no propensity model is included). Coffman D. Estimating causal effects in mediation analysis using propensity scores. Struct Equ Modeling. 2011; 18 (3): 357-369.

**A Capacity Building Program to Promote CBPR Partnerships between Academic Researchers and Community Members** Community-based participatory research (CBPR) adds community perspectives to research and aids translational research aims. There is a need for increased capacity in CBPR but few models exist for how to support the development of community/university partnerships. The objective of this study was to evaluate an approach to promote nascent CBPR partnerships. The study design was a mixed-methods evaluation using interviews, process notes, and open- and close-ended survey questions. The authors trained 10 community scholars, matched them with prepared researchers to form seven partnerships, and supported their developing partnerships. Sequential mixed-methods analysis assessed research and partnership processes and identified integrated themes. Four of seven partnerships were funded within 15 months; all self-reported their partnerships as successful. Themes were: (1)

motivators contributed to partnership development and resiliency; (2) partners took on responsibilities that used individuals ' strengths; (3) partners grappled with communication, decision making, and power dynamics; and (4) community-university infrastructure was essential to partnership development. This program for developing nascent partnerships between academicians and community members may guide others in increasing capacity for CBPR. Allen M, Culhane-Pera K, Pergament S, Call K. A capacity building program to promote CBPR partnerships between academic researchers and community members. Clin Transl Sci. 2011; 4 (6): 428-433.

**Developing a Collaboration with the Houston Independent School District: Testing the Generalizability of a Partnership Model** Moving evidence-based practices into real-world settings is a high priority for education and public health. This paper describes the development of a partnership among the Houston Independent School District, the American Institutes of Research, and the Houston Federation of Teachers to support research on and program sustainability for the Good Behavior Game, a team-based classroom behavior management strategy that has shown positive impact in randomized field trials. The conceptual framework guiding partnership development is presented, followed by an application of the framework in Houston. Lessons learned and implications for the next stage of research and practice are then discussed. Poduska J, Gomez M, Capo Z, Holmes V. Developing a collaboration with the houston independent school district: testing the generalizability of a partnership model. Adm Policy Ment Health. 2011; Epub ahead of print.

**Prevention of Alcohol Use in Middle School Students: Psychometric Assessment of the Decisional Balance Inventory** A measurement model should be equivalent across the different subgroups of a target population. The Decisional Balance Inventory for the Prevention of Alcohol Use is a 2-factor correlated model with 3 items for Pros of alcohol use and 3 items for Cons. The measure is part of a tailored intervention for middle school students. This study evaluated the important psychometric assumptions of factorial invariance and scale reliability with a large sample of sixth grade students (N=3565) from 20 schools. A measure is factorially invariant when the model is the same across subgroups. Three levels of invariance were assessed, from least restrictive to most restrictive: 1) Configural Invariance (unconstrained nonzero factor loadings); 2) Pattern Identity Invariance (equal factor loadings); and 3) Strong Factorial Invariance (equal factor loadings and measurement errors). Structural equation modeling was used to assess invariance over two levels of gender (male and female), race (white and black), ethnicity (Hispanic and non-Hispanic), and school size (large, indicating >200 students per grade, or small). The strongest level of invariance, Strong Factorial Invariance, was a good fit for the model across all of the subgroups: gender (CFI: 0.94), race (CFI: 0.96), ethnicity (CFI: 0.93), and school size (CFI: 0.97). Coefficient alpha was 0.61 for the Pros and 0.67 for Cons. Together, invariance and reliability provide strong empirical support for the validity of the measure. Babbin S, Harrington M, Burditt C, Redding C, Paiva A, Meier K, Oatley K, McGee H, Velicer W. Prevention of alcohol use in middle school students: psychometric assessment of the decisional balance inventory. Addict Behav. 2011; 36(5): 543-546.

**Psychometric Assessment of the Temptations to Try Alcohol Scale** Effective interventions require an understanding of the behaviors and cognitions that facilitate positive change as well as the development of psychometrically sound measures. This paper reports on the psychometric

properties of the Temptations to Try Alcohol Scale (TTAS), including factorial invariance across different subgroups. Data were collected from 3565 6th grade RI middle school students. Structural equation modeling was used to determine the appropriate factorial invariance model for the 9-item TTAS. The measure consists of three correlated subscales: Social Pressure, Social Anxiety, and Opportunity. Three levels of invariance, ranging from the least to the most restrictive, were examined: Configural Invariance, which constrains only the factor structure and zero loadings; Pattern Identity Invariance, which requires factor loadings to be equal across the groups; and Strong Factorial Invariance, which requires factor loadings and error variances to be constrained. Separate analyses evaluated the invariance across two levels of gender (males vs. females), race (white vs. black) ethnicity (Hispanic vs. Non-Hispanic) and school size (small, meaning <200 6th graders, or large). The highest level of invariance, Strong Factorial Invariance, provided a good fit to the model for gender (CFI: .95), race (CFI: .94), ethnicity (CFI: .94), and school size (CFI: .97). Coefficient Alpha was .90 for Social Pressure, .81 for Social Anxiety, and .82 for Opportunity. These results provide strong empirical support for the psychometric structure and construct validity of the TTAS in middle school students. Harrington M, Babbin S, Redding C, Burditt C, Paiva A, Meier K, Oatley K, McGee H, Velicer W. Psychometric assessment of the temptations to try alcohol scale. Addict Behav. 2011; 36(4): 431-433.

**Condom Use and Partnership Intimacy among Drug Injectors and their Sexual Partners in Estonia** Young age coupled with a high HIV prevalence among injection drug users (IDUs) and the prevalence of drug use in Eastern Europe can lead from an HIV epidemic concentrated among IDU to a self-sustained heterosexual HIV epidemic. The authors' objective was to explore the contexts of the prevention of sexual transmission of HIV among IDUs and their sexual partners and to provide insight into beliefs and behaviors related to condom use. The authors undertook in-depth qualitative interviews to explore narratives about experience of preventing sexual transmission of HIV among 27 individuals (15 current IDUs and 12 main sexual partners of IDUs) in Kohtla-Järve, Estonia. The safe-sex norm was not common and factors that tended to reduce condom use included valuing the relationship above health risks, established gender roles, perceptions that condoms distributed via harm reduction programmes were of low quality and the stigma attached to HIV status disclosure. HIV risk management strategies among participants included consistent condom use and serosorting but were countered by a fatalism that encompassed consciously subjecting oneself to the inevitability of HIV infection in an HIV-discordant sexual partnership. Qualitative methods can significantly contribute to the prevention of sexual transmission of HIV among and beyond IDUs by improving our understanding of risky behaviors and the reasons for such behaviors that can be incorporated into tailored public health interventions. Uusküla A, Abel-Ollo K, Markina A, McNutt L, Heimer R. Condom use and partnership intimacy among drug injectors and their sexual partners in Estonia. Sex Transm Infect. 2012; 88(1): 58-62.

**"We as Drug Addicts Need that Program": Insight from Rural African American Cocaine Users on Designing a Sexual Risk Reduction Intervention for their Community** This focused ethnographic study examines data collected in 2007 from four gender- and age-specific focus groups (FGs) (N = 31) to inform the development of a sexual risk reduction intervention for African American cocaine users in rural Arkansas. A semi-structured protocol was used to guide audio-recorded FGs. Data were entered into Ethnograph and analyzed using constant comparison and content analysis. Four codes with accompanying factors emerged from the data and revealed

recommendations for sexual risk reduction interventions with similar populations. Intervention design implications and challenges, study limitations, and future research are discussed. The study was supported by funds from the National Institute of Nursing Research (P20 NR009006-01) and the National Institute on Drug Abuse (1R01DA024575-01 and F31 DA026286-01). Montgomery B, Stewart K, Wright P, McSweeney J, Booth B. "We As Drug Addicts Need That Program": Insight from rural African American cocaine users on designing a sexual risk reduction intervention for their community. Subst Use Misuse. 2012; 47(1): 44-55.

**Correlates of Staying Safe Behaviors among Long-Term Injection Drug Users: Psychometric Evaluation of the Staying Safe Questionnaire** The authors report on psychometric properties of a new questionnaire to study long-term strategies, practices and tactics that may help injection drug users (IDUs) avoid infection with HIV and hepatitis C. Sixty-two long-term IDUs were interviewed in New York City in 2009. Five scales based on a total of 47 items were formed covering the following domains: stigma avoidance, withdrawal prevention, homeless safety, embedding safety within a network of users, and access to resources/social support. All scales (± e .79) except one (± = .61) were highly internally consistent. Seven single-item measures related to drug use reduction and injection practices were also analyzed. All variables were classified as either belonging to a group of symbiotic processes that are not directly focused upon disease prevention but nonetheless lead to risk reduction indirectly or as variables describing prevention tactics in risky situations. Symbiotic processes can be conceived of as unintentional facilitators of safe behaviors. Associations among variables offer suggestions for potential interventions. These Staying Safe variables can be used as predictors of risk behaviors and/or biological outcomes. Vazan P, Mateu-Gelabert P, Cleland C, Sandoval M, Friedman S. Correlates of staying safe behaviors among long-term injection drug users: Psychometric evaluation of the Staying Safe Questionnaire. AIDS Behav. 2011; Epub Oct 2011.

## CLINICAL NEUROSCIENCE RESEARCH

**The Association Between Frontal–Striatal Connectivity and Sensorimotor Control in Cocaine Users** In addition to cognitive and emotional processing dysfunction, chronic cocaine users are also impaired at simple sensorimotor tasks. Many diseases characterized by compulsive movements, repetitive actions, impaired attention and planning are associated with dysfunction in frontal–striatal circuits. The aim of this study was to determine whether cocaine users had impaired frontal–striatal connectivity during a simple movement task and whether this was associated with sensorimotor impairment. Functional MRI data were collected from 14 non-treatment seeking cocaine users and 15 healthy controls as they performed a finger-tapping task. Functional coupling was quantified by correlating the time-courses of each pair of anatomically connected regions of interest. Behavioral performance was correlated with all functional coupling coefficients. In controls there was a significant relationship between the primary motor cortex and the supplementary motor area (SMA), as well as the SMA and the dorsal striatum during ongoing movement. Cocaine users exhibited weaker fronto-striatal coupling than controls, while the cortical–cortical coupling was intact. Coupling strength between the SMA and the caudate was negatively correlated with reaction time in the users. The observation that cocaine users have impaired cortical–striatal connectivity during simple motor performance, suggests that these individuals may have a fundamental deficit in information processing that influences more complex cognitive processes. Hanlon CA, Wesley MJ, Stapleton JR, Laurienti PJ, Porrino LJ. The association between frontal–striatal connectivity and sensorimotor control in cocaine users. Drug and Alcohol Dependence. 2011 June 1; 115(3): 240–243.

**A VBM Study Demonstrating 'Apparent' Effects of a Single Dose of Medication on T1-Weighted MRIs** Voxel-based morphometry (VBM) studies have interpreted longitudinal medication- or behaviorally induced changes observed on T1-weighted magnetic resonance images (MRIs) as changes in neuronal structure. Although neurogenesis or atrophy certainly occurs, the use of T1-weighted scans to identify change in brain structure in vivo in humans has vulnerability. The T1 relaxation time for arterial blood and gray matter are not clearly distinguishable and therefore, apparent reported structural findings might be at least partially related to changes in blood flow or other physiological signals. To examine the hypothesis that apparent structural modifications may reflect changes introduced by additional mechanisms irrespective of potential neuronal growth/atrophy, the authors acquired a high-resolution T1-weighted structural scan and a 5-min perfusion fMRI scan (a measurement of blood flow), before and after administration of an acute pharmacological manipulation. In a within-subject design, 15 subjects were either un-medicated or were administered a 20 mg dose of baclofen (an FDA-approved anti-spastic) approximately 110 min before acquiring a T1-weighted scan and a pseudo continuous arterial spin labeled perfusion fMRI scan. Using diffeomorphic anatomical registration through exponentiated lie algebra within SPM7, we observed macroscopic, and therefore implausible, baclofen-induced decreases in VBM "gray matter" signal in the dorsal rostral anterior cingulate (family wise error corrected at $p < 0.04$, $T = 6.54$, extent: 1,460 voxels) that overlapped with changes in blood flow. Given that gray matter reductions are unlikely following a single dose of medication and these findings suggest that changes in blood flow are masquerading as reductions in gray matter on the T1-weighted scan irrespective of the temporal interval between baseline measures and longitudinal manipulations. These results underscore the crucial and immediate need to develop in vivo neuroimaging biomarkers for humans that can

uniquely capture changes in neuronal structure dissociable from those related to blood flow or other physiological signals. Franklin TR, Wang A, Shin J, Jagannathan K, Suh JJ, Detre JA, O'Brien CP, Childress AR. A VBM study demonstrating 'apparent' effects of a single dose of medication on T1-weighted MRIs. Brain Struct Funct. 2012;[Epub ahead of print: DOI 10.1007/s00429-012-0385-6].

**Childhood Maltreatment is Associated with Reduced Volume in the Hippocampal Subfields CA3, Dentate Gyrus, and Subiculum** Childhood maltreatment or abuse is a major risk factor for mood, anxiety, substance abuse, psychotic, and personality disorders, and it is associated with reduced adult hippocampal volume, particularly on the left side. Translational studies show that the key consequences of stress exposure on the hippocampus are suppression of neurogenesis in the dentate gyrus (DG) and dendritic remodeling in the cornu ammonis (CA), particularly the CA3 subfield. The hypothesis that maltreatment is associated with volume reductions in 3-T MRI subfields containing the DG and CA3 was assessed and made practical by newly released automatic segmentation routines for FreeSurfer. The sample consisted of 193 unmedicated right-handed subjects (38% male, 21.9 ± 2.1 y of age) selected from the community. Maltreatment was quantified using the Adverse Childhood Experience study and Childhood Trauma Questionnaire scores. The strongest associations between maltreatment and volume were observed in the left CA2-CA3 and CA4-DG subfields, and were not mediated by histories of major depression or posttraumatic stress disorder. Comparing subjects with high vs. low scores on the Childhood Trauma Questionnaire and Adverse Childhood Experience study showed an average volume reduction of 6.3% and 6.1% in the left CA2-CA3 and CA4-DG, respectively. Volume reductions in the CA1 and fimbria were 44% and 60% smaller than in the CA2-CA3. Interestingly, maltreatment was associated with 4.2% and 4.3% reductions in the left presubiculum and subiculum, respectively. These findings support the hypothesis that exposure to early stress in humans, as in other animals, affects hippocampal subfield development. Teicher MH, Anderson CM, Polcaria A. Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. PNAS. February 28, 2012; 109(9): E563-E572.

**Cumulative Adversity and Smaller Gray Matter Volume in Medial Prefrontal, Anterior Cingulate, and Insula Regions** Cumulative adversity and stress are associated with risk of psychiatric disorders. While basic science studies show repeated and chronic stress effects on prefrontal and limbic neurons, human studies examining cumulative stress and effects on brain morphology are rare. Thus, the authors assessed whether cumulative adversity is associated with differences in gray matter volume, particularly in regions regulating emotion, self-control, and top-down processing in a community sample. One hundred three healthy community participants, aged 18 to 48 and 68% male, completed interview assessment of cumulative adversity and a structural magnetic resonance imaging protocol. Whole-brain voxel-based-morphometry analysis was performed adjusting for age, gender, and total intracranial volume. Cumulative adversity was associated with smaller volume in medial prefrontal cortex (PFC), insular cortex, and subgenual anterior cingulate regions (family-wise error corrected, $p < .001$). Recent stressful life events were associated with smaller volume in two clusters: the medial PFC and the right insula. Life trauma was associated with smaller volume in the medial PFC, anterior cingulate, and subgenual regions. The interaction of greater subjective chronic stress and greater cumulative life events was associated with smaller volume in the orbitofrontal cortex, insula, and

anterior and subgenual cingulate regions. Current results demonstrate that increasing cumulative exposure to adverse life events is associated with smaller gray matter volume in key prefrontal and limbic regions involved in stress, emotion and reward regulation, and impulse control. These differences found in community participants may serve to mediate vulnerability to depression, addiction, and other stress-related psychopathology. Ansell EB, Rand K, Tuita K, Guarnacciab J, Sinha R. Cumulative adversity and smaller gray matter volume in medial prefrontal, anterior cingulate, and insula regions. Biol Psychiat. [Epub ahead of print: doi:10.1016/j.biopsych.2011.11.022].

**Evidence for Chronically Altered Serotonin Function in the Cerebral Cortex of Female 3,4-Methylenedioxymethamphetamine Polydrug Users** MDMA (3,4-methylenedioxy-methamphetamine, also popularly known as "ecstasy") is a popular recreational drug that produces loss of serotonin axons in animal models. Whether MDMA produces chronic reductions in serotonin signaling in humans remains controversial. The objective of this study was to determine whether MDMA use is associated with chronic reductions in serotonin signaling in the cerebral cortex of women as reflected by increased serotonin$_{2A}$ receptor levels. This was a cross-sectional case-control study comparing serotonin$_{2A}$ receptor levels in abstinent female MDMA polydrug users with those in women who did not use MDMA (within-group design assessing the association of lifetime MDMA use and serotonin$_{2A}$ receptors). Case participants were abstinent from MDMA use for at least 90 days as verified by analysis of hair samples. The serotonin$_{2A}$ receptor levels in the cerebral cortex were determined using serotonin$_{2A}$-specific positron emission tomography with radioligand fluorine 18–labeled setoperone as the tracer. A total of 14 female MDMA users and 10 women who did not use MDMA (controls). The main exclusion criteria were nondrug-related *DSM-IV* Axis I psychiatric disorders and general medical illness. MDMA users had increased serotonin$_{2A}$BP$_{ND}$ in occipital-parietal (19.7%), temporal (20.5%), occipitotemporal-parietal (18.3%), frontal (16.6%), and frontoparietal (18.5%) regions (corrected $P < .05$). Lifetime MDMA use was positively associated with serotonin$_{2A}$BP$_{ND}$ in frontoparietal ($\beta = 0.665$; $P = .007$), occipitotemporal ($\beta = 0.798$; $P = .002$), frontolimbic ($\beta = 0.634$; $P = .02$), and frontal ($\beta = 0.691$; $P = .008$) regions. In contrast, there were no regions in which MDMA use was inversely associated with receptor levels. There were no statistically significant effects of the duration of MDMA abstinence on serotonin$_{2A}$BP$_{ND.}$ The recreational use of MDMA is associated with long-lasting increases in serotonin$_{2A}$ receptor density. Serotonin$_{2A}$ receptor levels correlate positively with lifetime MDMA use and do not decrease with abstinence. These results suggest that MDMA use produces chronic serotonin neurotoxicity in humans. Given the broad role of serotonin in human brain function, the possibility for therapeutic MDMA use, and the widespread recreational popularity of this drug, these results have critical public health implications. Di Iorio CR, Watkins TJ, Dietrich MS, Cao A, Blackford JU, Rogers B, Ansari MS, Baldwin RM, Li R, Kessler RM, Salomon RM, Benningfield M, Cowan RL. Evidence for chronically altered serotonin function in the cerebral cortex of female 3,4-methylenedioxymethamphetamine polydrug users. Arch Gen Psychiatry. 2011 Dec. [Epub ahead of print: doi:10.1001/archgenpsychiatry.2011.156].

**Cortisol Levels Relate to the Altered Brain Activation of Chronic Active Cannabis Users During Visuomotor Integration** Cannabis is the most abused illegal substance in the United States. Alterations in brain function and motor behavior have been reported in chronic cannabis users, but the results have been variable. The current study aimed to determine whether chronic active cannabis use in humans may alter psychomotor function, brain activation, and hypothalamic-pituitary-axis (HPA) function in men and women. Thirty cannabis users (16 men, 14 women, 18-45 years old) and 30 nondrug user controls (16 men, 14 women, 19-44 years old) were evaluated with neuropsychological tests designed to assess motor behavior and with fMRI using a 3 Tesla scanner during a visually paced finger-sequencing task, cued by a flashing checkerboard (at 2 or 4 Hz). Salivary cortisol was measured to assess HPA function. Male, but not female, cannabis users had significantly slower performance on psychomotor speed tests. As a group, cannabis users had greater activation in BA 6 than controls, while controls had greater activation in the visual area BA 17 than cannabis users. Cannabis users also had higher salivary cortisol levels than controls ($p = 0.002$). Chronic active cannabis use is associated with slower and less efficient psychomotor function, especially in male users, as indicated by a shift from regions involved with automated visually guided responses to more executive or attentional control areas. The greater but altered brain activities may be mediated by the higher cortisol levels in the cannabis users, which in turn may lead to less efficient visual-motor function. King GR, Ernst T, Deng W, Stenger A, Gonzales RM, Nakama H, Chang L. Altered brain activation during visuomotor integration in chronic active cannabis users: relationship to cortisol levels. J Neurosci. 2011 Dec 7; 31(49): 17923-17931.

**Brain Activation during Delay-Discounting Decision-Making Relates to Both Preference for Delayed Reward and Consistency of Preferences** There is equivocal support for the hypothesis that preference for later larger (LL) over sooner smaller (SS) monetary alternatives (e.g., $50 in four months over $30 today) is associated with functioning of the insula and the prefrontal cortex (especially the lateral PFC). In the present study, the authors re-examined overall neural correlates of choice using a procedure to minimize potential confounds between choice (which is necessarily not under experimental control) and valuation. In addition, they assessed whether choice-related brain activity is moderated by 1) overall level of delay discounting and 2) the degree of stochasticity in individuals' intertemporal choices. Twenty-one participants completed an individualized intertemporal choice task while brain activity was measured using functional Magnetic Resonance Imaging (fMRI). Across participants, LL choice was associated with activity in left dorsolateral prefrontal cortex (dlPFC), left insula/inferior frontal gyrus (IFG), frontal pole and the anterior cingulate cortex (ACC). Stochasticity positively moderated the LL>SS activity within the left insula and left IFG. Degree of discounting also interacted with choice related activity, but only outside the LL vs. SS main effect map (in the posterior cingulate cortex, and precentral/postcentral gyrus and left dlPFC). Main effect results are consistent with the notion that lateral prefrontal activity during intertemporal decisions bias selection in the direction of LL. Correlation findings indicate that choice related activity in the left insula and IFG is moderated by the stochasticity of intertemporal choices, and may reflect reduced "executive function" demands among highly consistent participants. Luo S, Ainslie G, Pollini D, Giragosian L, Monterosso JR. Moderators of the association between brain activation and farsighted choice. Neuroimage. 2012 Jan 16; 59(2): 1469-1477.

**Use of Near-Infrared Spectroscopy to Assess and Control for Brain Blood Flow Improves fMRI Signal Detection** Confounding noise in BOLD fMRI data arises primarily from fluctuations in blood flow and oxygenation due to cardiac and respiratory effects, spontaneous low frequency oscillations (LFO) in arterial pressure, and non-task related neural activity. Cardiac noise is particularly problematic, as the low sampling frequency of BOLD fMRI ensures that these effects are aliased in recorded data. Various methods have been proposed to estimate the noise signal through measurement and transformation of the cardiac and respiratory waveforms (e.g. RETROICOR and respiration volume per time (RVT) and model-free estimation of noise variance through examination of spatial and temporal patterns. The authors have previously demonstrated that by applying a voxel-specific time delay to concurrently acquired near infrared spectroscopy (NIRS) data, they can generate regressors that reflect systemic blood flow and oxygenation fluctuations effects. Here, they apply this method to the task of removing physiological noise from BOLD data. They compare the efficacy of noise removal using various sets of noise regressors generated from NIRS data, and also compare the noise removal to RETROICOR+RVT. They compare the results of resting state analyses using the original and noise filtered data, and we evaluate the bias for the different noise filtration methods by computing null distributions from the resting data and comparing them with the expected theoretical distributions. Using the best set of processing choices, six NIRS-generated regressors with voxel-specific time delays explain a median of 10.5% of the variance throughout the brain, with the highest reductions being seen in gray matter. By comparison, the nine RETROICOR+RVT regressors together explain a median of 6.8% of the variance in the BOLD data. Detection of resting state networks was enhanced with NIRS denoising, and there were no appreciable differences in the bias of the different techniques. Physiological noise regressors generated using Regressor Interpolation at Progressive Time Delays (RIPTiDe) offer an effective method for efficiently removing hemodynamic noise from BOLD data. Frederick BD, Nickerson LD, Tong Y. Physiological denoising of BOLD fMRI data using Regressor Interpolation at Progressive Time Delays (RIPTiDe) processing of concurrent fMRI and near-infrared spectroscopy (NIRS). Neuroimage. 2012 Apr 15; 60(3): 1913-1923.

**Early Abstinent Methamphetamine-Dependent Subjects Show Prefrontal Hypoactivation During Cognitive Control** Individuals who abuse methamphetamine (MA) perform at levels below those of healthy controls on tests that require cognitive control. As cognitive control deficits may influence the success of treatment for addiction, the authors sought to help clarify the neural correlates of this deficit. MA-dependent (n=10, abstinent 4-7 days) and control subjects (n=18) performed a color-word Stroop task, which requires cognitive control, during functional MRI (fMRI). The task included a condition in which participants were required to respond to one stimulus dimension while ignoring another conflicting dimension, and another condition without conflict. The authors compared the groups on performance and neural activation in the two conditions. MA-dependent subjects made more errors and responded more slowly than controls. Controlling for response times in the incongruent condition, voxel-wise mixed effects analyses (whole-brain corrected) demonstrated that MA-dependent subjects had less activation than control subjects in the right inferior frontal gyrus, supplementary motor cortex/anterior cingulate gyrus and the anterior insular cortex during the incongruent condition only. MA-dependent subjects did not exhibit greater activation in any brain region in either of the Stroop conditions. These preliminary findings suggest that hypofunction in cortical areas that are important for executive function underlies cognitive control deficits associated with MA

dependence. Nestor LJ, Ghahremani DG, Monterosso J, London ED. Prefrontal hypoactivation during cognitive control in early abstinent methamphetamine-dependent subjects. Psychiatry Res. 2011 Dec 30; 194(3): 287-295.

**Advance Instruction of a Need to Withhold a Response Allows More Selective Suppression of Motor Circuitry by Stopping** Much research has focused on how people stop initiated response tendencies when instructed by a signal. Stopping of this kind appears to have global effects on the motor system. For example, by delivering transcranial magnetic stimulation (TMS) over the leg area of the primary motor cortex, it is possible to detect suppression in the leg when the hand is being stopped (Badry R et al. Suppression of human cortico-motoneuronal excitability during the stop-signal task. Clin Neurophysiol 120: 1717-1723, 2009). Here, the authors asked if such "global suppression" can be observed proactively, i.e., when people anticipate they might have to stop. They used a conditional stop signal task, which allows the measurement of both an "anticipation phase" (i.e., where proactive control is applied) and a "stopping" phase. TMS was delivered during the anticipation phase (experiment 1) and also during the stopping phase (experiments 1 and 2) to measure leg excitability. During the anticipation phase, they did not observe leg suppression, but they did during the stopping phase, consistent with Badry et al. (2009). Moreover, when they split the subject groups into those who slowed down behaviorally (i.e., exercised proactive control) and those who did not, they found that subjects who slowed did not show leg suppression when they stopped, whereas those who did not slow did show leg suppression when they stopped. These results suggest that if subjects prepare to stop, then they do so without global effects on the motor system. Thus, preparation allows them to stop more selectively. Greenhouse I, Oldenkamp CL, Aron AR. Stopping a response has global or nonglobal effects on the motor system depending on preparation. J Neurophysiol. 2012 Jan; 107(1): 384-392.

**Sex Similarities and Differences in Pain-related Periaqueductal Gray Connectivity** This study investigated sex similarities and differences in pain-related functional connectivity in 60 healthy subjects. The authors used functional magnetic resonance imaging and psychophysiological interaction analysis to investigate how exposure to low vs. high experimental pain modulates the functional connectivity of the periaqueductal gray (PAG). They found no sex differences in pain thresholds, and in both men and women, the PAG was more functionally connected with the somatosensory cortex, the supplemental motor area, cerebellum, and thalamus during high pain, consistent with anatomic predictions. Twenty-six men displayed a pain-induced increase in PAG functional connectivity with the amygdala caudate and putamen that was not observed in women. In an extensive literature search, the authors found that female animals have been largely overlooked when the connections between the PAG and the amygdala have been described, and that women are systematically understudied with regard to endogenous pain inhibition. These results emphasize the importance of including both male and female subjects when studying basic mechanisms of pain processing, and point toward a possible sex difference in endogenous pain inhibition. Linnman C, Beucke JC, Jensen KB, Gollub RL, Kong J. Sex similarities and differences in pain-related periaqueductal gray connectivity. Pain. 2012 Feb; 153(2): 444-454.

**Plasma Proteomic Profiling in HIV-1 Infected Methamphetamine Abusers** The authors wanted to determine whether methamphetamine use affects a subset of plasma proteins in HIV-infected persons. Plasma samples from two visits were identified for subjects from four groups: HIV+, ongoing, persistent METH use; HIV+, short-term METH abstinent; HIV+, long term METH abstinence; HIV negative, no history of METH use. Among 390 proteins identified, 28 showed significant changes in expression in the HIV+/persistent METH+ group over the two visits, which were not attributable to HIV itself. These proteins were involved in complement, coagulation pathways and oxidative stress. Continuous METH use is an unstable condition, altering levels of a number of plasma proteins. Pottiez G, Jagadish T, Yu F, Letendre S, Ellis R, Duarte NA, Grant I, Gendelman HE, Fox HS, Ciborowski P. Plasma proteomic profiling in HIV-1 infected methamphetamine abusers. PLoS One. 2012; 7(2): e31031.

**A Meta-analysis of Heart Rate Variability and Neuroimaging Studies: Implications for Heart Rate Variability as a Marker of Stress and Health** The intimate connection between the brain and the heart was enunciated by Claude Bernard over 150 years ago. In the authors' neurovisceral integration model they have tried to build on this pioneering work. In the present paper they further elaborate their model and update it with recent results. Specifically, they performed a meta-analysis of recent neuroimaging studies on the relationship between heart rate variability and regional cerebral blood flow. They identified a number of regions, including the amygdala and ventromedial prefrontal cortex, in which significant associations across studies were found. They further propose that the default response to uncertainty is the threat response and may be related to the well known negativity bias. Heart rate variability may provide an index of how strongly 'top-down' appraisals, mediated by cortical-subcortical pathways, shape brainstem activity and autonomic responses in the body. If the default response to uncertainty is the threat response, as the authors propose here, contextual information represented in 'appraisal' systems may be necessary to overcome this bias during daily life. Thus, HRV may serve as a proxy for 'vertical integration' of the brain mechanisms that guide flexible control over behavior with peripheral physiology, and as such provides an important window into understanding stress and health. Thayer JF, Ahs F, Fredrikson M, Sollers JJ 3rd, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci Biobehav Rev. 2012 Feb; 36(2): 747-756.

**Effects of Chronic Marijuana Use on Brain Activity During Monetary Decision-Making** Marijuana (MJ) acutely acts on cannabinoid receptors that are found in numerous brain regions, including those involved in reward processing and decision-making. However, it remains unclear how long-term, chronic MJ use alters reward-based decision-making. In the present study, using [(15)O]water PET imaging, the authors measured brain activity in chronic MJ users, who underwent monitored abstinence from MJ for approximately 24h before imaging, and control participants, while they took part in the Iowa Gambling Task (IGT), a monetary decision making task that strongly relies on the ventromedial prefrontal cortex (vmPFC). During PET imaging, participants took part in the standard and a variant version of the IGT as well as a control task. Chronic MJ users performed equally well on the standard IGT, but significantly worse than controls on the variant IGT. Chronic MJ users and control subjects showed increased regional cerebral blood flow (rCBF) in the vmPFC on both versions of the IGT compared to the control task. In the two-group comparison, chronic MJ users showed significantly greater rCBF than controls in the vmPFC on the standard IGT and greater activity in the cerebellum on both

versions of the IGT. Furthermore, duration of use, but not age of first use, was associated with greater activity in the vmPFC. Thus, chronic MJ users tend to strongly recruit neural circuitry involved in decision-making and reward processing (vmPFC), and probabilistic learning (cerebellum) when performing the IGT. Vaidya JG, Block RI, O'Leary DS, Ponto LB, Ghoneim MM, Bechara A. Effects of chronic marijuana use on brain activity during monetary decision-making. Neuropsychopharmacology. 2012 Feb; 37(3): 618-629.

**Lower Glial Metabolite Levels in Brains of Young Children with Prenatal Nicotine Exposure** Many pregnant women smoke cigarettes during pregnancy, but the effect of nicotine on the developing human brain is not well understood, especially in young children. This study aims to determine the effects of prenatal nicotine exposure (PNE) on brain metabolite levels in young (3-4 years old) children, using proton magnetic resonance spectroscopy ((1)H MRS). Twenty-six children with PNE and 24 nicotine-unexposed children (controls) were evaluated with a structured examination, a battery of neuropsychological tests, and MRI/(1)H MRS (without sedation). Concentrations of N-acetyl compounds (NA), total creatine (tCR), choline-containing compounds (CHO), myo-inositol (MI), and glutamate+glutamine (GLX) were measured in four brain regions. Children with PNE had similar performance to controls on neuropsychological testing. However, compared to controls, the PNE group had lower MI (repeated measures ANOVA-p = 0.03) and tCr levels (repeated measures ANOVA-p=0.003), especially in the basal ganglia of the girls (-19.3%, p=0.01). In contrast, GLX was elevated in the anterior cingulate cortex of the PNE children (+9.4%, p=0.03), and those with the highest GLX levels had the poorest performance on vocabulary (r=-0.67; P<0.001) and visual motor integration (r=-0.53; P=0.01). The amount of prenatal nicotine exposure did not correlate with metabolite concentrations. These findings suggest that PNE may lead to subclinical abnormalities in glial development, especially in the basal ganglia, and regionally specific changes in other neurometabolites. These alterations were not influenced by the amount of nicotine exposure prenatally. However, the effects of PNE on energy metabolism may be sex specific, with greater alterations in girls. Chang L, Cloak CC, Jiang CS, Hoo A, Hernandez AB, Ernst TM. Lower glial metabolite levels in brains of young children with prenatal nicotine exposure. J Neuroimmune Pharmacol. 2012 Mar; 7(1): 243-252.

**Glial Modulators: A Novel Pharmacological Approach to Altering the Behavioral Effects of Abused Substances** Commonly abused drugs including opioids, stimulants and alcohol activate glia cells, an effect that has been identified across species. Glia, specifically astrocytes and microglia, have been shown to contribute directly to behaviors predictive of the abuse liability of these drugs. Although still in its infancy, research investigating the effects of pharmacological modulation of glial activity on these behaviors has provided encouraging findings suggesting glial cell modulators as potential pharmacotherapies for substance-use disorders. This review first explores the evidence establishing glial-mediated modulations of behaviors associated with opioid, stimulant and alcohol exposure, with emphasis placed on the neuroanatomical substrates for these effects. Next, neurobiological and behavioral studies evaluating the ability of glial cell modulators to prevent and reverse the effects of these abused substances will be considered. Finally, the potential clinical efficacy of glial cell modulators as a novel pharmacological approach to treat substance-use disorders in relation to currently available, conventional pharmacotherapies will be discussed. Though the relationship between drug-induced glial activity and behaviors indicative of drug abuse and dependence is not yet fully elucidated, the

evidence for the association continues to grow. The use of glial modulators as pharmacological tools to investigate this relationship has also yielded findings supporting their potential clinical efficacy for treating substance-use disorders. Cooper ZD, Jones JD, Comer SD. Glial modulators: a novel pharmacological approach to altering the behavioral effects of abused substances. Expert Opin Investig Drugs. 2012 Feb; 21(2): 169-178.

**Negative Reinforcement Smoking Outcome Expectancies are Associated with Affective Response to Acute Nicotine Administration and Abstinence** Negative affect is an important predictor of smoking behavior, and many smokers believe that smoking reduces negative affect. However, it is unclear whether such beliefs, known as negative reinforcement smoking outcome expectancies (NRSOE), are associated with changes in negative affect in response to nicotine deprivation and administration. Smokers (N=114) participated in 4 sessions that balanced overnight smoking deprivation (12-h deprived vs. ad lib) and nasal spray administration (nicotine vs. placebo). Corrugator supercilii (COR) EMG, skin conductance (SCR), and in-session ratings were collected while the participants viewed affective, cigarette-related, and neutral slides. Retrospective questionnaire data were collected prior to slide viewing. NRSOE were determined using the Smoking Consequences Questionnaire - Adult Nicotine Affect Reduction scale (SCQ-NAR). High scores on the SCQ-NAR were associated with smaller COR EMG to unpleasant slides following nicotine nasal spray administration compared to placebo spray, regardless of overnight deprivation. Smokers who had high scores on the SCQ-NAR had smaller SCR, following nicotine nasal spray administration compared to placebo spray, but only after overnight deprivation. The in-session ratings and retrospective questionnaire measures indicated those smokers who had high scores on the SCQ-NAR experienced greater negative affect and craving, and less positive affect, than smokers with low scores on the SCQ-NAR, regardless of nicotine exposure. The authors' questionnaire results suggest that while smokers who have high NRSOE self-report greater overall levels of negative affect and craving, while the psychophysiological data suggest that such smokers may experience negative affect reduction when blindly administered a dose of nicotine. Robinson JD, Lam CY, Carter BL, Wetter DW, Cinciripini PM. Negative reinforcement smoking outcome expectancies are associated with affective response to acute nicotine administration and abstinence. Drug Alcohol Depend. 2012 Jan 1; 120(1-3): 196-201.

**Effect of d-Amphetamine on Post-error Slowing in Healthy Volunteers** Post-error slowing has long been considered a sign of healthy error detection and an important component of cognitive function. However, the neuropharmacological processes underlying post-error slowing are poorly understood. This study investigated the effect of the dopamine agonist d-amphetamine on post-error slowing and secondarily, the potential mediator of drug-induced euphoria and potential moderators of personality and baseline task performance. Healthy male and female participants (N=110) completed four study sessions, at which d-amphetamine (placebo 5, 10, 20 mg) was administered under double-blind, counter-balanced conditions. At each session, participants completed subjective drug effect assessments and a working memory task (N-back) to measure post-error slowing. They completed the Multidimensional Personality Questionnaire (MPQ) during screening. Amphetamine (20 mg) reduced post-error slowing, consistent with a dampened behavioral reactivity to errors. This was not related to drug-induced euphoria. Although higher scores on MPQ constraint were related to less post-error slowing under placebo conditions, neither personality nor baseline cognitive performance moderated the effects of

amphetamine on post-error slowing. The finding that amphetamine reduced post-error slowing supports the idea that dopamine plays a role in error stimulus processing. The finding is discussed in relation to an existing literature on the mechanisms and function of behavioral and electrophysiological indices of error sensitivity. Wardle MC, Yang A, de Wit H. Effect of d-amphetamine on post-error slowing in healthy volunteers. Psychopharmacology (Berl). 2012 Mar; 220(1): 109-115.

**Psychoactive Drugs and False Memory: Comparison of Dextroamphetamine and Delta-9-Tetrahydrocannabinol on False Recognition** Several psychoactive drugs are known to influence episodic memory. However, these drugs' effects on false memory, or the tendency to incorrectly remember non-studied information, remain poorly understood. Here, the authors examined the effects of two commonly used psychoactive drugs, one with memory-enhancing properties (dextroamphetamine;AMP), and another with memory-impairing properties (Δ(9)-tetrahydrocannabinol;THC), on false memory using the Deese/Roediger-McDermott (DRM) illusion. Two parallel studies were conducted in which healthy volunteers received either AMP (0, 10, and 20 mg) or THC (0, 7.5, and 15 mg) in within-subjects, randomized, double-blind designs. Participants studied DRM word lists under the influence of the drugs, and their recognition memory for the studied words was tested 2 days later, under sober conditions. As expected, AMP increased memory of studied words relative to placebo, and THC reduced memory of studied words. Although neither drug significantly affected false memory relative to placebo, AMP increased false memory relative to THC. Across participants, both drugs' effects on true memory were positively correlated with their effects on false memory. These results indicate that AMP and THC have opposing effects on true memory, and these effects appear to correspond to similar, albeit more subtle, effects on false memory. These findings are consistent with previous research using the DRM illusion and provide further evidence that psychoactive drugs can affect the encoding processes that ultimately result in the creation of false memories. Ballard ME, Gallo DA, de Wit H. Psychoactive drugs and false memory: comparison of dextroamphetamine and delta-9-tetrahydrocannabinol on false recognition. Psychopharmacology (Berl). 2012 Jan; 219(1): 15-24.

**Higher Binding of the Dopamine D3 Receptor-Preferring Ligand [11C]-(+)-Propyl-Hexahydro-Naphtho-Oxazin in Methamphetamine Polydrug Users: A Positron Emission Tomography Study** Positron emission tomography (PET) findings suggesting lower D2-type dopamine receptors and dopamine concentration in brains of stimulant users have prompted speculation that increasing dopamine signaling might help in drug treatment. However, this strategy needs to consider the possibility, based on animal and postmortem human data, that dopaminergic activity at the related D3 receptor might, in contrast, be elevated and thereby contribute to drug-taking behavior. The authors tested the hypothesis that D3 receptor binding is above normal in methamphetamine (MA) polydrug users, using PET and the D3-preferring ligand [11C]-(+)-propyl-hexahydro-naphtho-oxazin ([11C]-(+)-PHNO). Sixteen control subjects and 16 polydrug users reporting MA as their primary drug of abuse underwent PET scanning after [11C]-(+)-PHNO. Compared with control subjects, drug users had higher [11C]-(+)-PHNO binding in the D3-rich midbrain substantia nigra (SN;+46%; $P<0.02$) and in the globus pallidus (+9%; $P=0.06$) and ventral pallidum (+11%; $P=0.1$), whereas binding was slightly lower in the D2-rich dorsal striatum (approximately -4%, NS;-12% in heavy users, $p=0.01$) and related to drug-use severity. The [11C]-(+)-PHNO binding ratio in D3-rich SN versus D2-rich dorsal

striatum was 55% higher in MA users (p=0.004), with heavy but not moderate users having ratios significantly different from controls. [11C]-(+)-PHNO binding in SN was related to self-reported "drug wanting." The authors conclude that the dopamine D3 receptor, unlike the D2 receptor, might be upregulated in brains of MA polydrug users, although lower dopamine levels in MA users could have contributed to the finding. Pharmacological studies are needed to establish whether normalization of D3 receptor function could reduce vulnerability to relapse in stimulant abuse. Boileau I, Payer D, Houle S, Behzadi A, Rusjan PM, Tong J, Wilkins D, Selby P, George TP, Zacorsk M, Furukawa Y, McCluskey T, Wilson AA, Kish SJ. Higher binding of the dopamine D3 receptor-preferring ligand [11C]-(+)-propyl-hexahydro-naphtho-oxazin in methamphetamine polydrug users: a positron emission tomography study. J. Neurosci. 2012 Jan; 32(4): 1353–1359.

**Deficits in Dopamine D(2) Receptors and Presynaptic Dopamine in Heroin Dependence: Commonalities and Differences with other Types of Addiction** Positron emission tomography (PET) imaging studies have shown that addiction to a number of substances of abuse is associated with a decrease in dopamine D(2/3) receptor binding and decreased presynaptic dopamine release in the striatum. Some studies have also shown that these reductions are associated with the severity of addiction. For example, in cocaine dependence, low dopamine release is associated with the choice to self-administer cocaine. The goal of the present study was to investigate these parameters of striatal dopamine transmission in heroin dependence and their association with drug seeking behavior. Heroin-dependent and healthy control subjects were scanned with [(11)C]raclopride before and after stimulant administration (methylphenidate) to measure striatal D(2/3) receptor binding and presynaptic dopamine release. After the PET scans, the heroin-dependent subjects performed heroin self-administration sessions. Both striatal D(2/3) receptor binding and dopamine release were reduced in the heroin-dependent subjects compared with healthy control subjects. However, neither PET measure of dopamine transmission predicted the choice to self-administer heroin. These findings show that heroin addiction, like addiction to other drugs of abuse, is associated with low D(2/3) receptor binding and low presynaptic dopamine. However, neither of these outcome measures was associated with the choice to self-administer heroin. Martinez D, Saccone PA, Liu F, Slifstein M, Orlowska D, Grassetti A, Cook S, Broft A, Van Heertum R, Comer SD. Deficits in dopamine D(2) receptors and presynaptic dopamine in heroin dependence: commonalities and differences with other types of addiction. Biol. Psychiatry. 2012 Feb; 71(3): 192–198.

***In Vivo* Evidence for Low Striatal Vesicular Monoamine Transporter 2 (VMAT2) Availability in Cocaine Abusers** Positron emission tomography (PET) imaging studies in cocaine abusers have shown that low dopamine release in the striatum following an amphetamine challenge is associated with higher relapse rates. One possible mechanism that might lead to lower amphetamine-induced dopamine release is low availability of dopamine storage vesicles in the presynaptic terminals for release. Consistent with this hypothesis, postmortem studies have shown low levels of vesicular monoamine transporter, type 2 (VMAT2), the membrane protein that regulates the size of the vesicular dopamine pool, in cocaine abusers relative to healthy subjects. To confirm the postmortem findings, the authors used PET and the VMAT2 radioligand [$^{11}$C]-(+)-dihydrotetrabenazine (DTBZ) to assess the in vivo VMAT2 availability in a group of 12 recently abstinent cocaine-dependent subjects and matched healthy comparison subjects. [$^{11}$C]DTBZ nondisplaceable binding potential (BP(ND))

was measured by kinetic analysis using the arterial input function or, if arterial input was unavailable, by the simplified reference tissue method. [$^{11}$C]DTBZ BP(ND) was significantly lower in the cocaine abusers than in the comparison subjects in the limbic striatum (10.0% lower), associative striatum (-13.4%), and sensorimotor striatum (-11.5%). The results of this in vivo PET study confirm previous in vitro reports of low VMAT2 availability in the striatum of cocaine abusers. It also suggests a compensatory down-regulation of the dopamine storage vesicles in response to chronic cocaine abuse and/or a loss of dopaminergic terminals. Further research is necessary to understand the clinical relevance of this observation to relapse and outcome in abstinent cocaine abusers. Narendran R, Lopresti BJ, Martinez D, Mason NS, Himes M, May MA, Daley DC, Price JC, Mathis CA, Frankle WG. In vivo evidence for low striatal vesicular monoamine transporter 2 (VMAT2) availability in cocaine abusers. Am. J. Psychiatry. 2012 Jan; 169(1): 55–63.

**Imaging of Dopamine D(2/3) Agonist Binding in Cocaine Dependence: A [(11) C]NPA Positron Emission Tomography Study** Positron emission tomography (PET) studies performed with [(11) C]raclopride have consistently reported lower binding to D(2/3) receptors and lower amphetamine-induced dopamine (DA) release in cocaine abusers relative to healthy controls. A limitation of these studies that were performed with D(2/3) antagonist radiotracers such as [(11) C]raclopride is the failure to provide information that is specific to D(2/3) receptors configured in a state of high affinity for the agonists (i.e., D(2/3) receptors coupled to G-proteins, D(2/3 HIGH) ). As the endogenous agonist DA binds with preference to D(2/3 HIGH) relative to D(2/3 LOW) receptors (i.e., D(2/3) receptors uncoupled to G-proteins) it is critical to understand the in vivo status of D(2/3 HIGH) receptors in cocaine dependence. Thus, the authors measured the available fraction of D(2/3) (HIGH) receptors in 10 recently abstinent cocaine abusers (CD) and matched healthy controls (HC) with the D(2/3) antagonist and agonist PET radiotracers [(11) C]raclopride and [(11) C]NPA. [(11) C]raclopride and [(11) C]NPA binding potential (BP) (BP(ND) ) in the striatum were measured with kinetic analysis using the arterial input function. The available fraction of D(2/3 HIGH) receptors, i.e., % R(HIGH) available = D(2/3 HIGH) /(D(2/3 HIGH) + D(2/3 LOW) ) was then computed as the ratio of [(11) C]NPA BP(ND) /[(11) C]raclopride BP(ND) . No differences in striatal [(11) C]NPA BP(ND) (HC = 1.00 ± 0.17;CD = 0.97 ± 0.17, P = 0.67) or available % R(HIGH) (HC = 39% ± 5%;CD = 41% ± 5%, P = 0.50) was observed between cocaine abusers and matched controls. The results of this [(11) C]NPA PET study do not support alterations in D(2/3 HIGH) binding in the striatum in cocaine dependence. Narendran R, Martinez D, Mason NS, Lopresti BJ, Himes ML, Chen C-M, May MA, Price JC, Mathis CA, Frankle WG. Imaging of dopamine D(2/3) agonist binding in cocaine dependence: a [(11) C]NPA positron emission tomography study. Synapse. 2011 Dec; 65(12): 1344–1349.

**The Neurobiology of Cognitive Control in Successful Cocaine Abstinence** Extensive evidence demonstrates that current cocaine abusers show hypoactivity in anterior cingulate and dorsolateral prefrontal cortex and respond poorly relative to drug-naïve controls on tests of executive function. Relatively little is known about the cognitive sequelae of long-term abstinence in cocaine addicts. Here, the authors use a GO-NOGO task in which successful performance necessitated withholding a prepotent response to assay cognitive control in short- and long-term abstinent cocaine users (1-5 weeks and 40-102 weeks, respectively). They report significantly greater activity in prefrontal, cingulate, cerebellar and inferior frontal gyrii in

abstinent cocaine users for both successful response inhibitions and errors of commission. Moreover, this relative hyperactivity was present in both abstinent groups, which, in the presence of comparable behavioral performance, suggests a functional compensation. Differences between the short- and long-abstinence groups in the patterns of functional recruitment suggest different cognitive control demands at different stages in abstinence. Short-term abstinence showed increased inhibition-related dorsolateral and inferior frontal activity indicative of the need for increased inhibitory control while long-term abstinence showed increased error-related ACC activity indicative of heightened behavioral monitoring. The results suggest that the integrity of prefrontal systems that underlie cognitive control functions may be an important characteristic of successful long-term abstinence. Connolly CG, Foxe JJ, Nierenberg J, Shpaner M, Garavan H. The neurobiology of cognitive control in successful cocaine abstinence. Drug Alcohol Depend. 2012 Feb; 121(1-2): 45–53.

**Distributed Attentional Deficits in Chronic Methamphetamine Abusers: Evidence from the Attentional Network Task (ANT)** The goal of the present study was to examine distributed attentional functions in long-term but currently abstinent methamphetamine (MA) abusers using a task that measures attentional alertness, orienting, and conflict resolution. Thirty currently abstinent MA abusers (1 month-5 years) and 22 healthy non-substance using adults were administered a multimodal version of the Attentional Network Task (ANT-I). In this task subjects identified the direction of a centrally presented arrow using a key press. Analyses examined the interaction between alerting tones, location cueing and congruency between the target arrows and flanking distractor stimuli. All participants were faster when an auditory tone preceded the trial onset ($p<0.001$), on trials in which a valid cue preceded the location of the target arrow ($p<0.001$), and on congruent trials (i.e., when all display arrows faced in the same direction) ($p<0.001$). Of primary interest was the finding that MA abusers were more influenced by the conflict between the peripheral arrows and the central target arrow ($p=0.009$). There were also correlations between length of drug sobriety and executive function as well as between drug-induced psychiatric symptoms and alertness. These results suggest that chronic MA abusers display cognitive deficits that may reflect a specific vulnerability to distraction on a task of executive function. These findings are consistent with other studies that have reported deficits in anterior attentional systems and top-down cognitive control. Salo R, Gabay S, Fassbender C, Henik A. Distributed attentional deficits in chronic methamphetamine abusers: evidence from the Attentional Network Task (ANT). Brain Cogn 2011 Dec; 77(3): 446–452.

**Nothing To Lose: Processing Blindness to Potential Losses Drives Thrill and Adventure Seekers** Sensation seeking has been linked to increased risk taking and is therefore crucial in influencing behavioral outcomes of risk-taking behavior. Using functional magnetic resonance imaging (fMRI), the neural underpinnings of risk appraisal were studied in a large subject sample (n=188), stratified according to thrill and adventure seeking (TAS) ratings. As defined by a median split of the sample, low and high TAS groups were compared on a simple decision-making task completed during fMRI. The task was designed such that risk (i.e., magnitude of outcome) and gains (i.e., direction of outcome) could be mapped independently. Behavioral analysis indicated that high TAS individuals are more sensitive to rewards but less discriminating between risk with and without punishment and that low TAS individuals are less sensitive to rewards but quite sensitive to receiving punishments in risky situations. Imaging results on the group differences for the interaction between level of risk and level of gain showed

differences in the right superior frontal gyrus (BA6), left insula (BA21), right nucleus accumbens, left lentiform nucleus, and left precuneus (BA7). The presented data suggest a neural model of risk processing in sensation seeking individuals such that the positive response to reward outweighs the impact of equivalent loss. This imbalance in approach/avoidance is evident in differences in the underlying neural substrates in TAS individuals and leads to greater risk behavior in the face of potential loss. Kruschwitz JD, Simmons AN, Flagan T, Paulus MP. Nothing to lose: processing blindness to potential losses drives thrill and adventure seekers. Neuroimage. 2012 Feb; 59(3): 2850–2859.

**Implicit Signals In Small Group Settings and their Impact on the Expression of Cognitive Capacity and Associated Brain Responses** Measures of intelligence, when broadcast, serve as salient signals of social status, which may be used to unjustly reinforce low-status stereotypes about out-groups' cultural norms. Herein, the authors investigate neurobehavioural signals manifest in small (n = 5) groups using functional magnetic resonance imaging and a "ranked group IQ task" where implicit signals of social status are broadcast and differentiate individuals based on their expression of cognitive capacity. They report an initial overall decrease in the expression of cognitive capacity in the small group setting. However, the environment of the "ranked group IQ task" eventually stratifies the population into two groups ('high performers', HP and "low performers", LP) identifiable based on changes in estimated intelligence quotient and brain responses in the amygdala and dorsolateral prefrontal cortex. In addition, they demonstrate signals in the nucleus accumbens consistent with prediction errors in expected changes in status regardless of group membership. These results suggest that individuals express diminished cognitive capacity in small groups, an effect that is exacerbated by perceived lower status within the group and correlated with specific neurobehavioural responses. The impact these reactions have on intergroup divisions and conflict resolution requires further investigation, but suggests that low-status groups may develop diminished capacity to mitigate conflict using non-violent means. Kishida KT, Yang D, Quartz KH, Quartz SR, Montague PR. Implicit signals in small group settings and their impact on the expression of cognitive capacity and associated brain responses. Philos. Trans. R. Soc. Lond., B, Biol. Sci. 2012 Mar; 367(1589): 704–716.

**Aberrant Paralimbic Gray Matter in Criminal Psychopathy** Psychopaths impose large costs on society, as they are frequently habitual, violent criminals. The pervasive nature of emotional and behavioral symptoms in psychopathy suggests that several associated brain regions may contribute to the disorder. Studies employing a variety of methods have converged on a set of brain regions in paralimbic cortex and limbic areas that appear to be dysfunctional in psychopathy. The present study further tests this hypothesis by investigating structural abnormalities using voxel-based morphometry in a sample of incarcerated men (N = 296). Psychopathy was associated with decreased regional gray matter in several paralimbic and limbic areas, including bilateral parahippocampal, amygdala, and hippocampal regions, bilateral temporal pole, posterior cingulate cortex, and orbitofrontal cortex. The consistent identification of paralimbic cortex and limbic structures in psychopathy across diverse methodologies strengthens the interpretation that these regions are crucial for understanding neural dysfunction in psychopathy. Ermer E, Cope LM, Nyalakanti PK, Calhoun VD, Kiehl KA. Aberrant paralimbic gray matter in criminal psychopathy. Journal of Abnormal Psychology 2011 Dec 12. [Epub ahead of print. doi: 10.1037/a0026371].

## BEHAVIORAL AND INTEGRATIVE TREATMENT RESEARCH

**Front-Loaded versus Weekly Counseling for Treatment of Tobacco Addiction**
Approximately 60%-70% of cigarette smokers who try to quit relapse by 2 weeks post-cessation. The authors tested the efficacy of a front-loaded (FL) counseling intervention whose goal was to increase the likelihood of successful early abstinence and subsequent long-term abstinence. They randomized 278 adult smokers to an FL or weekly behavioral smoking cessation counseling schedule. The total number of sessions across treatment was the same for both groups. However, those assigned to the FL schedule received 6 counseling sessions in the first 2 weeks post-cessation, while those in the weekly condition received 2 sessions. Participants in both groups also received standard nicotine patch treatment. At 1 year post-cessation, FL participants were significantly less likely to have relapsed when continuous abstinence was used as the definition of abstinence/relapse (11.7% abstinent vs. 6.3%, hazard ratio [HR] = 0.69, p = .007); and there were nonsignificant trends -for FL subjects to have better outcomes when abstinence was defined as never smoking for 7 or more consecutive days nor for 7 or more consecutive episodes (18.4% abstinent vs. 14.8%, HR = 0.83, p = .20) and as point prevalence abstinence (15.6% abstinent vs. 12.9%, p = .11). The relationship between FL counseling treatment and continuous abstinence was partially mediated by higher post-cessation levels of social support perceived from counseling and greater use of cessation-related coping strategies. The authors conclude that FL counseling is a promising treatment model that should be evaluated further, perhaps using modifications of the FL schedule used in this study. Garvey AJ, Kalman D, Hoskinson RA Jr, Kinnunen T, Wadler BM, Thomson CC, Rosner B. Front-loaded versus weekly counseling for treatment of tobacco addiction. Nicotine Tob Res. 2011 Nov 4. [Epub ahead of print].

**Efficacy of Varenicline to Prompt Quit Attempts in Smokers not Currently Trying to Quit: A Randomized Placebo-Controlled Trial** Nicotine replacement therapy to aid smoking reduction increases the probability of a future quit attempt among smokers not currently planning to quit smoking. The authors tested whether varenicline, a partial nicotine agonist, would also increase future quit attempts. This randomized, placebo-controlled trial recruited 218 smokers who were interested in quitting but had no plans to quit in the next month. Participants used varenicline (2 mg/day) or placebo for 2–8 weeks plus received brief counseling on methods to reduce cigarettes/day. The primary measure was the incidence of a quit attempt within 6 months of study entry. Secondary measures were point prevalence abstinence, motivation to stop smoking, and reduction in cigarettes/day. Varenicline increased the incidence of a quit attempt more than placebo at the Nebraska site (73% vs. 41%; p < .001) but not at the Vermont site (45% vs. 51%; p = .45). Varenicline increased most other measures of quit attempts, motivation and abstinence, independent of site. The beneficial effects of varenicline in quit attempts appeared to be mediated by greater reductions in cigarettes/day, dependence, craving, and cigarette satisfaction. Varenicline had a greater effect on quit attempts in less-dependent smokers, in minority smokers, and in those who had less prior cessation or reduction activity. Adverse events were minimal. Varenicline increased quit attempts in smokers who are not currently trying to quit at one of the two study sites and improved most all secondary outcomes independent of site. This appeared to be due to decreasing cigarettes/day and level of dependence. Hughes JR, Rennard SI, Fingar JR, Talbot SK, Callas PW, Fagerstrom KO. Efficacy of varenicline to prompt quit attempts in smokers not currently trying to quit: a randomized placebo-controlled trial. Nicotine Tob Res. 2011 Oct;1 3(10): 955-964.

**Using Extended Cognitive Behavioral Treatment and Medication to Treat Dependent Smokers** The authors evaluated smoking-cessation efficacy of an extended course of sustained-release bupropion (bupropion SR) and cognitive-behavioral treatment (CBT). Participants who smoked at least 10 cigarettes per day and who smoked within 30 minutes of arising (n = 406) completed a 12-week smoking-cessation treatment including group counseling, nicotine-replacement therapy, and bupropion SR. Participants were then randomly assigned to 1 of 5 conditions: (1) no further treatment, (2) active bupropion SR for 40 weeks, (3) placebo for 40 weeks, (4) active bupropion SR and 11 sessions of CBT for 40 weeks (A-CBT), or (5) placebo and 11 sessions of CBT for 40 weeks. Participants were assessed at baseline and at weeks 12, 24, 52, 64, and 104. A-CBT was not superior to the other 3 extended treatments. From weeks 12 through 104, all extended treatment conditions were superior to standard treatment. At weeks 64 and 104, the 2 CBT conditions produced significantly higher abstinence rates than did the other 3 conditions. Brief contact with providers can increase abstinence during treatment. CBT may increase long-term abstinence after extended treatment is terminated. Hall SM, Humfleet GL, Muñoz RF, Reus VI, Prochaska JJ, Robbins JA. Using extended cognitive behavioral treatment and medication to treat dependent smokers. Am J Public Health. 2011 Dec; 101(12): 2349-2356.

**Marijuana Use and Tobacco Smoking Cessation among Heavy Alcohol Drinkers** Whereas problem drinking impedes smoking cessation, less is known whether marijuana use affects smoking cessation outcomes and whether smoking cessation treatment leads to changes in marijuana smoking. In a randomized clinical trial that recruited 236 heavy drinkers seeking smoking cessation treatment, the authors examined whether current marijuana smokers (n=57) differed from the rest of the sample in tobacco smoking and alcohol use outcomes and whether the patterns of marijuana use changed during treatment. Half of the marijuana users reported smoking marijuana at least weekly (an average of 42% of possible smoking days), the other half used infrequently, an average of 5% of possible days. There were no significant differences between the marijuana use groups and non-users on smoking outcomes and marijuana use did not predict smoking lapses. All participants made large reductions in weekly alcohol consumption during the trial, with weekly marijuana users reducing their drinking by 47% and at a faster rate than non-marijuana users after the 8-week follow-up. Weekly marijuana smokers also steadily decreased their marijuana use over the course of the study (at 8-, 16-, and 26-week follow-ups) by more than 24%. These data suggest that frequent marijuana smokers may benefit from smoking cessation interventions, even when marijuana use is not explicitly discussed. These individuals do not show any more difficulty than other cigarette smokers in making efforts to reduce tobacco smoking and in fact, make meaningful changes in marijuana use and heavy drinking. Future clinical trials should examine whether smoking cessation treatment that addresses both marijuana and tobacco smoking leads to substantial reductions in marijuana use. Metrik J, Spillane NS, Leventhal AM, Kahler CW. Marijuana use and tobacco smoking cessation among heavy alcohol drinkers. Drug Alcohol Depend. 2011 Dec 15; 119(3): 194-200.

**Mindfulness Training for Smoking Cessation: Results from a Randomized Controlled Trial** Cigarette smoking is the leading cause of preventable death in the world, and long-term abstinence rates remain modest. Mindfulness training (MT) has begun to show benefits in a number of psychiatric disorders, including depression, anxiety and more recently, in addictions. However, MT has not been evaluated for smoking cessation through randomized clinical trials. 88 treatment-seeking, nicotine-dependent adults who were smoking an average of 20

cigarettes/day were randomly assigned to receive MT or the American Lung Association's freedom from smoking (FFS) treatment. Both treatments were delivered twice weekly over 4 weeks (eight sessions total) in a group format. The primary outcomes were expired-air carbon monoxide-confirmed 7-day point prevalence abstinence and number of cigarettes/day at the end of the 4-week treatment and at a follow-up interview at week 17. 88% of individuals received MT and 84% of individuals received FFS completed treatment. Compared to those randomized to the FFS intervention, individuals who received MT showed a greater rate of reduction in cigarette use during treatment and maintained these gains during follow-up ($F=11.11$, $p=.001$). They also exhibited a trend toward greater point prevalence abstinence rate at the end of treatment (36% vs. 15%, $p=.063$), which was significant at the 17-week follow-up (31% vs. 6%, $p=.012$). This initial trial of mindfulness training may confer benefits greater than those associated with current standard treatments for smoking cessation. Brewer JA, Mallik S, Babuscio TA, Nich C, Johnson HE, Deleone CM, Minnix-Cotton CA, Byrne SA, Kober H, Weinstein AJ, Carroll KM, Rounsaville BJ. Mindfulness training for smoking cessation: Results from a randomized controlled trial. Drug Alcohol Depend. 2011 Dec 1; 119(1-2): 72-80.

**A Randomized Trial of Contingency Management Delivered by Community Therapists** Contingency management (CM) is an evidence-based treatment, but few clinicians deliver this intervention in community-based settings. In this study, twenty-three clinicians from 3 methadone maintenance clinics received training in CM. Following a didactic seminar and a training and supervision period in which clinicians delivered CM to pilot patients, a randomized trial evaluated the efficacy of CM when delivered entirely by clinicians. Sixteen clinicians treated 130 patients randomized to CM or standard care. In both conditions, urine and breath samples were collected twice weekly for 12 weeks. In the CM condition, patients earned the opportunity to win prizes ranging in value from $1 to $100 for submitting samples negative for cocaine and alcohol. Primary treatment outcomes were retention, longest continuous period of abstinence, and proportion of negative samples submitted. Results suggested that patients randomized to CM remained in the study longer ($9.5 \pm 3.6$ vs. $6.7 \pm 5.0$ weeks), achieved greater durations of abstinence ($4.7 \pm 4.7$ vs. $1.7 \pm 2.7$ weeks), and submitted a higher proportion of negative samples ($57.7\% \pm 40.0\%$ vs. $29.4\% \pm 33.3\%$) than those assigned to standard care. These data indicate that, with appropriate training, community-based clinicians can effectively administer CM. This study suggests that resources should be directed toward training and supervising community-based providers in delivering CM, as patient outcomes can be significantly improved by integrating CM in methadone clinics. Petry NM, Alessi SM, Ledgerwood DM. A randomized trial of contingency management delivered by community therapists. J Consult Clin Psychol. 2012 Jan 16. [Epub ahead of print].

**Contingency Management with Community Reinforcement Approach or Twelve-Step Facilitation Drug Counseling for Cocaine Dependent Pregnant Women or Women with Young Children** Cocaine abuse among women of child-bearing years is a significant public health problem. This study evaluated the efficacy of contingency management (CM), the community reinforcement approach (CRA), and twelve-step facilitation (TSF) for cocaine-dependent pregnant women or women with young children. Using a 2×2 study design, 145 cocaine dependent women were randomized to 24 weeks of CRA or TSF and to monetary vouchers provided contingent on cocaine-negative urine tests (CM) or non-contingently but yoked in value (voucher control, VC). Primary outcome measures included the longest

consecutive period of documented abstinence, proportion of cocaine-negative urine tests (obtained twice-weekly), and percent days using cocaine (PDC) during treatment. Documented cocaine abstinence at baseline and 3, 6, 9 and 12 months following randomization was a secondary outcome. CM was associated with significantly greater duration of cocaine abstinence, higher proportion of cocaine-negative urine tests, and higher proportion of documented abstinence across the 3-, 6-, 9- and 12-month assessments, compared to VC. The differences between CRA and TSF were not significant for any of these measures. The study findings support the efficacy of CM for cocaine dependent pregnant women and women with young children but do not support greater efficacy of CRA compared to TSF or differential efficacy of CM when paired with either CRA or TSF. Schottenfeld RS, Moore B, Pantalon MV. Contingency management with community reinforcement approach or twelve-step facilitation drug counseling for cocaine dependent pregnant women or women with young children. Drug Alcohol Depend. 2011 Oct 1; 118(1): 48-55.

**HealthCall: Technology-Based Extension of Motivational Interviewing to Reduce Non-Injection Drug Use in HIV Primary Care Patients - A Pilot Study** To reduce non-injection drug use (NIDU) among HIV primary care patients, more than a single brief intervention may be needed, but clinic resources are often too limited for extended interventions. To extend brief motivational interviewing (MI) to reduce NIDU, this pilot study of "HealthCall," consisted of brief (1-3 minutes) daily patient calls to report NIDU and health behaviors to a telephone-based interactive voice response (IVR) system, which provided data for subsequent personalized feedback. Urban HIV adult clinic patients reporting ≥4 days of NIDU in the previous month were randomized to two groups: MI-only (n=20) and MI+HealthCall (n=20). At 30 and 60 days, patients were assessed and briefly discussed their NIDU behaviors with their counselors. The outcome was the number of days patients used their primary drug in the prior 30 days. Medical marijuana issues precluded HealthCall with patients whose primary substance was marijuana (n=7); excluding these, 33 remained, of whom 28 patients (MI-only n=17; MI+HealthCall n=11) provided post-treatment data for analysis. Time significantly predicted reduction in "days used" in both groups. This pilot study suggests that HealthCall is feasible and acceptable to patients in resource-limited HIV primary care settings and can extend patient involvement in brief intervention with little additional staff time. Aharonovich E, Greenstein E, O'Leary A, Johnston B, Seol SG, Hasin DS. HealthCall: technology-based extension of motivational interviewing to reduce non-injection drug use in HIV primary care patients - A pilot study. AIDS Care. 2012 Mar 20. [Epub ahead of print].

**Delay Discounting Decreases in those Completing Treatment for Opioid Dependence** Several studies examining both control and substance-dependent populations have found delay discounting to remain stable over time. In this report, the authors examine whether delay discounting changes in opioid-dependent individuals who complete a 12-week treatment. The 159 subjects who completed discounting assessments at baseline and treatment-end come from two separate clinical trials: 56 from Chopra et al. (2009) and 103 from Christensen et al. (2012). Mean discounting at 12 weeks significantly decreased to less than half (44.8%) of the baseline level (95% CIs (27.5, 73.2)). Analyzing each subject's discounting data individually, over 3 times (95% CIs (1.9, 5.5)) as many subjects statistically decreased their discounting from their own baseline levels than those who exhibited a statistical increase. Though the authors failed to find any relationship among discounting measures and abstinence outcomes, the results from this

large study suggest that treatment for substance dependence promotes decreases in delay discounting. Landes RD, Christensen DR, Bickel WK. Delay discounting decreases in those completing treatment for opioid dependence. Exp Clin Psychopharmacol. 2012 Feb 27. [Epub ahead of print].

**Reinforcement-Based Treatment Improves the Maternal Treatment and Neonatal Outcomes of Pregnant Patients Enrolled in Comprehensive Care Treatment** This randomized clinical trial examined the efficacy of comprehensive usual care (UC) alone (n = 42) or enhanced by reinforcement-based treatment (RBT) (n = 47) to produce improved treatment outcomes, maternal delivery, and neonatal outcomes in pregnant women with opioid and/or cocaine substance use disorders. RBT participants spent, on average, 32.6 days longer in treatment ($p < .001$) and almost six times longer in recovery housing than did UC participants ($p = .01$). There were no significant differences between the RBT and UC conditions in proportion of participants testing positive for any illegal substance. Neonates in the RBT condition spent 1.3 fewer days hospitalized after birth than UC condition neonates ($p = .03$), although the two conditions did not differ significantly in neonatal gestational age at delivery, birth weight, or number of days hospitalized. Integrating RBT into a rich array of comprehensive care treatment components may be a promising approach to increase maternal treatment retention and reduce neonatal length of hospital stay. Jones HE, O'Grady KE, Tuten M. Reinforcement-based treatment improves the maternal treatment and neonatal outcomes of pregnant patients enrolled in comprehensive care treatment. Am J Addict. 2011 May-Jun; 20(3): 196-204.

**Treating the Partners of Opioid-Dependent Pregnant Patients: Feasibility and Efficacy** Drug-dependent pregnant women with intimate partners who are also drug-dependent have been found to have compromised treatment outcomes. Thus, developing a treatment to reduce a male partner's drug use is the first step in a line of research with a distal goal of improving pregnant patient's treatment outcomes. This study examined a novel intervention for engaging the male partner in drug treatment. Men targeted for intervention were non-treatment-seeking opioid users. Motivational enhancement therapy (MET), an effective non-confrontational intervention approach for evoking behavioral change, was employed to encourage treatment participation. This six-session intervention was followed by a drug-abstinent contingency-based voucher incentive program. Moreover, to help maintain drug abstinence, male partners had rapid facilitation into either opioid detoxification with aftercare or methadone maintenance. Interwoven into treatment were both couple's counseling and a men's group educational program designed to strengthen the support provided by the men to their partners during pregnancy and post-delivery. Men (n = 45) received either the novel intervention package called HOPE (Helping Other Partners Excel) or a control condition (n = 17) that received weekly support and referrals for treatment. Men in the HOPE condition, compared with the usual care condition, showed increased treatment retention, transient decreases in heroin use, increased involvement in recreational activities, less reliance on public assistance, and increased social support for their pregnant partners. Results suggest that treatment of male partners is feasible and efficacious in the short term but modifications to the intervention are needed to sustain results. Jones HE, Tuten M, O'Grady KE. Treating the partners of opioid-dependent pregnant patients: feasibility and efficacy. Am J Drug Alcohol Abuse. 2011 May; 37(3): 170-178.

**A Randomized Controlled Trial Comparing Integrated Cognitive Behavioral Therapy Versus Individual Addiction Counseling for Co-occurring Substance Use and Posttraumatic Stress Disorders** Co-occurring posttraumatic stress (PTSD) and substance use disorders provide clinical challenges to addiction treatment providers. Interventions are needed that are effective, well-tolerated by patients, and capable of being delivered by typical clinicians in community settings. This is a randomized controlled trial of integrated cognitive behavioral therapy for co-occurring PTSD and substance use disorders. Fifty-three participants sampled from seven community addiction treatment programs were randomized to integrated cognitive behavioral therapy plus standard care or individual addiction counseling plus standard care. Fourteen community therapists employed by these programs delivered both manual-guided therapies. Primary outcomes were PTSD symptoms, substance use symptoms and therapy retention. Participants were assessed at baseline, 3- and 6-month follow-up. Integrated cognitive behavioral therapy was more effective than individual addiction counseling in reducing PTSD re-experiencing symptoms and PTSD diagnosis. Individual addiction counseling was comparably effective to integrated cognitive behavioral therapy in substance use outcomes and on other measures of psychiatric symptom severity. Participants assigned to individual addiction counseling with severe PTSD were less likely to initiate and engage in the therapy than those assigned to integrated cognitive behavioral therapy. In general, participants with severe PTSD were more likely to benefit from integrated cognitive behavioral therapy. The findings support the promise of efficacy of integrated cognitive behavioral therapy in improving outcomes for persons in addiction treatment with PTSD. Community counselors delivered both interventions with satisfactory adherence and competence. Despite several limitations to this research, a larger randomized controlled trial of integrated cognitive behavioral therapy appears warranted. McGovern MP, Lambert-Harris C, Alterman AI, Xie H, Meier A. A randomized controlled trial comparing integrated cognitive behavioral therapy versus individual addiction counseling for co-occurring substance use and posttraumatic stress disorders. J Dual Diagn. 2011 Jan 1; 7(4): 207-227.

**Preliminary Results for an Adaptive Family Treatment for Drug Abuse in Hispanic Youth** A small randomized trial investigated a new family-based intervention for Hispanic adolescents who met DSM-IV criteria for substance abuse disorder. The Culturally Informed and Flexible Family-Based Treatment for Adolescents (CIFFTA) is a tailored/adaptive intervention that includes a flexible treatment manual and multiple treatment components. The study used an "add on" design to isolate the effects on substance abuse, behavior problems, and parenting practices attributable to the newly developed components. Twenty-eight Hispanic adolescents and their families were randomized either to the experimental treatment or to traditional family therapy (TFT) and were assessed at baseline and 8-month follow-up. Despite the small sample, results revealed statistically significant time × treatment effects on both self-reported drug use (marijuana + cocaine), $F(1, 22) = 10.59$, $p < .01$, $\eta^2 = .33$ and adolescent reports of parenting practices, $F(1, 22) = 9.01$, $p < .01$, $\eta^2 = .29$. Both sets of analyses favored CIFFTA participants. There was a significant time × treatment effect, $F(1, 22) = 6.72$, $p = .02$, $\eta^2 = .23$, favoring CIFFTA on parent report of parenting practices using a composite that matched the variables used for adolescents, but only a nonsignificant trend, $F(1, 22) = 2.43$, $p = .13$, $\eta^2 = .10$, with a composite that used all parenting subscales. Parent reports of adolescent behavior problems did not show a significant time or time × treatment effect. These results show the promise of this adaptive treatment for substance abuse in Hispanic adolescents and suggest the need for a larger

randomized trial to fully investigate this treatment. Santisteban DA, Mena MP, McCabe BE. Preliminary results for an adaptive family treatment for drug abuse in Hispanic youth. J Fam Psychol. 2011 Aug; 25(4): 610-614.

**Motivational Interviewing to Reduce Substance-Related Consequences: Effects for Incarcerated Adolescents with Depressed Mood** The impact of depressed mood on Motivational Interviewing (MI) to reduce risky behaviors and consequences in incarcerated adolescents was examined in this brief report. Adolescents (N=189) were randomly assigned to receive MI or Relaxation Training (RT). At 3-month follow-up assessment, MI significantly reduced risks associated with marijuana use, with a trend towards reducing risks associated with alcohol use. There was also a trend for depressive symptoms to be associated with reduced risks after release. Interaction effects were non-significant, indicating no moderating effects for depressed mood on treatment outcome. MI may be a useful treatment for incarcerated adolescents in order to reduce risks and consequences associated with substance use after release. Stein LA, Clair M, Lebeau R, Colby SM, Barnett NP, Golembeske C, Monti PM. Motivational interviewing to reduce substance-related consequences: effects for incarcerated adolescents with depressed mood. Drug Alcohol Depend. 2011 Nov 1; 118(2-3): 475-478.

**Social Norms and Self-Efficacy among Heavy Using Adolescent Marijuana Smokers** Adolescence is a time in which individuals are particularly likely to engage in health-risk behaviors, with marijuana being the most prevalent illicit drug used. Perceptions of others' use (i.e., norms) have previously been found to be related to increased marijuana use. Additionally, low refusal self-efficacy has been associated with increased marijuana consumption. This cross-sectional study examined the effects of normative perceptions and self-efficacy on negative marijuana outcomes for a heavy using adolescent population. A structural equation model was tested and supported such that significant indirect paths were present from descriptive norms to marijuana outcomes through self-efficacy. Implications for prevention and intervention with heavy using adolescent marijuana users are discussed. Walker DD, Neighbors C, Rodriguez LM, Stephens RS, Roffman RA. Social norms and self-efficacy among heavy using adolescent marijuana smokers. Psychol Addict Behav. 2011 Dec; 25(4): 727-732.

## RESEARCH ON PHARMACOTHERAPIES FOR DRUG ABUSE

**A Double-Blind, Placebo-Controlled Trial of Modafinil for Cocaine Dependence** This is a randomized, double-blind, placebo-controlled study of modafinil treatment for cocaine dependence. Patients (N = 210) who were actively using cocaine at baseline were randomized to 8 weeks of modafinil (0 mg/day, 200 mg/day, or 400 mg/day) combined with once-weekly cognitive-behavioral therapy. The primary efficacy measure was cocaine abstinence, based on urine benzoylecgonine (BE) levels, with secondary measures of craving, cocaine withdrawal, retention, and tolerability. The authors found no significant differences between modafinil and placebo patients on any of these measures. However, there was a significant gender difference in that male patients treated with 400 mg/day tended to be more abstinent than their placebo-treated counterparts (p = .06). These negative findings might be explained by gender differences and/or inadequate psychosocial treatment intensity in patients with severe cocaine dependence. Dackis CA, Kampman KM, Lynch KG, Plebani JG, Pettinati HM, Sparkman T, O'Brien CP. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. J Subst Abuse Treat 2012 Feb 27. Epub ahead of print.

**Noradrenergic $A_1$ Receptor Antagonist Treatment Attenuates Positive Subjective Effects of Cocaine in Humans: A Randomized Trial** Preclinical research implicates dopaminergic and noradrenergic mechanisms in mediating the reinforcing effects of drugs of abuse, including cocaine. The objective of this study was to evaluate the impact of treatment with the noradrenergic α(1) receptor antagonist doxazosin on the positive subjective effects of cocaine.Thirteen non-treatment seeking, cocaine-dependent volunteers completed this single-site, randomized, placebo-controlled, within-subjects study. In one study phase volunteers received placebo and in the other they received doxazosin, with the order counterbalanced across participants. Study medication was masked by over-encapsulating doxazosin tablets and matched placebo lactose served as the control. Study medication treatment was initiated at 1 mg doxazosin or equivalent number of placebo capsules PO/day and increased every three days by 1 mg. After receiving 4 mg doxazosin or equivalent number of placebo capsules participants received masked doses of 20 and 40 mg cocaine IV in that order with placebo saline randomly interspersed to maintain the blind. Doxazosin treatment was well tolerated and doxazosin alone produced minimal changes in heart rate and blood pressure. During treatment with placebo, cocaine produced dose-dependent increases in subjective effect ratings of "high", "stimulated", "like cocaine", "desire cocaine", "any drug effect", and "likely to use cocaine if had access" ($p<.001$). Doxazosin treatment significantly attenuated the effects of 20 mg cocaine on ratings of "stimulated", "like cocaine", and "likely to use cocaine if had access" ($p<.05$). There were trends for doxazosin to reduce ratings of "stimulated", "desire cocaine", and "likely to use cocaine if had access" ($p<.10$).Medications that block noradrenergic $\alpha_1$ receptors, such as doxazosin, may be useful as treatments for cocaine dependence, and should be evaluated further. Clinicaltrials.gov NCT01062945. Newton TF, Garza R de L, Brown G, Kosten TR, Mahoney JJ, Haile CN. Noradrenergic $\alpha_1$ receptor antagonist treatment attenuates positive subjective effects of cocaine in humans: a randomized trial. PLoS One 2012;7(2). Epub 2012 Feb 3.

**A Randomized, Placebo-Controlled Laboratory Study of the Effects of D-Cycloserine on Craving in Cocaine-Dependent Individuals** D-Cycloserine (DCS), a partial glutamate N-methyl-D-aspartate (NMDA) receptor agonist, enhances extinction of conditioned fear responding; preliminary data suggest that it may facilitate extinction of drug cue reactivity. This study investigates DCS effects on cocaine cue craving and drug use in cocaine-dependent subjects. Thirty-two subjects were randomly assigned to receive (1) DCS only, (2) DCS before sessions 1 and 3, placebo (PBO) before session 2, or (3) PBO only 15-min before each of 3 1-h cocaine cue exposure sessions conducted 1 day apart. Craving ratings were obtained before, during, and after sessions. Drug use and cue-induced craving were assessed 1 week after the last cue session. Repeated presentation of cocaine cues resulted in decreased craving both within and between sessions. DCS did not facilitate extinction learning and may have enhanced craving. The group that received three doses of DCS had significantly higher craving than the PBO group at the baseline ratings taken before sessions 2 and 3, as well as significantly higher cue-induced craving at follow-up. The group that received two doses of DCS did not differ from the PBO group. There were no group differences in postextinction cocaine use. The reduction of cocaine cue reactivity in the PBO group suggests that the study procedures were sufficient to produce extinction. Under these conditions, DCS did not facilitate extinction and may have enhanced craving. Further studies of glutamatergic agents and extinction in cocaine dependence should include consideration of procedural variables that could have a major impact on study outcomes. Price KL, Baker NL, McRae-Clark AL, Saladin ME, Desantis SM, Santa Ana EJ, Brady KT. A randomized, placebo-controlled laboratory study of the effects of D: -cycloserine on craving in cocaine-dependent individuals. Psychopharmacology (Berl) 2012 Jan 11; [Epub ahead of print]

**Guanfacine Effects on Stress, Drug Craving and Prefrontal Activation in Cocaine Dependent Individuals: Preliminary Findings** Cocaine dependence is associated with increased stress and drug cue-induced craving and physiological arousal but decreased prefrontal activity to emotional and cognitive challenge. As these changes are associated with relapse risk, the authors investigated the effects of α2 receptor agonist guanfacine on these processes. Twenty-nine early abstinent treatment-seeking cocaine dependent individuals were randomly assigned to either daily placebo or guanfacine (up to 3 mg) for four weeks. In a laboratory experiment, all patients were exposed to three 10-min guided imagery conditions (stress/stress, drug cue/drug cue, stress/drug cue), one per day, consecutively in a random, counterbalanced order. Subjective craving, anxiety and arousal as well as cardiovascular output were assessed repeatedly. Brain response to stress, drug cue and relaxing imagery was also assessed during a functional magnetic resonance (fMRI) imaging session. In the current study, guanfacine was found to be safe and well-tolerated. Lower basal heart rate and blood pressure was observed in the guanfacine versus placebo group. Guanfacine lowered stress and cue-induced nicotine craving and cue-induced cocaine craving, anxiety and arousal. The guanfacine group also showed increased medial and lateral prefrontal activity following stress and drug cue exposure compared with placebo. Data suggest further exploration of guanfacine is warranted in terms of its potential for reducing stress-induced and cue-induced drug craving and arousal. Fox H, Seo D, Tuit K, Hansen J, Kimmerling A, Morgan PT, Sinha R. Guanfacine effects on stress, drug craving and prefrontal activation in cocaine dependent individuals: preliminary findings. J Psychopharmacol 2012 Feb 17; [Epub ahead of print].

**Increased Serum Brain-Derived Neurotrophic Factor is Predictive of Cocaine Relapse Outcomes: A Prospective Study** Cocaine dependence is associated with high relapse rates, but few biological markers associated with relapse outcomes have been identified. Extending preclinical research showing a role for central brain-derived neurotrophic factor (BDNF) in cocaine seeking, the authors examined whether serum BDNF is altered in abstinent, early recovering, cocaine-dependent individuals and whether it is predictive of subsequent relapse risk. Serum samples were collected across three consecutive mornings from 35 treatment-engaged, 3-week-abstinent cocaine-dependent inpatients (17 males/18 females) and 34 demographically matched hospitalized healthy control participants (17 males/17 females). Cocaine-dependent individuals were prospectively followed on days 14, 30, and 90 posttreatment discharge to assess cocaine relapse outcomes. Time to cocaine relapse, number of days of cocaine use (frequency), and amount of cocaine use (quantity) were the main outcome measures. High correlations in serum BDNF across days indicated reliable and stable serum BDNF measurements. Significantly higher mean serum BDNF levels were observed for the cocaine-dependent patients compared with healthy control participants ($p < .001$). Higher serum BDNF levels predicted shorter subsequent time to cocaine relapse (hazard ratio: 1.09, $p < .05$), greater number of days ($p < .05$), and higher total amounts of cocaine used ($p = .05$).High serum BDNF levels in recovering cocaine-dependent individuals are predictive of future cocaine relapse outcomes and may represent a clinically relevant marker of relapse risk. These data suggest that serum BDNF levels may provide an indication of relapse risk during early recovery from cocaine dependence. D'Sa C, Fox HC, Hong AK, Dileone RJ, Sinha R. Increased serum brain-derived neurotrophic factor is predictive of cocaine relapse outcomes: a prospective study. Biol Psychiatry 2011 Oct; (8):706-11.

**Pharmacotherapeutics Directed at Deficiencies Associated with Cocaine Dependence: Focus on Dopamine, Norepinephrine and Glutamate** Much effort has been devoted to research focused on pharmacotherapies for cocaine dependence yet there are no FDA-approved medications for this brain disease. Preclinical models have been essential to defining the central and peripheral effects produced by cocaine. Recent evidence suggests that cocaine exerts its reinforcing effects by acting on multiple neurotransmitter systems within mesocorticolimbic circuitry. Imaging studies in cocaine-dependent individuals have identified deficiencies in dopaminergic signaling primarily localized to corticolimbic areas. In addition to dysregulated striatal dopamine, norepinephrine and glutamate are also altered in cocaine dependence. In this review, the authors present these brain abnormalities as therapeutic targets for the treatment of cocaine dependence. They then survey promising medications that exert their therapeutic effects by presumably ameliorating these brain deficiencies. Correcting neurochemical deficits in cocaine-dependent individuals improves memory and impulse control, and reduces drug craving that may decrease cocaine use. The authors hypothesize that using medications aimed at reversing known neurochemical imbalances is likely to be more productive than current approaches. This view is also consistent with treatment paradigms used in neuropsychiatry and general medicine. Haile CN, Mahoney JJ, Newton TF, De La Garza R. Pharmacotherapeutics directed at deficiencies associated with cocaine dependence: Focus on dopamine, norepinephrine and glutamate. Pharmacol Ther 2012 Jan 31; [Epub ahead of print].

**Opioid Detoxification and Naltrexone Induction Strategies: Recommendations for Clinical Practice** Opioid dependence is a significant public health problem associated with high risk for relapse if treatment is not ongoing. While maintenance on opioid agonists (i.e., methadone, buprenorphine) often produces favorable outcomes, detoxification followed by treatment with the μ-opioid receptor antagonist naltrexone may offer a potentially useful alternative to agonist maintenance for some patients. Treatment approaches for making this transition are described here based on a literature review and solicitation of opinions from several expert clinicians and scientists regarding patient selection, level of care, and detoxification strategies. Among the current detoxification regimens, the available clinical and scientific data suggest that the best approach may be using an initial 2-4 mg dose of buprenorphine combined with clonidine, other ancillary medications, and progressively increasing doses of oral naltrexone over 3-5 days up to the target dose of naltrexone. However, more research is needed to empirically validate the best approach for making this transition. Sigmon SC, Bisaga A, Nunes EV, O'Connor PG, Kosten T, Woody G. Opioid Detoxification and Naltrexone Induction Strategies: Recommendations for Clinical Practice. Am J Drug Alcohol Abuse 2012 Mar 12; [Epub ahead of print].

**Effects of Cold Pressor Pain on the Abuse Liability of Intranasal Oxycodone in Male and Female Prescription Opioid Abusers** Approximately 1.9 million persons in the U.S. have prescription opioid use disorders often with concomitant bodily pain, but systematic data on the impact of pain on abuse liability of opioids is lacking. The purpose of this study was to determine whether pain alters the intranasal abuse liability of oxycodone, a commonly prescribed and abused analgesic, in males and females. Sporadic prescription opioid abusers (10 females, 10 males) participated in this mixed (between and within-subject), randomized inpatient study. Experimental sessions (n=6) tested intranasal placebo, oxycodone 15 or 30mg/70kg during cold pressor testing (CPT) and a warm water control. Observer- and subject-rated drug effect measures, analgesia, physiologic and cognitive effects were assessed. The CPT significantly increased blood pressure, heart rate, pain, stress, and "opiate desire" compared to the no-pain control but did not alter opioid liking, high or street value. Intranasal oxycodone produced effects within 10min, significantly decreasing pain and significantly increasing subjective measures of abuse liability (e.g., high). Females had higher ratings of street value, high, and liking for one or both active doses. The CPT was a reliably painful and stressful stimulus that did not diminish the abuse liability of intranasal oxycodone. Females were more sensitive to oxycodone on several abuse liability measures that warrant further follow-up. Snorting oxycodone rapidly produced psychoactive effects indicative of substantial abuse liability. Lofwall MR, Nuzzo PA, Walsh SL. Effects of cold pressor pain on the abuse liability of intranasal oxycodone in male and female prescription opioid abusers. Drug Alcohol Depend 2011 Dec 30; [Epub ahead of print].

**A Multisite Pilot Study of Extended-Release Injectable Naltrexone Treatment for Previously Opioid-Dependent Parolees and Probationers** A feasibility study was conducted to pilot test the ability of 5 sites to recruit, treat, and retain opioid-dependent offenders in a trial of extended-release injectable naltrexone (XR-NTX). The participants, 61 previously opioid-dependent individuals under legal supervision in the community, received up to 6 monthly injections of Depotrex brand naltrexone and completed a 6-month follow-up interview. Six-month outcomes showed that those who completed treatment had significantly fewer opioid-positive urines and were less likely to have been incarcerated than those who had not completed treatment. The findings indicate that XR-NTX holds promise as a feasible, effective treatment

option for opioid-dependent offenders. Coviello DM, Cornish JW, Lynch KG, Boney TY, Clark CA, Lee JD, Friedmann PD, Nunes EV, Kinlock TW, Gordon MS, Schwartz RP, Nuwayser ES, O'Brien CP. A multisite pilot study of extended-release injectable naltrexone treatment for previously opioid-dependent parolees and probationers. Subst Abus 2012; (1):48-59.

**Buprenorphine-Naloxone Maintenance Following Release from Jail** Primary care is understudied as a reentry drug and alcohol treatment setting. This study compared treatment retention and opioid misuse among opioid-dependent adults seeking buprenorphine/naloxone maintenance in an urban primary care clinic following release from jail versus community referrals. Postrelease patients were either (a) induced to buprenorphine in-jail as part of a clinical trial, or (b) seeking buprenorphine induction post release. From 2007 to 2008, N = 142 patients were new to primary care buprenorphine: n = 32 postrelease; n = 110 induced after community referral and without recent incarceration. Jail-released patients were more likely African American or Hispanic and uninsured. Treatment retention rates for postrelease (37%) versus community (30%) referrals were similar at 48 weeks. Rates of opioid positive urines and self-reported opioid misuse were also similar between groups. Postrelease patients in primary care buprenorphine treatment had equal treatment retention and rates of opioid abstinence versus community-referred patients. Lee JD, Grossman E, Truncali A, Rotrosen J, Rosenblum A, Magura S, Gourevitch MN. Buprenorphine-naloxone maintenance following release from jail. Subst Abus 2012; (1):40-47.

**A Randomized Trial of Methadone Initiation Prior to Release from Incarceration**
Individuals who use heroin and illicit opioids are at high risk for infection with human immunodeficiency virus (HIV) and other blood-borne pathogens, as well as incarceration. The purpose of the randomized trial reported here is to compare outcomes between participants who initiated methadone maintenance treatment (MMT) prior to release from incarceration, with those who were referred to treatment at the time of release. Participants who initiated MMT prior to release were significantly more likely to enter treatment postrelease ($P < .001$) and for participants who did enter treatment, those who received MMT prerelease did so within fewer days ($P = .03$). They also reported less heroin use ($P = .008$), other opiate use ($P = .09$), and injection drug use ($P = .06$) at 6 months. Initiating MMT in the weeks prior to release from incarceration is a feasible and effective way to improve MMT access postrelease and to decrease relapse to opioid use. McKenzie M, Zaller N, Dickman SL, Green TC, Parihk A, Friedmann PD, Rich JD. A randomized trial of methadone initiation prior to release from incarceration. Subst Abus 2012 ; (1):19-29.

**Rivastigmine Reduces "Likely to use Methamphetamine" in Methamphetamine-Dependent Volunteers** The authors previously reported that treatment with the cholinesterase inhibitor rivastigmine (3mg, PO for 5days) significantly attenuated "Desire for METH". Given that higher dosages of rivastigmine produce greater increases in synaptic ACh, the authors predicted that 6mg should have more pronounced effects on craving and other subjective measures. In the current study, they sought to characterize the effects of short-term exposure to rivastigmine (0, 3 or 6mg) on the subjective and reinforcing effects produced by administration of methamphetamine (METH) in non-treatment-seeking, METH-dependent volunteers. This was a double-blind, placebo-controlled, crossover study. Participants received METH on day 1, and were then randomized to placebo or rivastigmine on day 2 in the morning and treatment

continued through day 8. METH dosing was repeated on day 6. The data indicate that METH (15 and 30mg), but not saline, increased several positive subjective effects, including "Any Drug Effect", "High", "Stimulated", "Desire METH", and "Likely to Use METH" (all p's<0.0001). In addition, during self-administration sessions, participants were significantly more likely to choose METH over saline (p<0.0001). Evaluating outcomes as peak effects, there was a trend for rivastigmine to reduce "Desire METH" (p=0.27), and rivastigmine significantly attenuated "Likely to Use METH" (p=0.01). These effects were most prominent for rivastigmine 6mg when participants were exposed to the low dose (15mg, IV), but not high dose (30mg, IV), of METH. The self-administration data reveal that rivastigmine did not alter total choices for METH (5mg, IV/choice). Overall, the results indicate some efficacy for rivastigmine in attenuating key subjective effects produced by METH, though additional research using higher doses and longer treatment periods is likely needed. These data extend previous findings and indicate that cholinesterase inhibitors, and other drugs that target acetylcholine systems, warrant continued consideration as treatments for METH dependence. De La Garza R, Newton TF, Haile CN, Yoon JH, Nerumalla CS, Mahoney JJ, Aziziyeh A. Rivastigmine reduces "likely to use methamphetamine" in methamphetamine-dependent volunteers. Prog Neuropsychopharmacol Biol Psychiatry 2012 Apr; (1):141-146.

**Comparison of Intranasal Methamphetamine and D-Amphetamine Self-Administration by Humans** There are no studies directly comparing self-administration of methamphetamine and d-amphetamine by humans. This study compared intranasal methamphetamine- and d-amphetamine self-administration and characterized the mood, performance and physiological effects produced by the drugs. The study design was a randomized, double-blind, placebo-controlled, cross-over study carried out at an out-patient research unit at the New York State Psychiatric Institute. Participants were male recreational methamphetamine users (n=13). Five 2-day blocks of sessions were conducted. On the first day of each block, participants 'sampled' a single methamphetamine or d-amphetamine dose (0, 12, 50 mg/70 kg) and a monetary reinforcer ($5 or $20). Amphetamine plasma levels, cardiovascular, mood, and psychomotor performance effects were assessed before drug administration and repeatedly thereafter. On the second day of each block, participants chose between the sampled reinforcers (drug or money). There were no significant differences between the drugs on the majority of measures. Under the $5 condition, both amphetamines increased self-administration dose-dependently, with 41% drug choices overall. Under the $20 condition, only 17% drug options were selected. Both drugs increased cardiovascular activity and 'positive' mood, although methamphetamine produced more prominent effects on some measures (e.g. heart rate and ratings of 'high'). Methamphetamine and d-amphetamines appear to produce a similar dose-related profile of effects in humans, which supports their equivalence for abuse potential. Kirkpatrick MG, Gunderson EW, Johanson CE, Levin FR, Foltin RW, Hart CL. Comparison of intranasal methamphetamine and d-amphetamine self-administration by humans. Addiction 2012 Apr; (4):783-791.

**Cigarette Smoking as a Target for Potentiating Outcomes for Methamphetamine Abuse Treatment** Cigarette smoking occurs frequently among individuals with methamphetamine (MA) dependence. Preclinical and clinical evidence has suggested that the common co-abuse of MA and cigarettes represents a pharmacologically meaningful pattern. The present study is a secondary analysis of a randomized, placebo-controlled trial of bupropion treatment for MA dependence (bupropion n=36; placebo n=37). A hierarchical logistic modelling approach

assessed the efficacy of bupropion for reducing MA use separately among smokers and non-smokers. Among smokers, relations between cigarettes smoked and MA use were assessed. Smoking status did not affect treatment responsiveness in either the bupropion condition or the placebo condition. In the placebo condition, increased cigarette use was associated with an increased probability of MA use during the same time period. This effect was not observed in the bupropion condition.Initial smoking status did not impact treatment outcomes. Among smokers, results suggest that bupropion may dissociate cigarette and MA use. The effect was modest and a precise pharmacological mechanism remains elusive. Cholinergic systems may be relevant for MA use outcomes. Future studies should continue to assess the role of smoking in MA treatment outcomes. Brensilver M, Heinzerling KG, Swanson A-N, Telesca D, Furst BA, Shoptaw SJ. Cigarette smoking as a target for potentiating outcomes for methamphetamine abuse treatment. Drug Alcohol Rev 2012 Mar 4.

**Comparison of Substance use Milestones in Cannabis- and Cocaine-Dependent Patients**
The objective of this study was to compare the progression of substance use milestones between cocaine- and cannabis-dependent patients. Using data gathered from two separate clinical studies for treatment of cocaine dependence and cannabis dependence, 130 cannabis-dependent and 112 cocaine-dependent individuals were compared on milestones related to their substance use. In cannabis- vs. cocaine-dependent patients, the mean age of first use, regular use and first treatment contact differed significantly. No statistically significant differences were found between the two groups for other measured milestones. These results differ from most epidemiologic studies that suggest cocaine users progress more rapidly to regular use and treatment contact. Horey JT, Mariani JJ, Cheng WY, Bisaga A, Sullivan M, Nunes E, Levin FR. Comparison of substance use milestones in cannabis- and cocaine-dependent patients. J Addict Dis 2012 Jan; (1): 60-66.

**Subjective, Cognitive and Cardiovascular Dose-Effect Profile of Nabilone and Dronabinol in Marijuana Smokers** Marijuana dependence is a substantial public health problem, with existing treatments showing limited efficacy. In laboratory and clinical studies, the cannabinoid receptor 1 agonist oral Δ9tetrahydrocannabinol (THC; dronabinol) has been shown to decrease marijuana withdrawal but not relapse. Dronabinol has poor bioavailability, potentially contributing to its failure to decrease relapse. The synthetic THC analogue, nabilone, has better bioavailability than dronabinol. The authors therefore aimed to characterize nabilone's behavioral and physiological effects across a range of acute doses in current marijuana smokers and compare these with dronabinol's effects. Participants (4 female; 10 male) smoking marijuana 6.6 (standard deviation=0.7) days/week completed this outpatient, within-subjects, double-blind, randomized protocol. Over seven sessions, the time-dependent subjective, cognitive and cardiovascular effects of nabilone (2, 4, 6, 8 mg), dronabinol (10, 20 mg) and placebo were assessed. Nabilone (4, 6, 8 mg) and dronabinol (10, 20 mg) increased ratings of feeling a good effect, a strong effect and/or 'high' relative to placebo; nabilone had a slower onset of peak subjective effects than dronabinol. Nabilone (6, 8 mg) modestly lowered psychomotor speed relative to placebo and dronabinol. There were dose-dependent increases in heart rate after nabilone, and nabilone (2 mg) and dronabinol (10 mg) decreased systolic blood pressure. Thus, nabilone produced sustained, dose-related increases in positive mood, few cognitive decrements and lawful cardiovascular alterations. It had a longer time to peak effects than dronabinol, and effects were more dose-related, suggesting improved bioavailability. Nabilone was well tolerated

by marijuana smokers, supporting further testing as a potential medication for marijuana dependence. Bedi G, Cooper ZD, Haney M. Subjective, cognitive and cardiovascular dose-effect profile of nabilone and dronabinol in marijuana smokers. Addict Biol 2012 Jan; [Epub ahead of print].

**A Proof-of-Concept Randomized Controlled Study of Gabapentin: Effects on Cannabis use, Withdrawal and Executive Function Deficits in Cannabis-Dependent Adults**
There are no FDA-approved pharmacotherapies for cannabis dependence. Cannabis is the most widely used illicit drug in the world, and patients seeking treatment for primary cannabis dependence represent 25% of all substance use admissions. The authors conducted a phase IIa proof-of-concept pilot study to examine the safety and efficacy of a calcium channel/GABA modulating drug, gabapentin, for the treatment of cannabis dependence. A 12-week, randomized, double-blind, placebo-controlled clinical trial was conducted in 50 unpaid treatment-seeking male and female outpatients, aged 18-65 years, diagnosed with current cannabis dependence. Subjects received either gabapentin (1200 mg/day) or matched placebo. Manual-guided, abstinence-oriented individual counseling was provided weekly to all participants. Cannabis use was measured by weekly urine toxicology and by self-report using the Timeline Followback Interview. Cannabis withdrawal symptoms were assessed using the Marijuana Withdrawal Checklist. Executive function was measured using subtests from the Delis-Kaplan Executive Function System. Relative to placebo, gabapentin significantly reduced cannabis use as measured both by urine toxicology ($p=0.001$) and by the Timeline Followback Interview ($p=0.004$), and significantly decreased withdrawal symptoms as measured by the Marijuana Withdrawal Checklist ($p<0.001$). Gabapentin was also associated with significantly greater improvement in overall performance on tests of executive function ($p=0.029$). This POC pilot study provides preliminary support for the safety and efficacy of gabapentin for treatment of cannabis dependence that merits further study, and provides an alternative conceptual framework for treatment of addiction aimed at restoring homeostasis in brain stress systems that are dysregulated in drug dependence and withdrawal. Mason BJ, Crean R, Goodell V, Light JM, Quello S, Shadan F, Buffkins K, Kyle M, Adusumalli M, Begovic A, Rao S. A Proof-of-Concept Randomized Controlled Study of Gabapentin: Effects on Cannabis Use, Withdrawal and Executive Function Deficits in Cannabis-Dependent Adults. Neuropsychopharmacology 2012 Feb; [Epub ahead of print].

**A Dimensional Approach to Understanding Severity Estimates and Risk Correlates of Marijuana Abuse and Dependence in Adults** While item response theory (IRT) research shows a latent severity trait underlying response patterns of substance abuse and dependence symptoms, little is known about IRT-based severity estimates in relation to clinically relevant measures. In response to increased prevalences of marijuana-related treatment admissions, an elevated level of marijuana potency, and the debate on medical marijuana use, the authors applied dimensional approaches to understand IRT-based severity estimates for marijuana use disorders (MUDs) and their correlates while simultaneously considering gender- and race/ethnicity-related differential item functioning (DIF). Using adult data from the 2008 National Survey on Drug Use and Health (N=37,897), Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for MUDs among past-year marijuana users were examined by IRT, logistic regression, and multiple indicators-multiple causes (MIMIC) approaches. Among 6917 marijuana users, 15% met criteria for a MUD; another 24% exhibited

subthreshold dependence. Abuse criteria were highly correlated with dependence criteria (correlation=0.90), indicating unidimensionality; item information curves revealed redundancy in multiple criteria. MIMIC analyses showed that MUD criteria were positively associated with weekly marijuana use, early marijuana use, other substance use disorders, substance abuse treatment, and serious psychological distress. African Americans and Hispanics showed higher levels of MUDs than Whites, even after adjusting for race/ethnicity-related DIF. The redundancy in multiple criteria suggests an opportunity to improve efficiency in measuring symptom-level manifestations by removing low-informative criteria. Elevated rates of MUDs among African Americans and Hispanics require research to elucidate risk factors and improve assessments of MUDs for different racial/ethnic groups. Wu LT, Woody GE, Yang C, Pan JJ, Reeve BB, Blazer DG. A dimensional approach to understanding severity estimates and risk correlates of marijuana abuse and dependence in adults. Int J Methods Psychiatr Res 2012 Feb; [Epub ahead of print].

**Immunotherapy for Drug Abuse** Substance use disorders continue to be major medical and social problems worldwide. Current medications for substance use disorders have many limitations such as cost, availability, medication compliance, dependence, diversion of some to illicit use and relapse to addiction after discontinuing their use. Immunotherapies using either passive monoclonal antibodies or active vaccines have distinctly different mechanisms and therapeutic utility from small molecule approaches to treatment. They have great potential to help the patient achieve and sustain abstinence and have fewer of the above limitations. This review covers the cocaine vaccine development in detail and provides an overview of directions for developing anti-addiction vaccines against the abuse of other substances. The notable success of the first placebo-controlled clinical trial of a cocaine vaccine, TA-CD, has led to an ongoing multi-site, Phase IIb clinical trial in 300 subjects. The results from these trials are encouarging further development of the cocaine vacine as one of the first anti-addiction vaccines to go forward to the U.S. Food and Drug Administration for review and approval for human use. Shen X, Kosten TR. Immunotherapy for drug abuse. CNS Neurol Disord Drug Targets 2011 Dec; (8): 876-879.

**Nicotine Vaccines** Smoking is a global healthcare problem. Current smoking cessation rates using behavioral counseling and pharmacotherapeutic interventions have had modest success, with ~1:5 smokers remaining abstinent long-term. Nicotine vaccines are a new class of immunotherapeutics under development. It is believed that anti-nicotine antibodies arising from vaccination capture nicotine and prevent or reduce its entry into the brain, as the antibody-bound nicotine is too large to cross the blood-brain barrier. This in turn decreases the pleasurable effects of smoking, reducing or eliminating positive reinforcement, thereby making it easier for a smoker to quit smoking. Four vaccine candidates have advanced into clinical testing with mixed success. Proof-of-concept has been established in that individuals with higher levels of anti-nicotine antibodies were observed to have higher smoking cessation and abstinence rates. Recently, the most advanced candidate vaccine, NicVAX, failed to meet the primary endpoint in two large phase III studies, although the correlation of higher abstinence rates in subjects with higher immunity to nicotine was observed. Although the field has had setbacks, the magnitude of the tobacco epidemic and the positive pre-clinical research and observed clinical trends indicate continued research is warranted. Several avenues are being actively pursued: a) improving vaccine potency by introducing novel carriers and/or adjuvants to stimulate higher immune response b) targeting subjects who have a robust response (e.g. personalized medicine) c)

combining vaccines with pharmacotherapy for maintenance of abstinence/relapse prevention. Fahim RE, Kessler PD, Fuller SA, Kalnik MW. Nicotine vaccines. CNS Neurol Disord Drug Targets 2011 Dec; (8): 905-915.

**Neonatal Abstinence Syndrome** This review discusses the complex nature of maternal and other factors that can affect the infant's display of neonatal abstinence syndrome (NAS), clinical presentation and treatment of NAS, and the impact of recent findings on future directions for research. NAS has traditionally been described as a constellation of signs/symptoms displayed by the neonate upon withdrawal of gestational opioid exposure; however, recent research has advanced our understanding of this disorder. Other psychoactive substances, such as increasingly prescribed serotonin reuptake inhibitors, may produce an independent or synergistic discontinuation syndrome. The wide variability in NAS presentation has generated interest in the interplay of prenatal and postnatal environmental and genetic factors that may moderate or mediate its expression. Finally, recent advances in the treatment of opioid-dependent pregnant women have suggested buprenorphine as an alternative treatment to methadone during pregnancy, largely due to reduced NAS severity in exposed neonates. Physicians should be aware of the complexity of the maternal, fetal, and infant factors that combine to create the infant's display of NAS, and incorporate these aspects into comprehensive assessment and care of the dyad. Further research regarding the pathophysiology and treatment of NAS is warranted. Jansson LM, Velez M. Neonatal abstinence syndrome. Curr Opin Pediatr 2012 Apr; (2): 252-258.

**Topiramate for the Treatment of Methamphetamine Addiction: A Multi-Center Placebo-Controlled Trial** Topiramate has shown efficacy at facilitating abstinence from alcohol and cocaine abuse. This double-blind, placebo-controlled out-patient trial tested topiramate for treating methamphetamine addiction. Participants (n=140) were randomized to receive topiramate or placebo (13 weeks) in escalating doses from 50 mg/day to the target maintenance of 200 mg/day in weeks 6-12 (tapered in week 13). Medication was combined with weekly brief behavioral compliance enhancement treatment. The trial was conducted at eight medical centers in the United States. One hundred and forty methamphetamine-dependent adults took part in the trial. The primary outcome was abstinence from methamphetamine during weeks 6-12. Secondary outcomes included use reduction versus baseline, as well as psychosocial variables. In the intent-to-treat analysis, topiramate did not increase abstinence from methamphetamine during weeks 6-12. For secondary outcomes, topiramate reduced weekly median urine methamphetamine levels and observer-rated severity of dependence scores significantly. Subjects with negative urine before randomization (n=26) had significantly greater abstinence on topiramate versus placebo during study weeks 6-12. Topiramate was safe and well tolerated. Topiramate does not appear to promote abstinence in methamphetamine users but can reduce the amount taken and reduce relapse rates in those who are already abstinent. Elkashef A, Kahn R, Yu E, Iturriaga E, Li SH, Anderson A, Chiang N, Ait-Daoud N, Weiss D, McSherry F, Serpi T, Rawson R, Hrymoc M, Weis D, McCann M, Pham T, Stock C, Dickinson R, Campbell J, Gorodetzky C, Haning W, Carlton B, Mawhinney J, Li MD, Johnson BA. Topiramate for the treatment of methamphetamine addiction: a multi-center placebo-controlled trial. Addiction 2011 Dec; [Epub ahead of print].

**A Double-Blind, Placebo-Controlled Trial of the NMDA Glycine Site Antagonist, GW468816, for Prevention of Relapse to Smoking in Females** Relapse to smoking is common after initial abstinence with pharmacotherapy and behavioral support and represents a major clinical challenge. Although mechanisms underlying relapse to smoking have not been elucidated, preclinical studies suggest that glutamate receptors may be involved. The authors sought to test a selective antagonist of the glycine coagonist site on the glutamate N-methyl-D-aspartate receptor, GW468816, for prevention of relapse in recently abstinent smokers. To do so, they enrolled 264 healthy female smokers in an open 8-week smoking cessation intervention with behavioral therapy and a standard dose of transdermal nicotine replacement therapy with taper and additional gum or lozenge as needed for nicotine withdrawal symptoms. Ninety-eight participants achieved 7-day point prevalence abstinence and were randomized into a 5-week double-blind, placebo-controlled, relapse-prevention trial of GW468816 (200 mg/d) and then followed for 60 days after randomization. There was no effect of treatment on abstinence rates at the end of treatment ($\chi^2$ [1, n = 96] = 0.168, P = 0.838), on the rates of relapse ($\chi^2$ [1, n = 98] = 0.031, P = 1.000) or lapse ($\chi^2$ [1, n = 62] = 0.802, P = 0.423), or on time to relapse ($\chi^2$ [1, n = 98) = 0.001, P = 0.972). No significant relationships were detected between plasma GW468816 concentrations and abstinence, time to relapse, or self-reported craving. In conclusion, despite promising preclinical data that support the use of a selective NMDA glycine site antagonist for prevention of relapse to smoking, the authors observed no effect of GW468816 on relapse or lapse rates, time to relapse, or craving compared to placebo. Evins AE, Pachas G, Mischoulon D, Urbanoski K, Carlini S, Sousa J, Bentley K, Rigotti NA, Nino-Gomez J, Loebl T, Janes AC, Kaufman MJ, Fava M. A double-blind, placebo-controlled trial of the NMDA glycine site antagonist, GW468816, for prevention of relapse to smoking in females. J Clin Psychopharmacol 2011 Oct; (5): 597-602.

**Effects of Cumulative Stress and Impulsivity on Smoking Status** The stress-vulnerability model of addiction predicts that environmental factors, such as cumulative stress, will result in individual adaptations that decrease self-control, increase impulsivity, and increase risk for addiction. Impulsivity and cumulative stress are risk factors for tobacco smoking that are rarely examined simultaneously in research. The authors examined the indirect and direct effects of cumulative adversity in a community sample consisting of 291 men and women who participated in an assessment of cumulative stress, self-reported impulsivity, and smoking history. Data were analyzed using bootstrapping techniques to estimate indirect effects of stress on smoking via impulsivity. Cumulative adversity is associated with smoking status via direct effects and indirect effects through impulsivity scores. Additional models examining specific types of stress indicate contributions of traumatic stress and recent life events as well as chronic relationship stressors. Overall, cumulative stress is associated with increased risk of smoking via increased impulsivity and via pathways independent of impulsivity. These findings support the stress-vulnerability model and highlight the utility of mediation models in assessing how, and for whom, cumulative stress increases risk of current cigarette smoking. Increasing self-control is a target for interventions with individuals who have experienced cumulative adversity. Ansell EB, Gu P, Tuit K, Sinha R. Effects of cumulative stress and impulsivity on smoking status. Hum Psychopharmacol 2012 Mar; (2): 200-208.

**Pharmacogenetic Association of the Galanin Receptor (GALR1) SNP rs2717162 with Smoking Cessation** Galanin modulates dopaminergic neurotransmission in the mesolimbic dopamine system, thereby influencing the rewarding effects of nicotine. Variants in the galanin receptor 1 (GALR1) gene have been associated with retrospective craving severity and heaviness of smoking in prior research. The authors investigated pharmacogenetic associations of the previously studied GALR1 polymorphism, rs2717162, in 1217 smokers of European ancestry who participated in one of three pharmacogenetic smoking cessation clinical trials and were treated with nicotine patch (n=623), nicotine nasal spray (n=189), bupropion (n=213), or placebo (n=192). The primary endpoint was abstinence (7-day point prevalence, biochemically confirmed) at the end of treatment. Cravings to smoke were assessed on the target quit day (TQD). The longitudinal regression model revealed a significant genotype by treatment interaction (P=0.03). There was a reduced odds of quitting success with the presence of at least one minor (C) allele in the bupropion-treated group (OR=0.43; 95% CI=0.22-0.77; P=0.005) but equivalent quit rates by genotype in the nicotine-replacement therapy groups. This genotype by treatment interaction was reproduced in a Cox regression model of time to relapse (P=0.04). In the bupropion trial, smokers carrying the C allele also reported more severe TQD cravings. Further research to identify functional variants in GALR1 and to replicate pharmacogenetic associations is warranted. Gold AB, Wileyto EP, Lori A, Conti D, Cubells JF, Lerman C. Pharmacogenetic Association of the Galanin Receptor (GALR1) SNP rs2717162 with Smoking Cessation. Neuropsychopharmacology 2012 Feb; [Epub ahead of print].

**Neural Correlates of Stress-Induced and Cue-Induced Drug Craving: Influences of Sex and Cocaine Dependence** Although stress and drug cue exposure each increase drug craving and contribute to relapse in cocaine dependence, no previous research has directly examined the neural correlates of stress-induced and drug cue-induced craving in cocaine-dependent women and men relative to comparison subjects. Functional MRI was used to assess responses to individualized scripts for stress, drug/alcohol cue and neutral-relaxing-imagery conditions in 30 abstinent cocaine-dependent individuals (16 women, 14 men) and 36 healthy recreational-drinking comparison subjects (18 women, 18 men). Significant three-way interactions between diagnostic group, sex, and script condition were observed in multiple brain regions including the striatum, insula, and anterior and posterior cingulate. Within women, group-by-condition interactions were observed involving these regions and were attributable to relatively increased regional activations in cocaine-dependent women during the stress and, to a lesser extent, neutral-relaxing conditions. Within men, group main effects were observed involving these same regions, with cocaine-dependent men demonstrating relatively increased activation across conditions, with the main contributions from the drug and neutral-relaxing conditions. In men and women, subjective drug-induced craving measures correlated positively with corticostriatal-limbic activations. In cocaine dependence, corticostriatal-limbic hyperactivity appears to be linked to stress cues in women, drug cues in men, and neutral-relaxing conditions in both. These findings suggest that sex should be taken into account in the selection of therapies in the treatment of addiction, particularly those targeting stress reduction. Potenza MN, Hong KI, Lacadie CM, Fulbright RK, Tuit KL, Sinha R. Neural correlates of stress-induced and cue-induced drug craving: influences of sex and cocaine dependence. Am J Psychiatry 2012 Jan. [Epub ahead of print].

**Pharmacogenetics of Smoking Cessation: Role of Nicotine Target and Metabolism Genes** Many smokers attempt to quit smoking but few are successful in the long term. The heritability of nicotine addiction and smoking relapse have been documented, and research is focused on identifying specific genetic influences on the ability to quit smoking and response to specific medications. Research in genetically modified cell lines and mice has identified nicotine acetylcholine receptor subtypes that mediate the pharmacological and behavioral effects of nicotine sensitivity and withdrawal. Human genetic association studies have identified single nucleotide polymorphisms (SNPs) in genes encoding nicotine acetylcholine receptor subunits and nicotine metabolizing enzymes that influence smoking cessation phenotypes. There is initial promising evidence for a role in smoking cessation for SNPs in the β2 and α5/α3/β4 nAChR subunit genes; however, effects are small and not consistently replicated. There are reproducible and clinically significant associations of genotypic and phenotypic measures of CYP2A6 enzyme activity and nicotine metabolic rate with smoking cessation as well as response to nicotine replacement therapies and bupropion. Prospective clinical trials to identify associations of genetic variants and gene-gene interactions on smoking cessation are needed to generate the evidence base for both medication development and targeted therapy approaches based on genotype. Gold AB, Lerman C. Pharmacogenetics of smoking cessation: role of nicotine target and metabolism genes. Hum Genet 2012 Jan. [Epub ahead of print].

**Effects of Pregabalin on Smoking Behavior, Withdrawal Symptoms, and Cognitive Performance in Smokers** In preclinical and clinical studies, medications enhancing the GABA neurotransmission attenuate nicotine reward. Pregabalin, a GABA analogue, presumably interacts with brain glutamate and GABA neurotransmission. The goal of this study was to determine pregabalin's effects on smoking behavior, nicotine withdrawal, craving for cigarettes, and cognitive performance. Twenty-four smokers participated in an outpatient double-blind, placebo-controlled, crossover study. Subjects had a 4-day treatment period with either pregabalin (300 mg/day) or placebo and following a washout period were then crossed over for 4 days to the other treatment. In each treatment period, starting at midnight of day 1, participants were asked to stop smoking until the experimental session on day 4. During the experimental session measures of ad lib smoking behavior, tobacco withdrawal, craving for cigarettes, and cognitive performance were obtained. Pregabalin treatment, compared to placebo, did not reduce the smoking behavior during the first 3 days of treatment or during ad lib smoking period. Pregabalin treatment attenuated some tobacco withdrawal symptoms including ratings of anxious, irritable, and frustrated in abstinent smokers. Pregabalin treatment also attenuated the subjective ratings of "liking" in response to smoking. Under pregabalin treatment, smokers made more errors in a sustained attention task. These findings provide limited support for pregabalin as a treatment for nicotine addiction. Herman AI, Waters AJ, McKee SA, Sofuoglu M. Effects of pregabalin on smoking behavior, withdrawal symptoms, and cognitive performance in smokers. Psychopharmacology (Berl) 2012 Apr; (3): 611-617.

**Translational and Reverse Translational Research on the Role of Stress in Drug Craving and Relapse** High relapse rates during abstinence are a pervasive problem in drug addiction treatment. Relapse is often associated with stress exposure, which can provoke a subjective state of drug craving that can also be demonstrated under controlled laboratory conditions. Stress-induced relapse and craving in humans can be modeled in mice, rats, and monkeys using a reinstatement model in which drug-taking behaviors are extinguished and then reinstated by

acute exposure to certain stressors. Studies using the reinstatement model in rats have identified the role of several neurotransmitters and brain sites in stress-induced reinstatement of drug seeking, but the degree to which these preclinical findings are relevant to the human condition is largely unknown. Here, the authors address this topic by discussing recent results on the effect of alpha-2 adrenoceptors and substance P-NK1 receptor antagonists on stress-induced reinstatement in mice and rats and stress-induced craving and potentially stress-induced relapse in humans. They also discuss brain sites and circuits involved in stress-induced reinstatement of drug seeking in rats and those activated during stress-induced craving in humans. There is evidence that alpha-2 adrenoceptor agonists and NK1 receptor antagonists decrease stress-induced drug seeking in rats and stress-induced craving in humans. Whether these drugs would also prevent stress-induced drug relapse in humans and whether similar or different brain mechanisms are involved in stress-induced reinstatement in non-humans and stress-induced drug craving and relapse in humans are subjects for future research. Sinha R, Shaham Y, Heilig M. Translational and reverse translational research on the role of stress in drug craving and relapse. Psychopharmacology (Berl) 2011 Nov; (1): 69-82.

**μ-Opioid Receptor Availability in the Amygdala is Associated with Smoking for Negative Affect Relief**: The perception that smoking relieves negative affect contributes to smoking persistence. Endogenous opioid neurotransmission, and the μ-opioid receptor (MOR) in particular, plays a role in affective regulation and is modulated by nicotine. The authors examined the relationship of MOR binding availability in the amygdala to the motivation to smoke for negative affect relief and to the acute effects of smoking on affective responses. Twenty-two smokers were scanned on two separate occasions after overnight abstinence using [(11)C]carfentanil positron emission tomography imaging: after smoking a nicotine-containing cigarette and after smoking a denicotinized cigarette. Self-reports of smoking motives were collected at baseline, and measures of positive and negative affect were collected pre- and post-cigarette smoking. Higher MOR availability in the amygdala was associated with motivation to smoke to relieve negative affect. However, MOR availability was unrelated to changes in affect after smoking either cigarette. Increased MOR availability in amygdala may underlie the motivation to smoke for negative affective relief. These results are consistent with previous data highlighting the role of MOR neurotransmission in smoking behavior. Falcone M, Gold AB, Wileyto EP, Ray R, Ruparel K, Newberg A, Dubroff J, Logan J, Zubieta JK, Blendy JA, Lerman C. μ-Opioid receptor availability in the amygdala is associated with smoking for negative affect relief. Psychopharmacology (Berl) 2012 Mar. [Epub ahead of print].

**Smoking Cessation Pharmacogenetics: Analysis of Varenicline and Bupropion in Placebo-Controlled Clinical Trials** Despite effective therapies for smoking cessation, most smokers find quitting difficult and most successful quitters relapse. Considerable evidence supports a genetic risk for nicotine dependence; however, less is known about the pharmacogenetics of smoking cessation. In the first pharmacogenetic investigation of the efficacy of varenicline and bupropion, the asuthors examined whether genes important in the pharmacodynamics and pharmacokinetics of these drugs and nicotine predict medication efficacy and adverse events. Subjects participated in randomized, double-blind, placebo-controlled smoking cessation clinical trials, comparing varenicline, a nicotinic acetylcholine receptor (nAChR) partial agonist, with bupropion, a norepinephrine/dopamine reuptake inhibitor, and placebo. Primary analysis included 1175 smokers of European ancestry, and 785 single nucleotide polymorphisms from 24

genes, representing 254 linkage disequilibrium (LD) bins (genes included nAChR subunits, additional varenicline-specific genes, and genes involved in nicotine or bupropion metabolism). For varenicline, continuous abstinence (weeks 9-12) was associated with multiple nAChR subunit genes (including CHRNB2, CHRNA5, and CHRNA4) (OR=1.76; 95% CI: 1.23-2.52) ($p<0.005$); for bupropion, abstinence was associated with CYP2B6 (OR=1.78; 95% CI: 1.27-2.50) ($p<0.001$). Incidence of nausea was associated with several nAChR subunit genes (OR=0.50; 95% CI: 0.36-0.70) ($p<0.0001$) and time to relapse after quitting was associated with HTR3B (HR=1.97; 95% CI: 1.45-2.68) ($p<0.0001$). These data provide evidence for multiple genetic loci contributing to smoking cessation and therapeutic response. Different loci are associated with varenicline vs. bupropion response, suggesting that additional research may identify clinically useful markers to guide treatment decisions. King DP, Paciga S, Pickering E, Benowitz NL, Bierut LJ, Conti DV, Kaprio J, Lerman C, Park PW. Smoking cessation pharmacogenetics: analysis of varenicline and bupropion in placebo-controlled clinical trials. Neuropsychopharmacology 2012 Feb; (3): 641-650.

**Blunted Vagal Reactivity Predicts Stress-Precipitated Tobacco Smoking** Long-term smoking can lead to changes in autonomic function, including decreased vagal tone and altered stress responses. One index of the inability to adapt to stress may be blunted vagal reactivity. Stress is a primary mechanism involved in relapse to smoking, but mechanisms leading to stress-precipitated relapse are not well understood. Using an experimental paradigm of stress-precipitated smoking behavior, the authors examined whether autonomic reactivity mediates the relationship between stress and smoking. High-frequency heart rate variability (HF-HRV), a putative measure of vagal tone, and the ratio of low-to-high frequency HRV (LF/HF), a measure of sympathovagal balance, were assessed. Using a within-subjects design, 32 nicotine-dependent, 15-h abstinent smokers (a subgroup from McKee et al. (J Psychopharmacol 25(4):490-502, 2011)) were exposed to individualized script-driven imagery of stressful and relaxing scenarios and assessed on the ability to resist smoking and subsequent ad-lib smoking. HRV was monitored throughout each laboratory session (maximum 60 min following imagery).As expected, stress and ad-lib smoking additively decreased HF-HRV and increased LF/HF. Blunted stress-induced HF-HRV responses reflecting decreased vagal reactivity were associated with less time to initiate smoking and increased craving relief and reinforcement from smoking. These relationships were specific to HF-HRV following stress as neither baseline HF-HRV, HF-HRV following relaxing imagery, or LF/HF predicted smoking behavior. The current findings are the first to experimentally demonstrate that stress-precipitated decreased vagal reactivity predicts the ability to resist smoking. Findings suggest that strategies that normalize vagal reactivity in early abstinent smokers may lead to improved smoking cessation outcomes. Ashare RL, Sinha R, Lampert R, Weinberger AH, Anderson GM, Lavery ME, Yanagisawa K, McKee SA. Blunted vagal reactivity predicts stress-precipitated tobacco smoking. Psychopharmacology (Berl) 2012 Mar; (2): 259-268.

**Association Between CHRNA5 Genetic Variation at Rs16969968 and Brain Reactivity to Smoking Images in Nicotine Dependent Women** Tobacco smoking is the leading preventable cause of death in the developed world. Identifying risk factors for smoking may lead to more effective treatments. Genome wide association studies revealed a relationship between development of nicotine dependence and a single-nucleotide polymorphism (SNP, rs16969968) of the nicotine acetylcholine receptor (nAChR) alpha-5 subunit gene (CHRNA5). The

relationship between this SNP and other factors contributing to smoking behavior such as smoking cue reactivity is unclear. The authors assessed the role of rs16969968 on brain functional MRI (fMRI) reactivity to smoking cues by studying nicotine dependent women with the nicotine dependence 'risk' allele (A allele, N=14) and without the 'risk' allele (G/G smokers, N=10). Nicotine dependence severity, as assessed with the Fagerstrom test for nicotine dependence, smoking pack-years, and expired carbon monoxide levels, were equivalent in these groups. They observed a group difference in fMRI reactivity; women without the A allele (G/G smokers) showed greater fMRI reactivity to smoking images in brain areas related to memory and habitual behavior such as the hippocampus and dorsal striatum. These finding suggest that nicotine-dependent smokers lacking the rs16969968 A allele are more likely to recall smoking-related memories and engage in habitual responding to smoking cues than A allele smokers. Although more studies are necessary to determine the mechanism underlying and significance of this cue reactivity difference, these data suggest that smokers may develop and remain nicotine dependent due to different factors including genetics and cue reactivity. This finding may have implications for personalizing smoking treatment. Janes AC, Smoller JW, David SP, Frederick BD, Haddad S, Basu A, Fava M, Evins AE, Kaufman MJ. Association between CHRNA5 genetic variation at rs16969968 and brain reactivity to smoking images in nicotine dependent women. Drug Alcohol Depend 2012 Jan; (1-3): 7-13.

**Varenicline as a Smoking Cessation Aid in Schizophrenia: Effects on Smoking Behavior and Reward Sensitivity** Smoking rates are up to five times higher in people with schizophrenia than in the general population, placing these individuals at high risk for smoking-related health problems. Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, is a promising aid for smoking cessation in this population. To maximize treatment efficacy while minimizing risks, it is critical to identify reliable predictors of positive response to varenicline in smokers with schizophrenia. Negative symptoms of schizophrenia are related to dysfunctions in the brain reward system, are associated with nicotine dependence, and may be improved by nicotine or nicotinic receptor agonists, suggesting that smoking cessation may be especially difficult for patients with substantial negative symptoms. The purpose of the study was to evaluate negative symptoms as predictors of response to varenicline. Patients with schizophrenia (N=53) completed a 12-week smoking cessation trial combining varenicline with cognitive behavioral therapy. Negative symptoms were assessed via the Scale for the Assessment of Negative Symptoms (Andreasen 1983). Outcomes included smoking abstinence as assessed by self-report and expired carbon monoxide. Change in performance on a probabilistic reward task was used as an index of change in reward sensitivity during treatment. At week 12, 32 participants met criteria for 14-day point-prevalence abstinence. Patients with lower baseline symptoms of affective flattening (more typical affect) were more likely to achieve smoking abstinence and demonstrated larger increases in reward sensitivity during treatment. These data suggest that affective flattening symptoms in smokers with schizophrenia may predict response to varenicline. Dutra SJ, Stoeckel LE, Carlini SV, Pizzagalli DA, Evins, AE. Varenicline as a smoking cessation aid in schizophrenia: effects on smoking behavior and reward sensitivity. Psychopharmacology (Berl) 2012 Jan; (1):25-34.

**Dopamine D4 Receptor Gene Variation Moderates the Efficacy of Bupropion for Smoking Cessation** Smokers (≥10 cigarettes per day, N=331) of European ancestry taking part in a double-blind placebo-controlled randomized trial of 12 weeks of treatment with bupropion along with counseling for smoking cessation were genotyped for a variable number of tandem repeats polymorphism in exon III of the dopamine D4 receptor gene. Generalized estimating equations predicting point-prevalence abstinence at end of treatment and 2, 6 and 12 months after the end of treatment indicated that bupropion (vs placebo) predicted increased odds of abstinence. The main effect of Genotype was not significant. A Genotype × Treatment interaction (P=0.005) showed that bupropion predicted increased odds of abstinence in long-allele carriers (odds ratios (OR)=1.31, P<0.0001), whereas bupropion was not associated with abstinence among short-allele homozygotes (OR=1.06, P=0.23). The Genotype × Treatment interaction remained when controlling for demographic and clinical covariates (P=0.01) and in analyses predicting continuous abstinence (P's≤0.054). Bupropion may be more efficacious for smokers who carry the long allele, which is relevant to personalized pharmacogenetic treatment approaches. Leventhal AM, David SP, Brightman M, Strong D, McGeary JE, Brown RA, Lloyd-Richardson EE, Munafò M, Uhl GR, Niaura R. Dopamine D4 receptor gene variation moderates the efficacy of bupropion for smoking cessation. Pharmacogenomics J 2012 Feb; (1): 86-92.

**Immune System Inflammation In Cocaine Dependent Individuals: Implications For Medications Development** Cocaine dependence is a chronic stress state. Furthermore, both stress and substance abuse have robust and reciprocal effects on immune system cytokines, which are known to be powerful modulators of mood. The authors therefore examine basal and provoked changes in peripheral cytokines in cocaine dependent individuals to better understand their role in the negative reinforcing effects of cocaine. Twenty-eight (16F/12M) treatment-seeking cocaine dependent individuals and 27 (14F/13M) social drinkers were exposed to three 5-min guided imagery conditions (stress, drug cue, relaxing) presented randomly across consecutive days. Measures of salivary cortisol, tumor necrosis factor alpha (TNFα), interleukin-10 (IL-10), and interleukin-1 receptor antagonist (IL-1ra) were collected at baseline and various post-imagery time-points. Cocaine abusers demonstrated decreased basal IL-10 compared with social drinkers. They also showed significant elevations in pro-inflammatory TNFα when exposed to stress compared with when they were exposed to relaxing imagery. This was not observed in the social drinkers. Conversely, social drinkers demonstrated increases in the anti-inflammatory markers, IL-10 and IL-1ra, following exposure to cue, which were not seen in the dependent individuals. Cocaine dependent individuals demonstrate an elevated inflammatory state both at baseline and following exposure to the stress imagery condition. Cytokines may reflect potentially novel biomarkers in addicted populations for treatment development. Fox HC, D'Sa C, Kimmerling A, Siedlarz KM, Tuit KL, Stowe R, Sinha R. Immune system inflammation in cocaine dependent individuals: implications for medications development. Hum Psychopharmacol 2012 Mar; (2): 156-166.

**Evaluation of the Effects of Rivastigmine on Cigarette Smoking by Methamphetamine-Dependent Volunteers** Compared to smokers alone, smokers with co-morbid substance use disorders are at greater risk of suffering from smoking-related death. Despite this, relatively few studies have examined smoking cessation treatments for those with stimulant dependence. In the current study, the authors sought to evaluate the effects produced by short-term exposure to the cholinesterase inhibitor rivastigmine (0, 3 or 6 mg) on cigarette smoking in non-treatment-

seeking, methamphetamine-dependent volunteers. This was a double-blind, placebo-controlled, crossover study that took place over 9 days. The data indicate that rivastigmine treatment did not alter Fagerström Test for Nicotine Dependence scores, carbon monoxide readings, or cigarettes smoked per day, but a trend toward reduced urges to smoke ($p<0.09$) was detected during treatment with rivastigmine 3mg. These data, while preliminary, indicate that cholinesterase inhibitors warrant consideration as treatments for nicotine dependence, including use in stimulant-dependent individuals who exhibit significantly higher rates of smoking than the general population. De la Garza R, Yoon JH. Evaluation of the effects of rivastigmine on cigarette smoking by methamphetamine-dependent volunteers. Prog Neuropsychopharmacol Biol Psychiatry 2011 Dec; (8): 1827-1830.

**Varenicline Versus Bupropion Xl for Smoking Cessation in Older Adolescents: A Randomized, Double-Blind Pilot Trial** Despite tremendous potential public health impact, little work has focused on development of evidence-based smoking cessation treatments for adolescents, including pharmacotherapies. No prior studies have explored the feasibility and safety of varenicline and bupropion XL, 2 potentially promising pharmacotherapies, as smoking cessation treatments in adolescents.Treatment-seeking older adolescent smokers (ages 15-20) were randomized (double-blind) to varenicline (n = 15) or bupropion XL (n = 14), with 1-week titration and active treatment for 7 weeks. Structured safety, tolerability, and efficacy assessments (cotinine-confirmed 7-day point prevalence abstinence) were conducted weekly. There were no serious adverse events. Two participants discontinued bupropion XL due to adverse effects, and none discontinued varenicline. Over the course of treatment, participants receiving varenicline reduced from 14.1 ± 6.3 (mean ± SD) to 0.9 ± 2.1 cigarettes/day (CPD, 4 achieved abstinence), while those receiving bupropion XL reduced from 15.8 ± 4.4 to 3.1 ± 4.0 CPD (2 achieved abstinence). These preliminary results support the feasibility and safety of conducting adequately powered, placebo-controlled efficacy studies of varenicline and bupropion XL for adolescent smoking cessation. Gray KM, Carpenter MJ, Lewis AL, Klintworth EM, Upadhyaya HP. Varenicline versus bupropion XL for smoking cessation in older adolescents: A randomized, double-blind pilot trial. Nicotine Tob Res 2012 Feb; (2): 234-239.

**A Placebo Controlled Trial Of Memantine As An Adjunct To Oral Naltrexone For Opioid Dependence** Preclinical findings suggest that the inhibition of NMDA glutamatergic neurotransmission may have beneficial effects in the treatment of opioid dependence. The authors hypothesized that memantine, a low-potency, uncompetitive NMDA receptor antagonist, would be safe and effective when used as an adjunct to oral naltrexone in the treatment of opioid dependence, particularly in preventing relapse to opiate use in detoxified individuals. Opioid-dependent participants (N=112) were enrolled. Following detoxification all participants were inducted onto oral naltrexone and were randomized to receive memantine 15 mg bid (N=27), memantine 30 mg bid (N=27) or placebo (N=27) for 12-weeks in combination with naltrexone 50mg/day and individual relapse-prevention therapy. The primary outcome was the retention in treatment since treatment dropout is most commonly associated with relapse to opiate use. Twenty-six percent of participants withdrew from treatment prior to starting naltrexone. Of those that were randomized 35% completed 4 weeks only, and 24% completed all 12 weeks of treatment. There was no significant difference in treatment retention or heroin use, opiate withdrawal symptoms and craving between the groups treated with memantine vs. placebo. Thus, the efficacy of memantine 30 or 60 mg/day as an adjunct to oral naltrexone for the

treatment of opiate dependence was not supported. Bisaga A, Sullivan MA, Cheng WY, Carpenter KM, Mariani JJ, Levin FR, Raby WN, Nunes EV. A placebo controlled trial of memantine as an adjunct to oral naltrexone for opioid dependence. Drug Alcohol Depend 2011 Dec; (1-2): e23-29.

**Methylphenidate Transdermal System in Adults with Past Stimulant Misuse: An Open-Label Trial** This 8-week, open-label trial assessed the efficacy of methylphenidate transdermal system (MTS) in 14 adult individuals diagnosed with ADHD and with a history of stimulant misuse, abuse, or dependence. The primary efficacy endpoint was the Wender-Reimherr Adult ADHD Scale (WRAADS), and secondary efficacy endpoints included the Clinical Global Impression (CGI) ratings and substance abuse as quantified by urine drug screens and self-reported use. Significant improvements from baseline were found on both the WRAADS and CGI measurements. No abuse of the study medication was observed. The findings suggested that MTS may improve ADHD symptoms in adults with a history of stimulant misuse; however, there were limitations. The study data showed the need for subsequent randomized studies that further explore findings made in this study. McRae-Clark AL, Brady KT, Hartwell KJ, White K, Carter RE. Methylphenidate transdermal system in adults with past stimulant misuse: An open-label trial. J Atten Disord 2011 Oct; (7): 539-544.

**Cocaine Hydrolase Encoded in Viral Vector Blocks the Reinstatement of Cocaine Seeking in Rats for 6 Months** Cocaine dependence is a pervasive disorder with high rates of relapse. In a previous study, direct administration of a quadruple mutant albumin-fused butyrylcholinesterase that efficiently catalyzes hydrolysis of cocaine to benzoic acid and ecgonine methyl ester acutely blocked cocaine seeking in an animal model of relapse. In the present experiments, these results were extended to achieve a long-duration blockade of cocaine seeking with a gene transfer paradigm using a related butyrylcholinesterase-based cocaine hydrolase (CocH). Male and female rats were allowed to self-administer cocaine under a fixed-ratio 1 schedule of reinforcement for approximately 14 days. Following the final self-administration session, rats were injected with CocH vector or a control injection (empty vector or saline), and their cocaine solutions were replaced with saline for 14 days to allow for extinction of lever pressing. Subsequently, they were tested for drug-primed reinstatement by administering intraperitoneal injections of saline (S), cocaine (C) (5, 10, and 15 mg/kg), and d-amphetamine according to the following sequence: S, C, S, C, S, C, S, d-amphetamine. Rats then received cocaine-priming injections once weekly for 4 weeks and, subsequently, once monthly for up to 6 months. Administration of CocH vector produced substantial and sustained CocH activity in plasma that corresponded with diminished cocaine-induced (but not amphetamine-induced) reinstatement responding for up to 6 months following treatment (compared with high-responding control animals). These results demonstrate that viral transfer of CocH may be useful in promoting long-term resistance to relapse to cocaine addiction. Anker JJ, Brimijoin S, Gao Y, Geng L, Zlebnik NE, Parks RJ, Carroll ME. Cocaine hydrolase encoded in viral vector blocks the reinstatement of cocaine seeking in rats for 6 months. Biol Psychiatry. 2011 Dec. [Epub ahead of print]

**An Oxycodone Conjugate Vaccine Elicits Drug-Specific Antibodies that Reduce Oxycodone Distribution to Brain and Hot-Plate Analgesia** Opioid conjugate vaccines have shown promise in attenuating the behavioral effects of heroin or morphine in animals. The goal of this study was to extend this approach to oxycodone (OXY), a commonly abused prescription opioid. Haptens were generated by adding tetraglycine (Gly)(4) or hemisuccinate (HS) linkers at the 6-position of OXY. Immunization of rats with OXY(Gly)(4) conjugated to the carrier proteins bovine serum albumin (BSA) or keyhole limpet hemocyanin (KLH) produced high-titer antibodies to OXY and its metabolite oxymorphone with substantially lower affinities for other structurally related opioid agonists and antagonists. There was no measurable binding of antibody by the (Gly)(4) linker alone or off-target opioids methadone and buprenorphine. OXY(HS) conjugates were less immunogenic despite achieving protein haptenation ratios comparable to OXY(Gly)(4)-BSA. In rats given a single intravenous dose of OXY, immunization with OXY(Gly)(4)-KLH increased OXY protein binding and retention in serum while decreasing its unbound (free) concentration in plasma and distribution to brain. Vaccine efficacy correlated with serum antibody titers, and it was greatest in rats given the lowest OXY dose (0.05 mg/kg) but was significant even after a larger OXY dose (0.5 mg/kg), equivalent to the high end of the therapeutic range in humans. These effects of OXY(Gly)(4)-KLH on drug disposition were comparable to those of nicotine or cocaine vaccines that are in clinical trials as addiction treatments. Immunization with OXY(Gly)(4)-KLH also reduced OXY analgesia in a thermal nociception test. These data support further study of vaccination with the OXY(Gly)(4)-KLH immunogen as a potential treatment option for OXY abuse or addiction. Pravetoni M, Le Naour M, Harmon TM, Tucker AM, Portoghese PS, Pentel PR. J Pharmacol Exp Ther. 2012 Apr; 341(1): 225-232.

**Structurally Distinct Nicotine Immunogens Elicit Antibodies with Non-overlapping Specificities** Nicotine conjugate vaccine efficacy is limited by the concentration of nicotine-specific antibodies that can be reliably generated in serum. Previous studies suggest that the concurrent use of 2 structurally distinct nicotine immunogens in rats can generate additive antibody responses by stimulating distinct B cell populations. In the current study the authors investigated whether it is possible to identify a third immunologically distinct nicotine immunogen. The new 1'-SNic immunogen (2S)-N,N'-(disulfanediyldiethane-2,1-diyl)bis[4-(2-pyridin-3-ylpyrrolidin-1-yl)butanamide] conjugated to keyhole limpet hemocyanin (KLH) differed from the existing immunogens 3'-AmNic-rEPA and 6-CMUNic-BSA in linker position, linker composition, conjugation chemistry, and carrier protein. Vaccination of rats with 1'-SNic-KLH elicited high concentrations of high affinity nicotine-specific antibodies. The antibodies produced in response to 1'-SNic-KLH did not appreciably cross-react in ELISA with either 3'-AmNic-rEPA or 6-CMUNic-BSA or vice versa, showing that the B cell populations activated by each of these nicotine immunogens were non-overlapping and distinct. Nicotine retention in serum was increased and nicotine distribution to brain substantially reduced in rats vaccinated with 1'-SNic-KLH compared to controls. Effects of 1'-SNic-KLH on nicotine distribution were comparable to those of 3'-AmNic-rEPA which has progressed to late stage clinical trials as an adjunct to smoking cessation. These data show that it is possible to design multiple immunogens from a small molecule such as nicotine which elicit independent immune responses. This approach could be applicable to other addiction vaccines or small molecule targets as well. Pravetoni M, Keyler DE, Pidaparthi RR, Carroll FI, Runyon SP, Murtaugh MP, Earley CA, Pentel PR. Biochem Pharmacol. 2012 Feb 15; 83(4): 543-550.

**Combined Active and Passive Immunization Against Nicotine: Minimizing Monoclonal Antibody Requirements Using a Target Antibody Concentration Strategy** Nicotine vaccines have shown preliminary evidence of efficacy for enhancing smoking cessation rates, but the serum nicotine-specific antibody (NicAb) concentrations produced are highly variable and many subjects do not develop effective levels. As an alternative to vaccination, passive immunization with nicotine-specific monoclonal antibodies could produce more uniform serum NicAb concentrations, but its use is limited by their high cost and shorter elimination half-life. This study investigated supplementing vaccination with monoclonal antibodies in a targeted fashion to increase vaccine efficacy while minimizing the required monoclonal antibody dose. Rats were vaccinated and then given individualized supplemental doses of the nicotine-specific monoclonal antibody Nic311 to achieve a target total serum NicAb concentration known to be effective for blocking locomotor sensitization (LMS) to nicotine. Rats received vaccine, Nic311, both, or neither, followed by 0.3 mg/kg nicotine s.c. for 10 days to produce LMS. Combination immunotherapy completely blocked the development of LMS, while monotherapy with vaccine or Nic311 alone was only minimally effective. Lower brain nicotine levels were associated with reduced locomotor activity averaged over days 7-10. Despite its greater efficacy, combination immunotherapy did not reduce the variability in the resulting total serum NicAb concentrations. Variability in total serum NicAb concentrations was contributed to by both vaccine-generated antibody and by Nic311. These data show that combination immunotherapy, using a Nic311 dose that is by itself only minimally effective, can substantially enhance nicotine vaccine efficacy. However, variability in serum NicAb levels with combination immunotherapy may make translation of this approach challenging. Cornish KE, Harris AC, LeSage MG, Keyler DE, Burroughs D, Earley C, Pentel PR. Int Immunopharmacol. 2011 Nov; 11(11): 1809-1815.

**Reaction Pathway and Free Energy Profiles for Butyrylcholinesterase-Catalyzed Hydrolysis of Acetylthiocholine** The catalytic mechanism for butyrylcholineserase (BChE)-catalyzed hydrolysis of acetylthiocholine (ATCh) has been studied by performing pseudobond first-principles quantum mechanical/molecular mechanical-free energy (QM/MM-FE) calculations on both acylation and deacylation of BChE. Additional quantum mechanical (QM) calculations have been carried out, along with the QM/MM-FE calculations, to understand the known substrate activation effect on the enzymatic hydrolysis of ATCh. It has been shown that the acylation of BChE with ATCh consists of two reaction steps including the nucleophilic attack on the carbonyl carbon of ATCh and the dissociation of thiocholine ester. The deacylation stage includes nucleophilic attack of a water molecule on the carboxyl carbon of substrate and dissociation between the carboxyl carbon of substrate and hydroxyl oxygen of Ser198 side chain. QM/MM-FE calculation results reveal that the acylation of BChE is rate-determining. It has also been demonstrated that an additional substrate molecule binding to the peripheral anionic site (PAS) of BChE is responsible for the substrate activation effect. In the presence of this additional substrate molecule at PAS, the calculated free energy barrier for the acylation stage (rate-determining step) is decreased by ~1.7 kcal/mol. All of the authors' computational predictions are consistent with available experimental kinetic data. The overall free energy barriers calculated for BChE-catalyzed hydrolysis of ATCh at regular hydrolysis phase and substrate activation phase are ~13.6 and ~11.9 kcal/mol, respectively, which are in reasonable agreement with the corresponding experimentally derived activation free energies of 14.0 kcal/mol (for regular hydrolysis phase) and 13.5 kcal/mol (for substrate activation phase). Chen X, Fang L, Liu J, Zhan CG. Biochemistry. 2012 Feb 14; 51(6): 1297-1305.

**CM156, A Sigma Receptor Ligand, Reverses Cocaine-Induced Place Conditioning and Transcriptional Responses in the Brain** Repeated exposure to cocaine induces neuroadaptations which contribute to the rewarding properties of cocaine. Using cocaine-induced conditioned place preference (CPP) as an animal model of reward, earlier studies have shown that sigma (σ) receptor ligands can attenuate the acquisition, expression and reactivation of CPP. However, the underlying molecular mechanisms that are associated with these changes are not yet understood. In the present study, CM156, a novel antagonist with high selectivity and affinity for σ receptors was used to attenuate the expression of cocaine-induced CPP in mice. Immediately following the behavioral evaluations, mouse brain tissues were collected and alterations in gene expression in half brain samples were profiled by cDNA microarray analysis. Microarray data was analyzed by three distinct normalization methods and four genes were consistently found to be upregulated by cocaine when compared to saline controls. Each of these gene changes were found by more than one normalization method to be reversed by at least one dose of CM156. Quantitative real time PCR confirmed that a single administration of CM156 was able to reverse the cocaine-induced increases in three of these four genes: metastasis associated lung adenocarcinoma transcript 1 (malat1), tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein (ywhaz), and transthyretin (ttr). These genes are involved in processes related to neuroplasticity and RNA editing. The data presented herein provides evidence that pharmacological intervention with a putative σ receptor antagonist reverses alterations in gene expression that are associated with cocaine-induced reward. Xu YT, Robson MJ, Szeszel-Fedorowicz W, Patel D, Rooney R, McCurdy CR, Matsumoto RR. Pharmacol Biochem Behav. 2012 Mar;101(1):174-180.

**Anti-Cocaine Vaccine Based on Coupling A Cocaine Analog to A Disrupted Adenovirus** The challenge in developing an anti-cocaine vaccine is that cocaine is a small molecule, invisible to the immune system. Leveraging the knowledge that adenovirus (Ad) capsid proteins are highly immunogenic in humans, we hypothesized that linking a cocaine hapten to Ad capsid proteins would elicit high-affinity, high-titer antibodies against cocaine, sufficient to sequester systemically administered cocaine and prevent access to the brain, thus suppressing cocaine-induced behaviors. Based on these concepts, we developed dAd5GNE, a disrupted E1-E3-serotype 5 Ad with GNE, a stable cocaine analog, covalently linked to the Ad capsid proteins. In pre-clinical studies, dAd5GNE evoked persistent, high titer, high affinity IgG anti-cocaine antibodies, and was highly effective in blocking cocaine-induced hyperactivity and cocaine self-administration behavior in rats. Future studies will be designed to expand the efficacy studies, carry out relevant toxicology studies, and test dAd5GNE in human cocaine addicts. Koob G, Hicks MJ, Wee S, Rosenberg JB, De BP, Kaminsky SM, Moreno A, Janda KD, Crystal RG. CNS Neurol Disord Drug Targets. 2011 Dec 1; 10(8): 899-904.

**Orexin-1 Receptor Mediation of Cocaine Seeking in Male and Female Rats** Previous studies have shown that female rats exhibit enhanced cocaine seeking during multiple phases of cocaine addiction compared with males. The orexin/hypocretin system recently has been implicated in drug addiction in male rats. Based on the known sex differences in cocaine addiction, in the current study the authors examined orexin-mediated cocaine seeking during self-administration, extinction, and reinstatement in age-matched male (initial weight 250-300 g) and female (initial weight 175-225 g) Sprague-Dawley rats by using the orexin-1 receptor (OX1R) antagonist 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-yl urea (SB-334867) (10-30 mg/kg). OX1R blockade had no effect on established cocaine self-administration, but attenuated cocaine seeking

during extinction in both male and female rats. It is noteworthy that OX1R blockade potently attenuated cue-induced reinstatement in males but had no effect on females. SB-334867 also reduced cocaine seeking during pharmacological stress-induced (yohimbine, 2.5 mg/kg) and yohimbine + cue-induced reinstatement in both sexes. SB-334867 failed to affect reinstatement induced by cocaine (10 mg/kg) in either male or female rats, but selectively reduced cocaine + cue-induced reinstatement only in males. In separate experiments examining basal and cocaine-induced locomotion, SB-334867 attenuated locomotion in both male and female rats. Finally, assessment of plasma and brain levels of SB-334867 showed that estrus females had slightly higher plasma levels than diestrus females, but no overall sex differences or estrous cycle differences were observed in plasma or brain SB-334867 concentrations. These results show that OX1R signaling plays a role in mediating cocaine seeking, but differs between the sexes for cue-induced reinstatement. Zhou L, Ghee SM, Chan C, Lin L, Cameron MD, Kenny PJ, See RE. J Pharmacol Exp Ther. 2012 Mar; 340(3): 801-809.

**Further Structure-Activity Relationship Studies on 8-Substituted-3-[2-(Diarylmethoxy ethylidenyl)]-8-Azabicyclo[3.2.1]Octane Derivatives at Monoamine Transporters** The synthesis and structure-activity relationships of 8-substituted-3-[2-(diarylmethoxy ethylidenyl)]-8-azabicyclo[3.2.1]octane derivatives were investigated at the dopamine transporter (DAT), the serotonin transporter (SERT) and norepinephrine transporter (NET). The rigid ethylidenyl-8-azabicyclic[3.2.1]octane skeleton imparted modestly stereoselective binding and uptake inhibition at the DAT. Additional structure-activity studies provided a transporter affinity profile that was reminiscent of the structure-activity of GBR 12909. From these studies, the 8-cyclopropylmethyl group has been identified as a unique moiety that imparts high SERT/DAT selectivity. In this study the 8-cyclopropylmethyl derivative 22e (DAT K(i) of 4.0 nM) was among the most potent compounds of the series at the DAT and was the most DAT selective ligand of the series (SERT/DAT: 1060). Similarly, the 8-chlorobenzyl derivative 22g (DAT K(i) of 3.9 nM) was found to be highly selective for the DAT over the NET (NET/DAT: 1358). Cararas SA, Izenwasser S, Wade D, Housman A, Verma A, Lomenzo SA, Trudell ML Bioorg Med Chem. 2011 Dec 15; 19(24): 7551-7558.

**Drug Discovery Targeting Human 5-HT(2C) Receptors: Residues S3.36 and Y7.43 Impact Ligand-Binding Pocket Structure via Hydrogen Bond Formation** Specific activation of serotonin (5-HT) 5-HT(2C) G protein-coupled receptors may be therapeutic for obesity and neuropsychiatric disorders. Mutagenesis coupled with computational and molecular modeling experiments based on the human $\beta_2$ adrenergic receptor structure was employed to delineate the interactions of different ligands at human 5-HT(2C) residues D3.32, S3.36 and Y7.43. No binding of the tertiary amine radioligand ([$^3$H]-mesulergine) could be detected when the 5-HT(2C) D3.32 residue was mutated to alanine (D3.32A). The S3.36A point-mutation greatly reduced affinity of primary amine ligands, modestly reduced affinity of a secondary amine, and except for the 5-HT(2C)-specific agonist $N(CH_3)_2$-PAT, affinity of tertiary amines was unaffected. Molecular modeling results indicated that the primary amines form hydrogen bonds with the S3.36 residue, whereas, with the exception of $N(CH_3)_2$-PAT, tertiary amines do not interact considerably with this residue. The Y7.43A point-mutation greatly reduced affinity of 5-HT, yet reduced to a lesser extent the affinity of tryptamine that lacks the 5-hydroxy moiety present in 5-HT; modeling results indicated that the 5-HT 5-hydroxy moiety hydrogen bonds with Y7.43 at the 5-HT(2C) receptor. Additional modeling results showed that 5-HT induced a

hydrogen bond between Y7.43 and D3.32. Finally, modeling results revealed two low-energy binding modes for 5-HT in the 5-HT(2C) binding pocket, supporting the concept that multiple agonist binding modes may stabilize different receptor active conformations to influence signaling. Ligand potencies for modulating WT and point-mutated 5-HT(2C) receptor-mediated phospholipase C activity were in accordance with the affinity data. Ligand efficacies, however, were altered considerably by the S3.36A mutation only. Canal CE, Cordova-Sintjago TC, Villa NY, Fang LJ, Booth RG. Eur J Pharmacol. 2011 Dec 30; 673(1-3): 1-12.

**The Fate of Bacterial Cocaine Esterase (Coce): An In Vivo Study of Coce-Mediated Cocaine Hydrolysis, Coce Pharmacokinetics, and Coce Elimination** Cocaine abuse and toxicity remain widespread problems in the United States. Currently cocaine toxicity is treated only symptomatically, because there is no Food and Drug Administration-approved pharmacotherapy for this indication. To address the unmet need, a stabilized mutant of bacterial cocaine esterase [T172R/G173Q-CocE (DM-CocE)], which hydrolyzes cocaine into inactive metabolites and has low immunogenic potential, has been developed and previously tested in animal models of cocaine toxicity. Here, the authors document the rapid cocaine hydrolysis by low doses of DM-CocE in vitro and in vivo, as well as the pharmacokinetics and distribution of the DM-CocE protein in rats. DM-CocE at 50.5 μg/kg effectively eliminated 4 mg/kg cocaine within 2 min in both male and female rats as measured by mass spectrometry. They expanded on these findings by using a pharmacologically relevant dose of DM-CocE (0.32 mg/kg) in rats and monkeys to hydrolyze convulsant doses of cocaine. DM-CocE reduced cocaine to below detection limits rapidly after injection; however, elimination of DM-CocE resulted in peripheral cocaine redistribution by 30 to 60 min. Elimination of DM-CocE was quantified by using [$^{35}$S] labeling of the enzyme and was found to have a half-life of 2.1 h in rats. Minor urinary output of DM-CocE was also observed. Immunohistochemistry, Western blotting, and radiography all were used to elucidate the mechanism of DM-CocE elimination, rapid proteolysis, and recycling of amino acids into all tissues. This rapid elimination of DM-CocE is a desirable property of a therapeutic for cocaine toxicity and should reduce the likelihood of immunogenic or adverse reactions as DM-CocE moves toward clinical use. Brim RL, Noon KR, Collins GT, Stein A, Nichols J, Narasimhan D, Ko MC, Woods JH, Sunahara RK. J Pharmacol Exp Ther. 2012 Jan; 340(1): 83-95.

**Subunit Stabilization and Polyethylene Glycolation of Cocaine Esterase Improves In Vivo Residence Time** No small-molecule therapeutic is available to treat cocaine addiction, but enzyme-based therapy to accelerate cocaine hydrolysis in serum has gained momentum. Bacterial cocaine esterase (CocE) is the fastest known native enzyme that hydrolyzes cocaine. However, its lability at 37°C has limited its therapeutic potential. Cross-linking subunits through disulfide bridging is commonly used to stabilize multimeric enzymes. Herein the authors use structural methods to guide the introduction of two cysteine residues within dimer interface of CocE to facilitate intermolecular disulfide bond formation. The disulfide-crosslinked enzyme displays improved thermostability, particularly when combined with previously described mutations that enhance stability (T172R-G173Q). The newly modified enzyme yielded an extremely stable form of CocE (CCRQ-CocE) that retained greater than 90% of its activity after 41 days at 37°C, representing an improvement of more than 4700-fold over the wild-type enzyme. CCRQ-CocE could also be modified by polyethylene glycol (PEG) polymers, which improved its in vivo residence time from 24 to 72 h, as measured by a cocaine lethality assay, by self-administration in

rodents, and by measurement of inhibition of cocaine-induced cardiovascular effects in rhesus monkeys. PEG-CCRQ elicited negligible immune response in rodents. Subunit stabilization and PEGylation has thus produced a potential protein therapeutic with markedly higher stability both in vitro and in vivo. Narasimhan D, Collins GT, Nance MR, Nichols J, Edwald E, Chan J, Ko MC, Woods JH, Tesmer JJ, Sunahara RK. Mol Pharmacol. 2011 Dec; 80(6): 1056-1065.

**The Ability of Bacterial Cocaine Esterase to Hydrolyze Cocaine Metabolites and Their Simultaneous Quantification Using High-Performance Liquid Chromatography-Tandem Mass Spectrometry** Cocaine toxicity is a widespread problem in the United States, responsible for more than 500,000 emergency department visits a year. There is currently no U.S. Food and Drug Administration-approved pharmacotherapy to directly treat cocaine toxicity. To this end, the authors have developed a mutant bacterial cocaine esterase (DM-CocE), which has been previously shown to rapidly hydrolyze cocaine into inert metabolites, preventing and reversing toxicity with limited immunogenic potential. Herein they describe the ability of DM-CocE to hydrolyze the active cocaine metabolites norcocaine and cocaethylene and its inability to hydrolyze benzoylecgonine. DM-CocE hydrolyzes norcocaine and cocaethylene with 58 and 45% of its catalytic efficiency for cocaine in vitro as measured by a spectrophotometric assay. The authors have developed a mass spectrometry method to simultaneously detect cocaine, benzoylecgonine, norcocaine, and ecgonine methyl ester to quantify the effect of DM-CocE on normal cocaine metabolism in vivo. DM-CocE administered to rats 10 min after a convulsant dose of cocaine alters the normal metabolism of cocaine, rapidly decreasing circulating levels of cocaine and norcocaine while increasing ecgonine methyl ester formation. Benzoylecgonine was not hydrolyzed in vivo, but circulating concentrations were reduced, suggesting that DM-CocE may bind and sequester this metabolite. These findings suggest that DM-CocE may reduce cocaine toxicity by eliminating active and toxic metabolites along with the parent cocaine molecule. Brim RL, Noon KR, Collins GT, Nichols J, Narasimhan D, Sunahara RK, Woods JH. Mol Pharmacol. 2011 Dec; 80(6): 1119-1127.

**Effects of Pramipexole on the Reinforcing Effectiveness of Stimuli That Were Previously Paired with Cocaine Reinforcement in Rats** Dopamine D(2)-like agonists maintain responding when substituted for cocaine in laboratory animals. However, these effects appear to be mediated by an interaction with stimuli that were previously paired with cocaine reinforcement (CS). To evaluate the extent to which the pramipexole-maintained and pramipexole-induced responding are influenced by cocaine-paired stimuli rats were trained to nosepoke for cocaine under fixed ratio 1 (FR1) or progressive ratio (PR) schedules of reinforcement. In FR1-trained rats, pramipexole was substituted for cocaine with injections either paired with CSs, or delivered in their absence. The capacity of experimenter-administered pramipexole to induce FR1 and PR responding for CS presentation was evaluated. The effects of altering stimulus conditions, as well as pretreatments with D(2)- (L: -741,626) and D(3)-preferring (PG01037) antagonists on pramipexole-induced PR responding were also evaluated. When substituted for cocaine, pramipexole maintained responding at high rates when injections were paired with CSs, but low rates when CSs were omitted. Similarly, experimenter-administered pramipexole induced dose-dependent increases in FR1 or PR responding, with high rates of responding observed when the CS was presented, and low rates of responding when CS presentation was omitted. D(2) and D(3) antagonists differentially affected pramipexole-induced PR responding, with L: -741,626 and PG01037 producing rightward, and downward shifts in the

dose-response curve for CS-maintained responding, respectively. These data indicate that pramipexole is capable of enhancing the reinforcing effectiveness of conditioned stimuli, and raise the possibility that similar mechanisms are responsible for the increased occurrence of impulse control disorders in patients being treated with pramipexole. Collins GT, Cunningham AR, Chen J, Wang S, Newman AH, Woods JH. Psychopharmacology (Berl). 2012 Jan; 219(1): 123-135.

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

**Cannabinoid Receptor 2-Mediated Attenuation of CXCR4-Tropic HIV Infection in Primary CD4+ T Cells** Agents that activate cannabinoid receptor pathways have been tested as treatments for cachexia, nausea or neuropathic pain in HIV-1/AIDS patients. The cannabinoid receptors (CB(1)R and CB(2)R) and the HIV-1 co-receptors, CCR5 and CXCR4, all signal via Gαi-coupled pathways. The authors hypothesized that drugs targeting cannabinoid receptors modulate chemokine co-receptor function and regulate HIV-1 infectivity. They found that agonism of CB(2)R, but not CB(1)R, reduced infection in primary CD4+ T cells following cell-free and cell-to-cell transmission of CXCR4-tropic virus. As this change in viral permissiveness was most pronounced in unstimulated T cells, the authors investigated the effect of CB(2)R agonism on to CXCR4-induced signaling following binding of chemokine or virus to the co-receptor. They found that CB(2)R agonism decreased CXCR4-activation mediated G-protein activity and MAPK phosphorylation. Furthermore, CB(2)R agonism altered the cytoskeletal architecture of resting CD4+ T cells by decreasing F-actin levels. These findings suggest that CB(2)R activation in CD4+ T cells can inhibit actin reorganization and impair productive infection following cell-free or cell-associated viral acquisition of CXCR4-tropic HIV-1 in resting cells. Therefore, the clinical use of CB(2)R agonists in the treatment of AIDS symptoms may also exert beneficial adjunctive antiviral effects against CXCR4-tropic viruses in late stages of HIV-1 infection. Costantino CM, Gupta A, Yewdall AW, Dale BM, Devi LA, Chen BK. Cannabinoid Receptor 2-Mediated Attenuation of CXCR4-Tropic HIV Infection in Primary CD4+ T Cells. PLoS One. 2012; 7(3): e33961. Epub 2012 Mar 20.

**Provider And Clinic-Level Correlates Of Deferring Antiretroviral Therapy For People Who Inject Drugs: A Survey Of North American HIV Providers** Injection drug users (IDUs) face numerous obstacles to receiving optimal HIV care, and have been shown to underutilize antiretroviral therapy (ART). The authors sought to estimate the degree to which providers of HIV care defer initiation of ART because of injection drug use and to identify clinic and provider-level factors associated with resistance to prescribing ART to IDUs. They administered an Internet-based survey to 662 regular prescribers of ART in the United States and Canada. Questionnaire items assessed characteristics of providers' personal demographics and training, site of clinical practice and attitudes about drug use. Respondents then rated whether they would likely prescribe or defer ART for hypothetical patients in a series of scenarios involving varying levels of drug use and HIV disease stage. Survey responses were received from 43% of providers invited by email and direct mail, and 8.5% of providers invited by direct mail only. Overall, 24.2% of providers reported that they would defer ART for an HIV-infected patient with a CD4+ cell count of 200 cells/mm3 if the patient actively injected drugs, and 52.4% would defer ART if the patient injected daily. Physicians were more likely than non-physician providers to defer ART if a patient injected drugs (adjusted odds ratio 2.6, 95% CI 1.4-4.9). Other predictors of deferring ART for active IDUs were having fewer years of experience in HIV care, regularly caring for fewer than 20 HIV-infected patients, and working at a clinic serving a population with low prevalence of injection drug use. Likelihood of deferring ART was directly proportional to both CD4+ cell count and increased frequency of injecting. Many providers of HIV care defer initiation of antiretroviral therapy for patients who inject drugs, even in the setting of advanced immunologic suppression. Providers with more experience in treating

HIV, those in high injection drug use prevalence areas and non-physician providers may be more willing to prescribe ART despite on-going injection drug use. Because of limitations, including low response rate and use of a convenience sample, these findings may not be generalizable to all HIV care providers in North America. Westergaard RP, Ambrose BK, Mehta SH, Kirk GD. Provider and clinic-level correlates of deferring antiretroviral therapy for people who inject drugs: a survey of North American HIV providers. J Int AIDS Soc. 2012 Feb 23; 15: 10.

**Correlates of Antiretroviral Utilization Among Hospitalized HIV-Infected Crack Cocaine Users** Despite the availability of antiretroviral therapy (ART), HIV-infected drug users, particularly crack cocaine users, continue to have high HIV-related morbidity and mortality. The authors conducted a cross-sectional analysis of the baseline data for hospitalized HIV-infected crack cocaine users recruited for Project HOPE (Hospital Visit Is an Opportunity for Prevention and Engagement with HIV-Positive Crack Users) in Atlanta and Miami who were eligible for ART (reported any lifetime use of ART or CD4 <350 cells/μl). Among 350 eligible participants, whose mean age was 44.9 years (SD 7.0), 49% were male, 90% were black, and 81% were heterosexual. The median CD4 count was 144 cells/μl, and 78 of 350 (22%) were taking ART. The authors conducted a multivariable logistic regression to examine individual, interpersonal, and structural factors as potential correlates of ART use. Reporting ≥2 visits to outpatient HIV care in the past 6 months (AOR 7.55, 95% CI 3.80-14.99), drug or alcohol treatment in the past 6 months (AOR 2.29, 95% CI 1.06-4.94), and study site being Miami (AOR 2.99, 95% CI 1.56-5.73) were associated with ART use. Current homelessness (AOR 0.41, 95% CI 0.20-0.84) and CD4 <200 cells/μl (AOR 0.29, 95% CI 0.15-0.55) were negatively associated with ART use. Among those taking ART, 60% had an HIV-1 viral load <400 copies/ml; this represented 9% of the eligible population. For HIV-infected crack cocaine users, structural factors may be as important as individual and interpersonal factors in facilitating ART utilization. Few HIV(+) crack cocaine users had viral suppression, but among those on ART, viral suppression was achievable. Doshi RK, Vogenthaler NS, Lewis S, Rodriguez A, Metsch L, Rio CD. Correlates of antiretroviral utilization among hospitalized HIV-infected crack cocaine users. AIDS Res Hum Retroviruses. 2012 Mar 2. [Epub ahead of print]

**Assessing Mortality In Women With Hepatitis C Virus And HIV Using Indirect Markers Of Fibrosis** OBJECTIVE: Co-infection with hepatitis C virus (HCV) is a major cause of morbidity and mortality in HIV-infected individuals. However, predictors of mortality are poorly defined and most studies have focused predominantly on co-infection in men. The authors evaluated whether two indirect markers of hepatic fibrosis, aspartate aminotransferase-to-platelet ratio index (APRI) and FIB-4 scores, were predictive of mortality in a well defined longitudinal cohort of HCV/HIV-co-infected women on HAART. HCV/HIV-co-infected women on antiretroviral therapy enrolled in Women's Interagency HIV Study (WIHS), a National Institutes of Health-funded prospective, multicenter, cohort study of women with and at risk for HIV infection were included. Using Cox regression analysis, associations between APRI and FIB-4 with all-cause mortality were assessed. Four hundred and fifty HCV/HIV-co-infected women, of whom 191 women died, had a median follow-up of 6.6 years and 5739 WIHS visits. Compared with women with low APRI or FIB-4 levels, severe fibrosis was significantly associated with an increased risk of all-cause mortality {APRI: hazard ratio 2.78 [95% confidence interval (CI) 1.87, 4.12]; FIB-4: hazard ratio 2.58 (95% CI 1.68, 3.95)}. Crude death rates per 1000 patient-years increased with increasing liver fibrosis: 34.8 for mild, 51.3 for moderate and 167.9 for

severe fibrosis as measured by FIB-4. Importantly, both APRI and FIB-4 increased during the 5 years prior to death for all women: the slope of increase was greater for women dying a liver-related death compared with nonliver-related death. Both APRI and FIB-4 are independently associated with all-cause mortality in HCJ \V/HIV-co-infected women and may have clinical prognostic utility among women with HIV and HCV. Bambha K, Pierce C, Cox C, French AL, Tien PC, Sharp GB, Augenbraun M, Glesby MJ, Villacres MC, Plankey M, Strickler HD, Gange SJ, Peters MG. Assessing mortality in women with hepatitis C virus and HIV using indirect markers of fibrosis. AIDS. 2012 Mar 13; 26(5): 599-607.

**Vitamin D Deficiency is Associated with Significant Coronary Stenoses in Asymptomatic African American Chronic Cocaine Users** Chronic cocaine use may lead to premature atherosclerosis, however, the prevalence of and risk factors for coronary artery disease in asymptomatic cocaine users have not been reported. Between August 2007 and June 2010, 385 African American chronic cocaine users aged 25 to 54 years were consecutively enrolled in a study to investigate the prevalence of CT angiographically-defined significant (≥50%) coronary stenosis and related risk factors. Sociodemographic, drug-use behavior, medical history and medication data were obtained by interview and confirmed by medical chart review. Clinical examinations were performed as well as extensive laboratory tests including those for fasting lipid profiles, HIV, high sensitivity C-reactive protein, and vitamin D. Contrast-enhanced coronary CT angiography was performed. Significant coronary stenosis was detected in 52 of 385 participants (13.5%). The prevalences were 12% and 30% in those with low risk and with middle-high risk Framingham score, respectively. In those with low risk scores, the prevalences of significant stenosis were 10% and 18% in those without and with vitamin D deficiency, defined as serum 25-(OH) vitamin D<10ng/mL (p=0.08). Multiple logistic regression analysis revealed that vitamin D deficiency (adjusted OR=2.18, 95% CI: 1.07-4.43) is independently associated with the presence of significant coronary stenosis after controlling for traditional risk factors. The study indicates that the prevalence of significant coronary stenoses is high in asymptomatic young and middle-aged African American chronic cocaine users. These findings emphasize the importance of aggressive reduction of risk factors, including vitamin D deficiency in this population. Lai H, Fishman EK, Gerstenblith G, Brinker JA, Tong W, Bhatia S, Detrick B, Lai S. Vitamin D deficiency is associated with significant coronary stenoses in asymptomatic African American chronic cocaine users. Int J Cardiol. 2011 Feb 2. [Epub ahead of print**]**

**Vitamin D Deficiency is Associated with Silent Coronary Artery Disease in Cardio-vascularly Asymptomatic African Americans with HIV Infection** Growing evidence suggests that vitamin D deficiency is associated with clinical coronary artery disease (CAD). The relationship between vitamin D deficiency and subclinical CAD in HIV-infected individuals is not well-characterized. CT coronary angiography was performed using contrast-enhanced 64-slice multidector CT imaging, and vitamin D levels and the presence of traditional and novel risk factor for CAD were obtained in 674 HIV-infected African American (AA) participants aged 25 to 54 years in Baltimore, Maryland without symptoms/clinical evidence of CAD. The prevalence of vitamin D deficiency (25 (OH) vitamin D <10 ng/mL) was 20.0% (95% CI: 16.9 - 23.1%). Significant (≥50%) coronary stenosis was present in 64 (9.5%) of 674 participants. Multiple logistic regression analysis revealed that male gender (adjusted OR: 2.19, 95% CI:1.17-4.10), diastolic BP ≥ 85 mmHg (adjusted OR: 1.94, 95% CI: 1.02 -3.68), LDL-cholesterol ≥100 mg/dL (adjusted OR: 1.95, 95% CI:1.13- 3.36), cocaine use for ≥15 years (adjusted OR: 1.77,

95% CI:1.01-3.10), use of ARTs for ≥6 months (adjusted OR: 2.26, 95% CI: 1.17-4.36), year of enrollment after 2005 (adjusted ORs for 2006-2007, 2008-2009, and 2010 were 0.32 (95% CI: 0.13-0.76), 0.26 (95% CI: 0.12-0.56), and 0.32 (95% CI: 0.15-0.65), respectively), and vitamin D deficiency (adjusted OR: 2.28, 95% CI:1.23-4.21) were independently associated with significant coronary stenosis. Both vitamin D deficiency and silent CAD are prevalent in HIV-infected AAs. In addition to management of traditional CAD risk factors and substance abuse, Vitamin D deficiency should be evaluated in HIV-infected AAs. These data support the conduct of a prospective trial of Vitamin D in this high risk patient population. Lai H, Gerstenblith G, Fishman EK, Brinker J, Kickler T, Tong W, Bhatia S, Hong T, Chen S, Li J, Detrick B, Lai S. Vitamin D deficiency is associated with silent coronary artery disease in cardiovascularly asymptomatic African Americans with HIV infection. Clin Infect Dis. 2012 Mar 15. [Epub ahead of print]

**Vitamin D Deficiency and Persistent Proteinuria Among HIV-infected and Uninfected Injection Drug Users** Proteinuria occurs commonly among HIV-infected and uninfected injection drug users (IDUs) and is associated with increased mortality risk. Vitamin D deficiency, highly prevalent among IDUs and potentially modifiable, may contribute to proteinuria. To determine whether vitamin D is associated with proteinuria in this population, the authors conducted a cross-sectional study in the AIDS Linked to the IntraVenous Experience (ALIVE) Study. 25(OH)-vitamin D levels were measured in 268 HIV-infected and 614 HIV-uninfected participants. The association between vitamin D deficiency (<10 ng/ml) and urinary protein excretion was evaluated by linear regression. The odds of persistent proteinuria (urine protein-to-creatinine ratio >200 mg/g on two occasions) associated with vitamin D deficiency was examined using logistic regression. One-third of participants were vitamin D-deficient. Vitamin D deficiency was independently associated with higher urinary protein excretion (P<0.05) among HIV-infected and diabetic IDUs (P-interaction<0.05 for all). Persistent proteinuria occurred in 18% of participants. Vitamin D deficiency was associated with greater than six-fold odds of persistent proteinuria among diabetic IDUs [odds ratio (OR) 6.29, 95% confidence interval (CI) 1.54, 25.69] independent of sociodemographic characteristics, comorbid conditions, body mass index, and impaired kidney function [estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m(2)]; no association, however, was observed among nondiabetic IDUs (OR 1.06, 95% CI 0.64, 1.76) (P-interaction <0.05). Vitamin D deficiency was associated with higher urinary protein excretion among those with HIV infection and diabetes. Vitamin D deficiency was independently associated with persistent proteinuria among diabetic IDUs, although not in nondiabetic persons. Whether vitamin D repletion ameliorates proteinuria in these patients requires further study. Estrella MM, Kirk GD, Mehta SH, Brown TT, Fine DM, Atta MG, Lucas GM. Vitamin D deficiency and persistent proteinuria among HIV-infected and uninfected injection drug users. AIDS. 2012 Jan 28; 26(3): 295-302.

**Micronutrients in HIV/AIDS: Is there Evidence to Change the WHO 2003 Recommendations?** To establish whether there is new evidence to inform changes to WHO 2003 recommendations for micronutrient intake in persons with HIV/AIDS, the authors conducted a narrative review of the literature published from 2003 to 2010. Although the review focused on new randomized controlled trials of multiple micronutrients in HIV-infected adults, including pregnant and lactating women, the authors also considered randomized trials of single micronutrients. The review found that there are few published randomized controlled trials of

micronutrients in HIV-infected persons and that most trials used high-dose multiple micronutrient supplementation. The trials were heterogeneous with respect to the composition and dose of micronutrients used and the target population studied. Despite this heterogeneity, 5 of 6 trials that used high-dose multiple micronutrients showed benefits in terms of either improved CD4 cell counts or survival. However, many of these trials were small and of short duration, and therefore the long-term risks and benefits of high-dose multiple micronutrients are not established. The current WHO recommendation for an intake of micronutrients at Recommended Dietary Allowance amounts continues to be a reasonable target for persons with clinically stable HIV infection. In light of new data that show adverse effects of high-dose vitamin A, the current recommendation for a single high dose of vitamin A in HIV-infected women within 6 wk of delivery should be reviewed. Forrester JE, Sztam KA. Micronutrients in HIV/AIDS: Is there evidence to change the WHO 2003 recommendations? Am J Clin Nutr. 2011 Dec; 94(6): 1683S-1689S. Epub 2011 Nov 16.

**A Systematic Review of Behavioral and Treatment Outcome Studies among HIV-infected Men who have Sex with Men who Abuse Crystal Methamphetamine** Men who have sex with men (MSM) have the highest incidence of HIV infection in the United States. One of the contributing factors to HIV spread among this group is the use of crystal methamphetamine ("meth"). The objective of this study was to review the behavioral impact of crystal meth use in HIV-infected MSM and potential treatment options. A systematic review of MEDLINE identified studies that evaluated the clinical effects of crystal meth on the HIV-infected MSM population. Search terms included HIV, methamphetamine, MSM, antiretroviral therapy, adherence, resistance, and treatment. U.S. citations in the English language in peer-reviewed journals until December 2010 were included. The primary author reviewed eligible articles, and relevant data including study design, sample, and outcomes were entered into an electronic data table. The 61 included studies highlight that HIV-infected MSM who use crystal meth are more likely to report high-risk sexual behaviors, incident sexually transmitted infections, and serodiscordant unprotected anal intercourse, compared to HIV-infected MSM who do not use crystal meth. Medication adherence in this population is notably low, which may contribute to transmission of resistant virus. No medications have proven effective in the treatment of crystal meth addiction, and the role of behavioral therapies, such as contingency management are still in question. HIV-infected MSM who abuse crystal meth have worse HIV-related health outcomes. Behavioral interventions have shown variable results in treating crystal meth addiction, and more investigation into rehabilitation options are needed. The results presented support efforts to develop and implement novel interventions to reduce crystal meth use in HIV-infected MSM. Rajasingham R, Mimiaga MJ, White JM, Pinkston MM, Baden RP, Mitty JA. A systematic review of behavioral and treatment outcome studies among HIV-infected men who have sex with men who abuse crystal methamphetamine. AIDS Patient Care STDS. 2012 Jan; 26(1): 36-52. Epub 2011 Nov 9.

**Complex Drug Interactions of the HIV Protease Inhibitors 3: Effect of Simultaneous or Staggered Dosing of Digoxin and Ritonavir, Nelfinavir, Rifampin, or Bupropion** As part of a larger clinical drug-drug interaction (DDI) study aimed at in vitro to in vivo prediction of HIV protease inhibitor metabolic and transporter-based DDIs, the authors measured the inductive (staggered administration) and inductive plus inhibitory (simultaneously administered) effect of multiple dose ritonavir (RTV), nelfinavir (NFV), or rifampin (RIF) on the pharmacokinetics of

the P-glycoprotein probe, digoxin (DIG), when administered simultaneously or staggered with the protease inhibitors or RIF. In both cases, NFV did not significantly affect DIG disposition. RTV decreased DIG renal clearance (Cl(renal)) when administered simultaneously or staggered but significantly increased DIG area under the curve from time zero to 24 h (AUC(0-24 h)) only when administered simultaneously. RIF decreased DIG AUC(0-24 h) only when RIF and DIG administration was staggered. When RIF and DIG were administered simultaneously, DIG maximal observed plasma concentration and area under the curve from time zero to 4 h were significantly increased, and DIG Cl(renal) was decreased. An unexpected and potentially clinically significant DDI was observed between DIG and the CYP2B6 probe, bupropion, which decreased DIG AUC(0-24 h) 1.6-fold and increased Cl(renal) 1.8-fold. Because this was an unexpected DDI and our studies were not specifically designed to quantify this interaction, further studies are required to confirm the interaction and understand the mechanistic basis of the DDI. In summary, RTV or NFV do not induce P-glycoprotein activity measured with DIG, and RIF does so only under staggered administration. Kirby BJ, Collier AC, Kharasch ED, Whittington D, Thummel KE, Unadkat JD. Complex drug interactions of the HIV protease inhibitors 3: effect of simultaneous or staggered dosing of digoxin and ritonavir, nelfinavir, rifampin, or bupropion. Drug Metab Dispos. 2012 Mar; 40(3): 610-616. Epub 2011 Dec 21.

**Interactions Between Buprenorphine and the Protease Inhibitors Darunavir-Ritonavir and Fosamprenavir-Ritonavir** This study examined drug interactions between buprenorphine, a partial opioid agonist used for opioid dependence treatment and pain management, and the protease inhibitors (PIs) darunavir-ritonavir and fosamprenavir-ritonavir. The pharmacokinetics of buprenorphine and its metabolites and symptoms of opioid withdrawal or excess were compared in opioid-dependent, buprenorphine-naloxone-maintained, human immunodeficiency virus (HIV)-negative volunteers (11 for darunavir-ritonavir and 10 for fosamprenavir-ritonavir) before and after 15 days of PI administration. PI pharmacokinetics and adverse effects were compared between the buprenorphine-maintained participants and an equal number of sex-, age-, race-, and weight-matched, healthy, non-opioid-dependent volunteers who received darunavir-ritonavir or fosamprenavir-ritonavir but not buprenorphine. There were no significant changes in buprenorphine or PI plasma levels and no significant changes in medication adverse effects or opioid withdrawal. Increased concentrations of the inactive metabolite buprenorphine-3-glucuronide suggested that darunavir-ritonavir and fosamprenavir-ritonavir induced glucuronidation of buprenorphine. Dose adjustments are not likely to be necessary when buprenorphine and darunavir-ritonavir or fosamprenavir-ritonavir are coadministered for the treatment of opioid dependence and HIV disease. Gruber VA, Rainey PM, Moody DE, Morse GD, Ma Q, Prathikanti S, Pade PA, Alvanzo AA, McCance-Katz EF. Interactions between buprenorphine and the protease inhibitors darunavir-ritonavir and fosamprenavir-ritonavir. Clin Infect Dis. 2012 Feb 1; 54(3): 414-423. Epub 2011 Nov 18.

**Lack of Indinavir Effects on Methadone Disposition Despite Inhibition of Hepatic and Intestinal Cytochrome P4503A (CYP3A)** Methadone disposition and pharmacodynamics are highly susceptible to interactions with antiretroviral drugs. Methadone clearance and drug interactions have been attributed to cytochrome P4503A4 (CYP3A4), but actual mechanisms are unknown. Drug interactions can be clinically and mechanistically informative. This investigation assessed effects of the protease inhibitor indinavir on methadone pharmacokinetics and pharmacodynamics, hepatic and intestinal CYP3A4/5 activity (using alfentanil), and intestinal

transporter activity (using fexofenadine). Twelve healthy volunteers underwent a sequential crossover. On three consecutive days they received oral alfentanil plus fexofenadine, intravenous alfentanil, and intravenous plus oral (deuterium-labeled) methadone. This was repeated after 2 weeks of indinavir. Plasma and urine analytes were measured by mass spectrometry. Opioid effects were measured by miosis. Indinavir significantly inhibited hepatic and first-pass CYP3A activity. Intravenous alfentanil systemic clearance and hepatic extraction were reduced to 40-50% of control, apparent oral clearance to 30% of control, and intestinal extraction decreased by half, indicating 50% and 70% inhibition of hepatic and first-pass CYP3A activity. Indinavir increased fexofenadine area under the plasma concentration-time curve 3-fold, suggesting significant P-glycoprotein inhibition. Indinavir had no significant effects on methadone plasma concentrations, methadone N-demethylation, systemic or apparent oral clearance, renal clearance, hepatic extraction or clearance, or bioavailability. Methadone plasma concentration-effect relationships were unaffected by indinavir. Despite significant inhibition of hepatic and intestinal CYP3A activity, indinavir had no effect on methadone N-demethylation and clearance, suggesting little or no role for CYP3A in clinical disposition of single-dose methadone. Inhibition of gastrointestinal transporter activity had no influence of methadone bioavailability. Kharasch ED, Bedynek PS, Hoffer C, Walker A, Whittington D. Lack of indinavir effects on methadone disposition despite inhibition of hepatic and intestinal cytochrome P4503A (CYP3A). Anesthesiology. 2012 Feb; 116(2): 432-447.

**Interactions Between Buprenorphine and the Protease Inhibitors Darunavir-Ritonavir and Fosamprenavir-Ritonavir** This study examined drug interactions between buprenorphine, a partial opioid agonist used for opioid dependence treatment and pain management, and the protease inhibitors (PIs) darunavir-ritonavir and fosamprenavir-ritonavir. The pharmacokinetics of buprenorphine and its metabolites and symptoms of opioid withdrawal or excess were compared in opioid-dependent, buprenorphine-naloxone-maintained, human immunodeficiency virus (HIV)-negative volunteers (11 for darunavir-ritonavir and 10 for fosamprenavir-ritonavir) before and after 15 days of PI administration. PI pharmacokinetics and adverse effects were compared between the buprenorphine-maintained participants and an equal number of sex-, age-, race-, and weight-matched, healthy, non-opioid-dependent volunteers who received darunavir-ritonavir or fosamprenavir-ritonavir but not buprenorphine. There were no significant changes in buprenorphine or PI plasma levels and no significant changes in medication adverse effects or opioid withdrawal. Increased concentrations of the inactive metabolite buprenorphine-3-glucuronide suggested that darunavir-ritonavir and fosamprenavir-ritonavir induced glucuronidation of buprenorphine. Dose adjustments are not likely to be necessary when buprenorphine and darunavir-ritonavir or fosamprenavir-ritonavir are coadministered for the treatment of opioid dependence and HIV disease. Gruber VA, Rainey PM, Moody DE, Morse GD, Ma Q, Prathikanti S, Pade PA, Alvanzo AA, McCance-Katz EF. Interactions between buprenorphine and the protease inhibitors darunavir-ritonavir and fosamprenavir-ritonavir. Clin Infect Dis. 2012 Feb 1; 54(3): 414-423. Epub 2011 Nov 18.

**Role of Retroviral Restriction Factors in the Interferon-α-mediated Suppression of HIV-1 In Vivo** The antiviral potency of the cytokine IFN-α has been long appreciated but remains poorly understood. A number of studies have suggested that induction of the apolipoprotein B mRNA editing enzyme, catalytic polypeptide 3 (APOBEC3) and bone marrow stromal cell antigen 2 (BST-2/tetherin/CD317) retroviral restriction factors underlies the IFN-α-mediated

suppression of HIV-1 replication in vitro. The authors sought to characterize the as-yet-undefined relationship between IFN-α treatment, retroviral restriction factors, and HIV-1 in vivo. APOBEC3G, APOBEC3F, and BST-2 expression levels were measured in HIV/hepatitis C virus (HCV)-coinfected, antiretroviral therapy-naïve individuals before, during, and after pegylated IFN-α/ribavirin (IFN-α/riba) combination therapy. IFN-α/riba therapy decreased HIV-1 viral load by -0.921 (±0.858) log(10) copies/mL in HIV/HCV-coinfected patients. APOBEC3G/3F and BST-2 mRNA expression was significantly elevated during IFN-α/riba treatment in patient-derived CD4+ T cells ($P < 0.04$ and $P < 0.008$, paired Wilcoxon), and extent of BST-2 induction was correlated with reduction in HIV-1 viral load during treatment ($P < 0.05$, Pearson's r). APOBEC3 induction during treatment was correlated with degree of viral hypermutation ($P < 0.03$, Spearman's ρ), and evolution of the HIV-1 accessory protein viral protein U (Vpu) during IFN-α/riba treatment was suggestive of increased BST-2-mediated selection pressure. These data suggest that host restriction factors play a critical role in the antiretroviral capacity of IFN-α in vivo, and warrant investigation into therapeutic strategies that specifically enhance the expression of these intrinsic immune factors in HIV-1-infected individuals. Pillai SK, Abdel-Mohsen M, Guatelli J, Skasko M, Monto A, Fujimoto K, Yukl S, Greene WC, Kovari H, Rauch A, Fellay J, Battegay M, Hirschel B, Witteck A, Bernasconi E, Ledergerber B, Günthard HF, Wong JK. Role of retroviral restriction factors in the interferon-α-mediated suppression of HIV-1 in vivo. Proc Natl Acad Sci U S A. 2012 Feb 21; 109(8): 3035-3040. Epub 2012 Feb 6.

**Hepatitis C Virus Epitope Exposure and Neutralization by Antibodies is Affected by Time and Temperature** A recent study with flaviviruses suggested that structural dynamics of the virion impact antibody neutralization via exposure of ostensibly cryptic epitopes. To determine whether this holds true for the distantly related hepatitis C virus (HCV), whose neutralizing epitopes may be obscured by a glycan shield, apolipoprotein interactions, and the hypervariable region on the E2 envelope protein, the authors assessed how time and temperature of pre-incubation altered monoclonal antibody (MAb) neutralization of HCV. Notably, several MAbs showed increased inhibitory activity when pre-binding was performed at 37°C or after longer pre-incubation periods, and a corresponding loss-of-neutralization was observed when pre-binding was performed at 4°C. A similar profile of changes was observed with acute and chronic phase sera from HCV-infected patients. These data suggest that time and temperature of incubation modulate epitope exposure on the conformational ensembles of HCV virions and thus, alter the potency of antibody neutralization. Sabo MC, Luca VC, Ray SC, Bukh J, Fremont DH, Diamond MS. Hepatitis C virus epitope exposure and neutralization by antibodies is affected by time and temperature. Virology. 2012 Jan 20; 422(2): 174-184. Epub 2011 Nov 12.

**Hepatitis C Virus Infection is Associated with Painful Symptoms in HIV-infected Adults** The study aim was to assess whether hepatitis C virus (HCV) was associated with painful symptoms among patients with HIV. Using data from a prospective cohort of HIV-infected adults with alcohol problems, the authors assessed the effects of HCV on pain that interfered with daily living and painful symptoms (muscle/joint pain, headache and peripheral neuropathy). Exploratory analyses assessed whether depressive symptoms and inflammatory cytokines mediated the relationship between HCV and pain. HCV-infected participants (n = 200) had higher odds of pain that interfered with daily living over time (adjusted odds ratio [AOR] 1.43; 95% CI: 1.02-2.01; p = 0.04) compared to those not infected with HCV. HIV/HCV co-infected participants had higher odds of muscle or joint pain (AOR 1.45; 95% CI: 1.06-1.97; p = 0.02) and headache (AOR 1.57; 95% CI: 1.18-2.07; p<0.01). The association between HCV and

peripheral neuropathy did not reach statistical significance (AOR 1.33; 95% CI: 0.96-1.85; p = 0.09). Depressive symptoms and inflammatory cytokines did not appear to mediate the relationship between HCV and pain. Adults with HIV who are also co-infected with HCV are more likely to experience pain that interfered with daily living, muscle or joint pain, and headaches compared to those not co-infected. Research is needed to explore the association between HCV infection and pain, and to determine whether HCV treatment is an effective intervention. Tsui JI, Cheng DM, Libman H, Bridden C, Samet J. Hepatitis C virus infection is associated with painful symptoms in HIV-infected adults. AIDS Care. 2012 Jan 24. [Epub ahead of print]

**Assessing Candidacy for Acute Hepatitis C Treatment Among Active Young Injection Drug Users: A Case-Series Report** Treatment for acute hepatitis C virus (HCV) infection has significantly better outcomes than treatment for chronic infection. The short window of the acute period poses challenges for young injection drug users (IDU), who are at highest risk of HCV infection, to demonstrate treatment candidacy. The authors recruited patients with acute HCV from a prospective cohort study to examine clinical and behavioral issues related to treatment candidacy. They report on outcomes and how nursing case management affected candidacy. All five acutely-infected participants reported daily drug use at baseline. All established primary care and decreased their drug use. None received treatment for their acute infection; one was treated within 12 months of infection. Establishing treatment candidacy for young IDU in the acute phase involves various health domains. An acute infection's short period poses many challenges to establishing candidacy, but it is a window of opportunity to engage young IDU in health care. Asher A, Lum PJ, Page K. Assessing candidacy for acute hepatitis C treatment among active young injection drug users: a case-series report. J Assoc Nurses AIDS Care. 2012 Jan-Feb; 23(1): 16-29. Epub 2011 Apr 15.

**Perioperative Pharmacokinetics of Methadone in Adolescents** Methadone is frequently administered to adults experiencing anesthesia and receiving pain treatment. Methadone pharmacokinetics in adults are well characterized, including the perioperative period. Methadone is also used in children. There is, however, no information on methadone pharmacokinetics in children of any age. The purpose of this investigation was to determine the pharmacokinetics of intravenous methadone in children undergoing surgery. Perioperative opioid-sparing effects were also assessed. Eligible subjects were children 5-18 yr undergoing general anesthesia and surgery, with an anticipated postoperative inpatient stay exceeding 3 days. Three groups of 10 to 11 patients each received intravenous methadone hydrochloride after anesthetic induction in ascending dose groups of 0.1, 0.2, and 0.3 mg/kg (up to 20 mg). Anesthetic care was not otherwise changed. Venous blood was obtained for 4 days, for stereoselective determination of methadone and metabolites. Pain assessments were made each morning. Daily and total opioid consumption was determined. Perioperative opioid consumption and pain was determined in a second cohort, which was matched to age, sex, race, ethnicity, surgical procedure, and length of stay, but not receiving methadone. The final methadone study cohort was 31 adolescents (14 ± 2 yr, range 10-18) undergoing major spine surgery for a diagnosis of scoliosis. Methadone pharmacokinetics were linear over the dose range 0.1-0.3 mg/kg. Disposition was stereoselective. Methadone administration did not dose-dependently affect postoperative pain scores, and did not dose-dependently decrease daily or total postoperative opioid consumption in spinal fusion patients. Methadone enantiomer disposition in adolescents undergoing surgery was

similar to that in healthy adults. Sharma A, Tallchief D, Blood J, Kim T, London A, Kharasch ED. Perioperative pharmacokinetics of methadone in adolescents. Anesthesiology. 2011 Dec; 115(6): 1153-1161.

**Sentiment Analysis of Suicide Notes: A Shared Task** This paper reports on a shared task involving the assignment of emotions to suicide notes. Two features distinguished this task from previous shared tasks in the biomedical domain. One is that it resulted in the corpus of fully anonymized clinical text and annotated suicide notes. This resource is permanently available and will (we hope) facilitate future research. The other key feature of the task is that it required categorization with respect to a large set of labels. The number of participants was larger than in any previous biomedical challenge task. The authors describe the data production process and the evaluation measures, and give a preliminary analysis of the results. Many systems performed at levels approaching the inter-coder agreement, suggesting that human-like performance on this task is within the reach of currently available technologies. Pestian JP, Matykiewicz P, Linn-Gust M, South B, Uzuner O, Wiebe J, Cohen KB, Hurdle J, Brew C. Sentiment Analysis of Suicide Notes: A Shared Task. Biomed Inform Insights. 2012 Jan 30; 5(Suppl 1): 3-16.

**Adjunctive Counseling During Brief and Extended Buprenorphine-Naloxone Treatment for Prescription Opioid Dependence: A 2-Phase Randomized Controlled Trial** No randomized trials have examined treatments for prescription opioid dependence, despite its increasing prevalence. The objective of this study was to evaluate the efficacy of brief and extended buprenorphine hydrochloride-naloxone hydrochloride treatment, with different counseling intensities, for patients dependent on prescription opioids. The study design was a randomized clinical trial using a 2-phase adaptive treatment research design. Brief treatment (phase 1) included 2-week buprenorphine-naloxone stabilization, 2-week taper, and 8-week postmedication follow-up. Patients with successful opioid use outcomes exited the study; unsuccessful patients entered phase 2: extended (12-week) buprenorphine-naloxone treatment, 4-week taper, and 8-week postmedication follow-up. The setting was 10 US sites. Patients comprised a total of 653 treatment-seeking outpatients dependent on prescription opioids. In both phases, patients were randomized to standard medical management (SMM) or SMM plus opioid dependence counseling; all received buprenorphine-naloxone. Predefined "successful outcome" in each phase included composite measures indicating minimal or no opioid use based on urine test-confirmed self-reports. During phase 1, only 6.6% (43 of 653) of patients had successful outcomes, with no difference between SMM and SMM plus opioid dependence counseling. In contrast, 49.2% (177 of 360) attained successful outcomes in phase 2 during extended buprenorphine-naloxone treatment (week 12), with no difference between counseling conditions. Success rates 8 weeks after completing the buprenorphine-naloxone taper (phase 2, week 24) dropped to 8.6% (31 of 360), again with no counseling difference. In secondary analyses, successful phase 2 outcomes were more common while taking buprenorphine-naloxone than 8 weeks after taper (49.2% [177 of 360] vs 8.6% [31 of 360], $P < .001$). Chronic pain did not affect opioid use outcomes; a history of ever using heroin was associated with lower phase 2 success rates while taking buprenorphine-naloxone. The authors conclude that prescription opioid-dependent patients are most likely to reduce opioid use during buprenorphine-naloxone treatment; if tapered off buprenorphine-naloxone, even after 12 weeks of treatment, the likelihood of an unsuccessful outcome is high, even in patients receiving counseling in addition to SMM. Weiss RD, Potter JS, Fiellin DA, Byrne M, Connery HS, Dickinson W, Gardin J,

Griffin ML, Gourevitch MN, Haller DL, Hasson AL, Huang Z, Jacobs P, Kosinski AS, Lindblad R, McCance-Katz EF, Provost SE, Selzer J, Somoza EC, Sonne SC, Ling W. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. Arch Gen Psychiatry. 2011 Dec; 68(12): 1238-1246. Epub 2011 Nov 7.

## SERVICES RESEARCH

**Counselor Training in Evidence-Based Psychosocial Treatments** Given that most addiction counselors enter the field unprepared to implement psychosocial evidence-based practices (EBPs), surprisingly little is known about the extent to which substance abuse treatment centers provide their counselors with formal training in these treatments. This study examines the extent of formal training that treatment centers provide their counselors in cognitive behavioral therapy (CBT), motivational interviewing (MI), contingency management (CM), and brief strategic family therapy (BSFT). Face-to-face interviews were conducted with 340 directors of a nationally representative sample of privately funded US substance abuse treatment centers. Although a substantial number of treatment centers provide their counselors with formal training in EBPs that they use with their clients, coverage is far from complete. For example, of those centers that use CBT, 34% do not provide their counselors with any formal training in CBT (either initially or annually), and 61% do not provide training in CBT that includes supervised training cases. Sizable training gaps exist for MI, CM, and BSFT as well. The large training gaps found in this study give rise to concerns regarding the integrity with which CBT, MI, CM, and BSFT are being delivered by counselors in private US substance abuse treatment centers. Future research should examine the generalizability of these findings to other types of treatment centers (e.g., public) and to the implementation of other EBPs. Olmstead TA, Abraham AJ, Martino S, Roman PM. Counselor training in several evidence-based psychosocial addiction treatments in private u.s. substance abuse treatment centers. Drug Alcohol Depend. 2012; 120: 149-154.

**What Oregon's Parity Law Can Tell us About The Federal Mental Health Parity and Addiction Equity Act and Spending on Substance Abuse Treatment Services** The Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act of 2008 (MHPAEA) requires commercial group health plans offering coverage for mental health and substance abuse services to offer those services at a level that is no more restrictive than for medical-surgical services. The MHPAEA is notable in restricting the extent to which health plans can use managed care tools on the behavioral health benefit. The only precedent for this approach is Oregon's 2007 state parity law. This study aims to provide evidence on the effect of comprehensive parity on utilization and expenditures for substance abuse treatment services. A difference-in-difference analysis compared individuals in five Oregon commercial plans (n=103,820) from 2005 to 2008 to comparison groups exempt from parity in Oregon (n=19,633) and Washington (n=39,447). The primary outcome measures were annual use and total expenditures. Spending for alcohol treatment services demonstrated statistically significant increase in comparison to the Oregon and Washington comparison groups. Spending on other drug abuse treatment services was not associated with statistically significant spending increases, and the effect of parity on overall spending (alcohol plus other drug abuse treatment services) was positive but not statistically significant from zero. Oregon's experience suggests that behavioral health insurance parity that places restrictions on how plans manage the benefit may lead to increases in expenditures for alcohol treatment services but is unlikely to lead to increases in spending for other drug abuse treatment services. McConnell K, Ridgely M, McCarty D. What Oregon's Parity Law can tell us about the Federal Mental Health Parity and Addiction Equity Act and spending on substance abuse treatment services. Drug Alc. Depend. 2012: 1-1.

**Behavioral Health Insurance Parity: Does Oregon's Experience Presage the National Experience With the Mental Health Parity and Addiction Equity Act?** The Mental Health Parity and Addiction Equity Act of 2008 prohibits commercial group health plans from imposing spending and visit limitations for mental health and substance abuse services that are not imposed on medical-surgical services. The act also restricts the use of managed care tools that apply to behavioral health benefits in ways that differ from how they apply to medical-surgical benefits. The only precedent for this approach is Oregon's state parity law, which was implemented in 2007. The goal of this study was to estimate the effect of Oregon's parity law on expenditures for mental health and substance abuse treatment services. The authors compared expenditures for commercially insured individuals in four Oregon health plans from 2005 through 2008 and a matched group of commercially insured individuals in Oregon who were exempt from parity. Using a difference-in-differences analysis, the authors analyzed the effect of comprehensive parity on spending for mental health and substance abuse services. Increases in spending on mental health and substance abuse services after implementation of Oregon's parity law were almost entirely the result of a general trend observed among individuals with and without parity. Expenditures per enrollee for mental health and substance abuse services attributable to parity were positive, but they did not differ significantly from zero in any of the four plans. Behavioral health insurance parity rules that place restrictions on how plans manage mental health and substance abuse services can improve insurance protections without substantial increases in total costs. McConnell K, Gast S, Ridgely M, Wallace N, Jacuzzi N, Rieckmann T, McFarland B, McCarty D. Behavioral health insurance parity: Does Oregon's experience presage the national experience with the Mental Health Parity And Addiction Equity Act? Am J Psychiatry. 2012; 169(1): 31-38.

**Association between Marijuana Exposure and Pulmonary Function Over 20 Years**
Marijuana smoke contains many of the same constituents as tobacco smoke, but whether it has similar adverse effects on pulmonary function is unclear. The objective of this study was to analyze associations between marijuana (both current and lifetime exposure) and pulmonary function. Data are from the Coronary Artery Risk Development in Young Adults (CARDIA) study, a longitudinal study collecting repeated measurements of pulmonary function and smoking over 20 years (March 26, 1985-August 19, 2006) in a cohort of 5115 men and women in 4 US cities. Mixed linear modeling was used to account for individual age-based trajectories of pulmonary function and other covariates including tobacco use, which was analyzed in parallel as a positive control. Lifetime exposure to marijuana joints was expressed in joint-years, with 1 joint-year of exposure equivalent to smoking 365 joints or filled pipe bowls. The primary outcome measure was forced expiratory volume in the first second of expiration (FEV(1)) and forced vital capacity (FVC). Marijuana exposure was nearly as common as tobacco exposure but was mostly light (median, 2-3 episodes per month). Tobacco exposure, both current and lifetime, was linearly associated with lower FEV(1) and FVC. In contrast, the association between marijuana exposure and pulmonary function was nonlinear ($P < .001$): at low levels of exposure, FEV(1) increased by 13 mL/joint-year (95% CI, 6.4 to 20; $P < .001$) and FVC by 20 mL/joint-year (95% CI, 12 to 27; $P < .001$), but at higher levels of exposure, these associations leveled or even reversed. The slope for FEV(1) was -2.2 mL/joint-year (95% CI, -4.6 to 0.3; $P = .08$) at more than 10 joint-years and -3.2 mL per marijuana smoking episode/mo (95% CI, -5.8 to -0.6; $P = .02$) at more than 20 episodes/mo. With very heavy marijuana use, the net association with FEV(1) was not significantly different from baseline, and the net association with FVC remained

significantly greater than baseline (e.g., at 20 joint-years, 76 mL [95% CI, 34 to 117]; P < .001). Occasional and low cumulative marijuana use was not associated with adverse effects on pulmonary function. Pletcherm M, Vittinghoffm E, Kalhanm R, Richmanm J, Saffordm M, Sidney S, Lin F, Kertesz S. Association between marijuana exposure and pulmonary function over 20 years. JAMA. 2012; 307(2): 173-181.

**Interorganizational and Resource Linkages are Associated with Timing of Buprenorphine Adoption** Identifying facilitators of more rapid buprenorphine adoption may increase access to this effective treatment for opioid dependence. Using a diffusion of innovations theoretical framework, the authors examine the extent to which programs' interorganizational institutional and resource-based linkages predict the likelihood of being an earlier adopter, later adopter, or non-adopter of buprenorphine. Data were derived from face-to-face interviews with administrators of 345 privately funded substance abuse treatment programs in 2007–2008. Results of multinomial logistic regression models show that interorganizational and resource linkages were associated with timing of adoption. Programs reporting membership in provider associations were more likely to be earlier adopters of buprenorphine. Programs that relied more on resource linkages, such as detailing activities by pharmaceutical companies and the National Institute on Drug Abuse website, were more likely to be earlier adopters of buprenorphine. These findings suggest that institutional and resource-based interorganizational linkages may expose programs to effective treatments, thereby facilitating more rapid and sustained adoption of innovative treatment techniques. Savage SA, Abraham AJ, Knudsen HK, Rotherauff TC, Roman PM. Timing of buprenorphine adoption by privately funded substance abuse treatment programs: The role of institutional and resource-based interorganizational linkages. J Subst Abuse Treat. 2012; 42: 16-24.

**Counselor Attitudes Related to Buprenorphine Adoption** Despite evidence that buprenorphine is effective and safe and offers greater access as compared with methadone, implementation for treatment of opiate dependence continues to be weak. Research indicates that legal and regulatory factors, state policies, and organizational and provider variables affect adoption of buprenorphine. This study uses hierarchical linear modeling to examine National Treatment Center Study data to identify counselor characteristics (attitudes, training, and beliefs) and organizational factors (accreditation, caseload, access to buprenorphine, and other evidence-based practices) that influence implementation of buprenorphine for treatment of opiate dependence. Analyses showed that provider training about buprenorphine, higher prevalence of opiate-dependent clients, and less treatment program emphasis on a 12-step model predicted greater counselor acceptance and perceived effectiveness of buprenorphine. Results also indicate that program use of buprenorphine for any treatment purpose (detoxification, maintenance, and/or pain management) and time (calendar year in data collection) was associated with increased diffusion of knowledge about buprenorphine among counselors and with more favorable counselor attitudes toward buprenorphine. Rieckmann TR, Kovas AE, McFarland BH, Abraham AJ. A multi-level analysis of counselor attitudes toward the use of buprenorphine in substance abuse treatment. J Subst Abuse Treat. 2012; 41: 374-385.

**Availability of Nicotine Replacement Therapy in Substance Use Disorder Treatment: Longitudinal Patterns of Adoption, Sustainability, and Discontinuation** There is growing recognition regarding the clinical importance of integrating smoking cessation services, such as nicotine replacement therapy (NRT), within programs that treat substance use disorders (SUDs) since the majority of individuals receiving treatment also smoke. Previous research has not examined the organizational characteristics associated with NRT availability over time in SUD treatment programs. Using longitudinal data collected from administrators of 868 SUD treatment programs over a four-year period, the availability of NRT in the forms of the nicotine patch or nicotine gum was measured. Associations between organizational covariates and NRT adoption were estimated using multinomial logistic regression. The rate of NRT availability significantly decreased over time from 38.0% of SUD programs at baseline to 33.8% at follow-up. The multinomial logistic regression model indicated programs that sustained adoption of NRT over time were more medically oriented, as measured by location in a hospital setting and access to physicians, and were less likely to offer outpatient services. Sustained and recent adopters of NRT were more likely to offer other smoking cessation interventions at follow- up than NRT discontinuers or NRT non-adopters. These findings suggest that patients' access to NRT varies across different types of treatment organizations. Future research should continue to measure the availability of NRT and other smoking cessation interventions in SUD treatment since these services may help patients to quit smoking and reduce the likelihood of SUD relapse. Knudsen H, Studts J. Availability of nicotine replacement therapy in substance use disorder treatment: Longitudinal patterns of adoption, sustainability, and discontinuation. Drug Alcohol Depend. 2011; 118(2-3): 244-250.

**A Model for Implementing Integrated Smoking Cessation and Addiction Treatment** Smoking prevalence among persons in addiction treatment is 3–4 times higher than in the general population. However, treatment programs often report organizational barriers to providing tobacco-related services. This study assessed the effectiveness of a six month organizational change intervention, Addressing Tobacco through Organizational Change (ATTOC), to improve how programs address tobacco dependence. The ATTOC intervention, implemented in three residential treatment programs, included consultation, staff training, policy development, leadership support and access to nicotine replacement therapy (NRT) medication. Program staff and clients were surveyed at pre- and post-intervention, and at 6 month follow-up. The staff survey measured knowledge of the hazards of smoking, attitudes about and barriers to treating smoking, counselor self-efficacy in providing such services, and practices used to address tobacco. The client survey measured knowledge, attitudes, and tobacco-related services received. NRT use was tracked. From pre- to post-intervention, staff beliefs became more favorable toward treating tobacco dependence ($F(1, 163) = 7.15$, $p = 0.008$), NRT use increased, and tobacco-related practices increased in a non-significant trend ($F(1, 123) = 3.66$, $p = 0.058$). Client attitudes toward treating tobacco dependence became more favorable ($F(1, 235) = 10.58$, $p = 0.0013$) and clients received more tobacco-related services from their program ($F(1, 235) = 92.86$, $p < 0.0001$) and from their counselors ($F(1, 235) = 61.59$, $p < 0.0001$). Most changes remained at follow-up. The ATTOC intervention can help shift the treatment system culture and increase tobacco services in addiction treatment programs. Guydish J, Ziedonis D, Tajima B, Seward G, Passalacqua E, Chan M, Delucchi K, Levy M, Kolodzeij M, Bingham G. Addressing Tobacco Through Organizational Change (ATTOC) in residential addiction treatment settings. Drug Alcohol Depend. 2012; 121: 30-37.

**Surviving Drug Addiction: The Effect of Treatment and Abstinence on Mortality** The authors examined the relationships between substance abuse treatment, abstinence, and mortality in a sample of individuals entering treatment. They also estimated overall mortality rates and the extent to which they varied according to demographic, clinical severity, and treatment variables. They used data from a 9-year longitudinal study of 1326 adults entering substance abuse treatment on the west side of Chicago, of who 131 died (11.0 per 1000 person-years). Baseline predictors, initial and long-term treatment response, and substance use patterns were used to predict mortality rates and time to mortality. Older age, health problems, and substance use were associated with an increased risk of mortality, and higher percentages of time abstinent and longer durations of continuous abstinence were associated with a reduced risk of mortality. Treatment readmission in the first 6 months after baseline was related to an increased likelihood of abstinence, whereas readmission after 6 months was related to a decreased likelihood of abstinence, suggesting that treatment timing is significant. These findings suggest the need to shift the addiction treatment field from an acute care model to a chronic disease management paradigm and the need for more aggressive screening, intervention, and addiction management over time. Scott C, Dennis M, Laudet A, Funk R, Simeone R. Surviving drug addiction: The effect of treatment and abstinence on mortality. Am J Public Health. 2011; 101(4): 737-744.

**Training and Retaining Staff to Competently Deliver an Evidence-Based Practice: The Role of Staff Attributes and Perceptions of Organizational Functioning** Within the context of an initiative to implement evidence-based practices (EBPs) for adolescents with substance use disorders, this study examined the extent to which staff factors measured at an initial EBP training workshop were predictive of EBP competence and turnover status of staff (N = 121) measured 6, 9, and 12 months post training. By the final assessment point, 52.3% of staff transitioned to the employed/EBP-competent category, 26.6% transitioned to the not employed/not EBP-competent category, 4.6% transitioned to the not employed/EBP-competent category, and 16.5% had not transitioned out of the initial category. Multilevel multinomial regression analysis identified several measures that were significant predictors of staff transitions to the not employed/not EBP-competent category (e.g., program needs, job satisfaction, burnout) and transitions to the employed/EBP-competent category (e.g., months in position, pressures for change, influence). Findings have implications for the development and testing of strategies to train and retain staff to deliver EBPs in practice settings. Garner B, Hunter B, Godley S, Godley M. Training and retaining staff to competently deliver an evidence-based practice: The role of staff attributes and perceptions of organizational functioning. J Subst Abuse Treat. 2012; 42: 191-200.

**Promising Comprehensive Adolescent Juvenile Justice Intervention Requires Macrosystem Commitment, Adequate Personnel and Funding for Sustainability** Responding to urgent calls for effective interventions to address young offenders' multiple and interconnected problems, a new variant of an existing empirically-validated intervention for drug-using adolescents, Multidimensional Family Therapy (MDFT)-Detention to Community (DTC) was tested in a two-site controlled trial. This article (a) outlines the rational and protocol basics of the MDFT-DTC intervention, a program for substance-using juvenile offenders that links justice and community reintegration; (b) presents implementation outcomes, including fidelity, satisfaction, and substance abuse-juvenile justice system collaboration outcomes; and (c) details the implementation and sustainability challenges in a cross-system (substance abuse treatment and

juvenile justice) adolescent intervention. Findings support the effectiveness of the MDFT-DTC intervention, and the need to develop a full implementation model in which transfer and dissemination issues could be explored more fully, and tested experimentally. Liddle HA, Dakof GA, Henderson C, Rowe C. Implementation outcomes of multidimensional family therapy-detention to community: A reintegration program for drug-using juvenile detainees. Int J Offender Ther Comp Criminol. 2011; 55(4): 587-604.

**Early Re-Intervention Promotes More Durable Abstinence from Drug Use** People suffering from the "chronic relapsing disease of addiction" face decades of attempts to achieve abstinence with numerous relapses to illicit drug use. These patients seem to be stuck in a proverbial public health revolving door. One intervention designed to slow the revolving door is early re-intervention (ERI). This ERI study examined 446 adult addicts randomly assigned to either quarterly assessments (control), or quarterly recovery management checkups (RMCs) which included an assessment of relapse potential, and an intervention to encourage and assist patients to re-enter treatment when needed. Results showed that RMCs led patients to return to treatment sooner than controls, and relative to controls, they received more total days of treatment, experienced fewer quarters in need of treatment (in relapse), fewer substance use-related problems per month, and more total days of abstinence from drugs. Dennis ML, Scott CK. Four-year outcomes from the early re-intervention (ERI) experiment using recovery management checkups (RMCS). Drug Alcohol Depend. 2012; 121: 10-17.

**The Economic Costs of Quarterly Monitoring and Recovery Management Checkups for Adults with Chronic Substance Use Disorders** Recovery management checkups (RMCs) for clients with substance use disorders reduce the time from relapse to treatment reentry, increase treatment retention, and improve long-term outcomes. The objectives of this article are to calculate and compare the economic costs of providing outcome monitoring (OM) only with those of providing OM + RMC to help understand the feasibility of disseminating this model more widely. The authors estimate the total and incremental costs of OM and OM + RMC using data from a recently completed randomized controlled trial with adult chronic substance users (N = 446). Adding RMC to OM increased total intervention costs by about 50% per person per year ($707 to $1,283) and quarter ($177 to $321). It cost an average of $834 to identify a person in relapse and $2,699 to identify, link, and retain them in treatment. The increased costs of RMC are modest relative to the substantial societal costs of chronic substance users returning to regular use, crime, and other risk behaviors. Dennis M, French M, McCollister K, Scott C. The economic costs of quarterly monitoring and recovery management checkups for adults with chronic substance use disorders. J Subst Abuse Treat. 2011; 41(2): 201-207.

**Barriers to the Implementation of Medication-Assisted Treatment for Substance Use Disorders: The Importance of Funding Policies and Medical Infrastructure** Despite growing interest in the use of evidence-based treatment practices, adoption of pharmacotherapies for treating substance use disorders (SUDs) remains modest. Using data from telephone interviews with 250 administrators of publicly funded SUD treatment programs, this study estimated a model of adoption of medication assisted treatment (MAT) for SUDs and examined the relative importance of regulatory, cultural, medical resource, patient-level, and funding barriers to MAT implementation. MAT-adopting programs had significantly greater medical resources, as measured by the employment of physicians and nurses, than non-adopting programs.

Administrators of non-adopting programs were asked to rate the importance of 18 barriers to MAT implementation. The most strongly endorsed barriers were regulatory prohibitions due to the program's lack of medical staff, funding barriers to implementing MAT, and lack of access to medical personnel with expertise in delivering MAT. Barriers related to insufficient information about MAT and unsupportive staff attitudes were not widely endorsed. These findings suggest that efforts to promote the implementation of MAT that are inattentive to funding barriers and weaknesses in medical infrastructure may achieve sub-optimal results. Knudsen H, Abraham A, Oser C. Barriers to the implementation of medication-assisted treatment for substance use disorders: The importance of funding policies and medical infrastructure. Eval Program Plann. 2011; 34(4): 375-381.

**Using Medication-Assisted Treatment for Substance Use Disorders: Evidence of Barriers and Facilitators of Implementation** The use of medications to treat substance use disorders (SUDs) has emerged as a potentially central part of the treatment armamentarium. In this paper the authors present data from several recent US national surveys showing that despite the clinical promise of these medications, there has been limited adoption of pharmacotherapies in the treatment of SUDs. The data reveal variable patterns of use of disulfiram, buprenorphine, tablet naltrexone, acamprosate and injectable naltrexone. After examining the environmental and institutional context for the adoption of pharmacotherapies, the specific organizational facilitators and barriers of medication adoption are considered. The paper concludes with a discussion of the minimal clinical and administrative guidance available to enhance adoption, the lack of client and consumer knowledge of medications that puts a brake on their adoption and availability, and the difficulties that must be surmounted in bringing new medications to market. Roman P, Abraham A, Knudsen H. Using medication-assisted treatment for substance use disorders: evidence of barriers and facilitators of implementation. Addict Behav. 2011; 36(4): 584-590.

**Adoption of Medication in Substance Abuse Treatment Is Affected By Awareness of Funding Policies and Beliefs about Single State Agency Support** Despite growing interest in the use of evidence-based treatment practices for treating substance use disorders, adoption of medications by treatment programs remains modest. Drawing on resource dependence and institutional theory, this study examined the relationships between adoption of medications by treatment programs and their perceptions about the state policy environment. Data were collected through mailed surveys and telephone interviews with 250 administrators of publicly funded substance abuse treatment programs in the United States between 2009 and 2010. Multiple imputation and multivariate logistic regression were used to estimate the associations between perceptions of the state policy environment and the odds of adopting at least one medication for the treatment of substance use disorders. A total of 91 (37%) programs reported having prescribed any medication for treatment of a substance use disorder. Programs were significantly more likely to have adopted at least one medication if they perceived greater support for medications by the Single State Agency. The odds of adoption were significantly greater if the program was aware that at least one medication was included on their state's Medicaid formulary and that state-contract funding permitted the purchase of medications. States may play significant roles in promoting the adoption of medications, but adequate dissemination of information about state policies and priorities may be vital to further adoption. Future research should continue to study the relationships between the adoption of medications for treating

substance use disorders and the evolving policy environment. Knudsen HK, Abraham AJ. Perceptions of the state policy environment and adoption of medications in the treatment of substance use disorders. Psychiatric Serv. 2012; 63(1): 19-25.

**Methadone Initiation Prior to Release from Incarceration Improves Post-Release Treatment Continuation** Individuals who use heroin and illicit opioids are at high risk for infection with human immunodeficiency virus (HIV) and other blood-borne pathogens, as well as incarceration. The purpose of the randomized trial reported here is to compare outcomes between participants who initiated methadone maintenance treatment (MMT) prior to release from incarceration, with those who were referred to treatment at the time of release. Participants who initiated MMT prior to release were significantly more likely to enter treatment post release ($P < .001$) and for participants who did enter treatment, those who received MMT prerelease did so within fewer days ($P = .03$). They also reported less heroin use ($P = .008$), other opiate use ($P = .09$), and injection drug use ($P = .06$) at 6 months. Initiating MMT in the weeks prior to release from incarceration is a feasible and effective way to improve MMT access post release and to decrease relapse to opioid use. McKenzie M, Zaller N, Dickman SL, Green TC, Parihk A, Friedmann PD, Rich JD. A randomized trial of methadone initiation prior to release from incarceration. Subst Abus. 2012; 33: 19-21.

**Provider and Practice Characteristics Associated With Use of Rapid HIV Testing By General Internists** Rapid HIV testing could increase routine HIV testing. Most previous studies of rapid testing were conducted in acute care settings, and few described the primary care providers' perspective. The objective of this study was to identify characteristics of general internal medicine physicians with access to rapid HIV testing, and to determine whether such access is associated with differences in HIV-testing practices or perceived HIV-testing barriers. The study design was a Web-based cross-sectional survey conducted in 2009. Participants comprised a total of 406 physician members of the Society of General Internal Medicine who supervise residents or provide care in outpatient settings. Surveys assessed provider and practice characteristics, HIV-testing types, HIV-testing behavior, and potential barriers to HIV testing. Among respondents, 15% had access to rapid HIV testing. In multivariable analysis, physicians were more likely to report access to rapid testing if they were non-white (OR 0.45, 95% CI 0.22, 0.91), had more years since completing training (OR 1.06, 95% CI 1.02, 1.10), practiced in the northeastern US (OR 2.35; 95% CI 1.28, 4.32), or their practice included a higher percentage of uninsured patients (OR 1.03; 95% CI 1.01, 1.04). Internists with access to rapid testing reported fewer barriers to HIV testing. More respondents with rapid than standard testing reported at least 25% of their patients received HIV testing (51% versus 35%, p=0.02). However, access to rapid HIV testing was not significantly associated with the estimated proportion of patients receiving HIV testing within the previous 30 days (7.24% vs. 4.58%, p=0.06). Relatively few internists have access to rapid HIV testing in outpatient settings, with greater availability of rapid testing in community-based clinics and in the northeastern US. Future research may determine whether access to rapid testing in primary care settings will impact routinizing HIV testing. Korthius PT. Provider and practice characteristics associated with use of rapid HIV testing by general internists. J Gen Intern Med. 2011; 26: 1258-1264.

**NIATx Model Improved EBP Implementation in VA Hospitals** The objective of this study was to examine how attributes affecting sustainability differ across Veterans Health Administration organizational components and by staff characteristics. Subjects comprised surveys of 870 change team members and 50 staff interviews within the Veterans Affairs' Mental Health System Redesign initiative. A 1-way ANOVA with a Tukey post hoc test examined differences in sustainability by Veteran Integrated Service Networks, job classification, and tenure from staff survey data of the Sustainability Index. Qualitative interviews used an iterative process to identify "a priori" and "in vivo" themes. A simple stepwise linear regression explored predictors of sustainability. Sustainability differed across Veteran Integrated Service Networks and staff tenure. Job classification differences existed for the following: (1) benefits and credibility of the change and (2) staff involvement and attitudes toward change. Sustainability barriers were staff and institutional resistance and non-supportive leadership. Facilitators were commitment to veterans, strong leadership, and use of quality improvement tools. Sustainability predictors were outcomes tracking, regular reporting, and use of Plan, Do, Study, Adjust cycles. Creating homogeneous implementation and sustainability processes across a national health system is difficult. Despite the Veterans Affairs' best evidence-based implementation efforts, there was significant variance. Locally tailored interventions might better support sustainability than "one-size-fits-all" approaches. Further research is needed to understand how participation in a quality improvement collaborative affects sustainability. Ford JH, Krahn D, Wise M, Anderson OK. Measuring sustainability within the Veterans Administration Mental Health System Redesign Initiative. Q Manger Health Care. 2011; 20(4): 263-279.

**Implementing The NIATx Model Of Quality Improvement Improves Financial Performance And Staff Retention** The Network for the Improvement of Addiction Treatment (NIATx) promotes treatment access and retention through a customer-focused quality improvement model. This paper explores the issue of the "business case" for quality improvement in addiction treatment from the provider's perspective. The business case model developed in this paper is based on case examples of early NIATx participants coupled with a review of the literature. Process inefficiencies indicated by long waiting times, high no-show rates, and low continuation rates cause underutilization of capacity and prevent optimal financial performance. By adopting customer-focused practices aimed at removing barriers to treatment access and retention, providers may be able to improve financial performance, increase staff retention, and gain long-term strategic advantage. Quanbeck AR, Madden L, Edmondson E, Ford KH, McConnell KJ, McCarty D, Gustafson DH. A business case for quality improvement in addiction treatment: Evidence from the NIATx Collaborative. J Behav Health Serv Res. 2012; 39(1): 91-100.

**Public Health Implications for Adequate Transitional Care for HIV-Infected Prisoners: Five Essential Components** In the United States, 10 million inmates are released every year and human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) prevalence is several-fold greater in criminal justice populations than in the community. Few effective linkage-to-the-community programs are currently available for prisoners infected with HIV. As a result, combination antiretroviral therapy (cART) is seldom continued after release, and virological and immunological outcomes worsen. Poor HIV treatment outcomes result from a myriad of obstacles that released prisoners face upon reentering the community,

including homelessness, lack of medical insurance, relapse to drug and alcohol use, and mental illness. This article will focus on 5 distinct factors that contribute significantly to treatment outcomes for released prisoners infected with HIV and have profound individual and public health implications: (1) adaptation of case management services to facilitate linkage to care; (2) continuity of cART; (3) treatment of substance use disorders; (4) continuity of mental illness treatment; and (5) reducing HIV-associated risk-taking behaviors as part of secondary prevention. Altice FL. Public health implications for adequate transitional care for HIV-infected prisoners: Five essential components. Clin Infect Dis. 2011; 53: 469-479.

**Is Primary Care Providers' Trust in Socially Marginalized Patients Affected by Race?** Interpersonal trust plays an important role in the clinic visit. Clinician trust in the patient may be especially important when prescribing opioid analgesics because of concerns about misuse. Previous studies have found that non-white patients are perceived negatively by clinicians. The objective of this study was to examine whether clinicians' trust in patients differed by patients' race/ethnicity in a socially marginalized cohort. This was a cross-sectional study of patient-clinician dyads. Participants were 169 HIV infected indigent patients recruited from the community and their 61 primary care providers (PCPs.) Main outcome measure was the Physician Trust in Patients Scale (PTPS), a validated scale that measures PCPs' trust in patients. The mean PTPS score was 43.2 (SD 10.8) out of a possible 60. Reported current illicit drug use and prescription opioid misuse were similar across patients' race or ethnicity. However, both patient illicit drug use and patient non-white race/ethnicity were associated with lower PTPS scores. In a multivariate model, non-white race/ethnicity was independently associated with PTPS scores 6.3 points lower than whites (95% CI: -9.9, -2.7). Current illicit drug use was associated with PTSP scores 5.5 lower than no drug use (95% CI -8.5, -2.5). In a socially marginalized cohort, non-white patients were trusted less than white patients by their PCPs, despite similar rates of illicit drug use and opioid analgesic misuse. The effect was independent of illicit drug use. This finding may reflect unconscious stereotypes by PCPs and may underlie disparities in chronic pain management. Moskowitz D, Thom D, Guzman D, Penko J, Miaskowski C, Kushel M. Is primary care providers' trust in socially marginalized patients affected by race? J Gen Intern Med. 2011; 26(28): 846-851.

**Bending the Prescription Opioid Dosing and Mortality Curves: Impact of the Washington State Opioid Dosing Guideline** Opioid use and dosing for patients with chronic non-cancer pain have dramatically increased over the past decade, resulting in a national epidemic of mortality associated with unintentional overdose, and increased risk of disability among injured workers. The authors assessed changes in opioid dosing patterns and opioid-related mortality in the Washington State (WA) workers ' compensation system following implementation of a specific WA opioid dosing guideline in April, 2007. Using detailed computerized billing data from WA workers' compensation, the authors report overall prevalence of opioid prescriptions, average morphine-equivalent dose (MED)/day, and proportion of workers on disability compensation receiving opioids and high-dose (≥ 120 mg/day MED) opioids over the past decade. They also report the trend of unintentional opioid deaths during the same time period. Compared to before 2007, there has been a substantial decline in both the MED/day of long-acting DEA Schedule II opioids (by 27%) and the proportion of workers on doses ≥ 120 md/day MED (by 35%). There was a 50% decrease from 2009 to 2010 in the number of deaths. The introduction in WA of an opioid dosing guideline appears to be associated temporally with a decline in the mean dose for

long-acting opioids, percent of claimants receiving opioid doses ≥ 120 mg MED per day, and number of opioid-related deaths among injured workers. Franklin G, Mai J, Turner J, Sullivan M, Wickizer T, Fulton-Kehoe D. Bending the prescription opioid dosing and mortality curves: Impact of the Washington State Opioid Dosing Guideline. Am J Ind Med. 2011; 12: 1-4.

**Occurrence and Characteristics of Chronic Pain in a Community-Based Cohort of Indigent Adults Living With HIV Infection** Pain is common among people living with HIV/AIDS (PLWHA), but little is known about chronic pain in socioeconomically disadvantaged HIV-infected populations with high rates of substance abuse in the post antiretroviral era. This cross-sectional study describes the occurrence and characteristics of pain in a community-based cohort of 296 indigent PLWHA. Participants completed questionnaires about sociodemographics, substance use, depression, and pain. Cut-point analysis was used to generate categories of pain severity. Of the 270 participants who reported pain or the use of a pain medication in the past week, 8.2% had mild pain, 38.1% had moderate pain, and 53.7% had severe pain. Female sex and less education were associated with more severe pain. Depression was more common among participants with severe pain than among those with mild pain. Increasing pain severity was associated with daily pain and with chronic pain. Over half of the participants reported having a prescription for an opioid analgesic. Findings from this study suggest that chronic pain is a significant problem in this high risk, socioeconomically disadvantaged group of patients with HIV disease and high rates of previous or concurrent use of illicit drugs. This article presents epidemiological data showing that unrelieved chronic pain is a significant problem for indigent people living with HIV. Participants reported pain severity similar to those with metastatic cancer. Despite high rates of substance use disorders, approximately half received prescriptions for opioid analgesics, although few for long-acting agents. Miaskowski C, Penko J, Guzman D, Mattson J, Bangsberg D, Kushel M. Occurrence and characteristics of chronic pain in a community-based cohort of indigent adults living with HIV infection. J Pain. 2011; 12(9): 1004-1016.

**Long-Term Opioid Therapy Reconsidered** In the past 20 years, primary care physicians have greatly increased prescribing of long-term opioid therapy. However, the rise in opioid prescribing has outpaced the evidence regarding this practice. Increased opioid availability has been accompanied by an epidemic of opioid abuse and overdose. The rate of opioid addiction among patients receiving long-term opioid therapy remains unclear, but research suggests that opioid misuse is not rare. Recent studies report increased risks for serious adverse events, including fractures, cardiovascular events, and bowel obstruction, although further research on medical risks is needed. New data indicate that opioid-related risks may increase with dose. From a societal perspective, higher-dose regimens account for the majority of opioids dispensed, so cautious dosing may reduce both diversion potential and patient risks for adverse effects. Limiting long-term opioid therapy to patients for whom it provides decisive benefits could also reduce risks. Given the warning signs and knowledge gaps, greater caution and selectivity are needed in prescribing long-term opioid therapy. Until stronger evidence becomes available, clinicians should err on the side of caution when considering this treatment. Von Korff M, Kolodny A, Deyo R, Chou R. Long-term opioid therapy reconsidered. Ann Intern Med. 2011; 155(5): 325-328.

**Trajectories of Drug Use and Mortality Outcomes Among Adults Followed Over 18 Years**
For adults in general population community settings, data regarding long-term course and outcomes of illicit drug use are sparse, limiting the formulation of evidence-based recommendations for drug use screening of adults in primary care. The objective of this study was to describe trajectories of three illicit drugs (cocaine, opioids, amphetamines) among adults in community settings and to assess their relation to all-cause mortality. The study design employed a longitudinal cohort, 1987/88 - 2005/06 in community-based recruitment from four cities (Birmingham, Chicago, Oakland, Minneapolis). Participants were healthy adults, balanced for race (black and white) and gender were assessed for drug use from 1987/88-2005/06, and for mortality through 12/31/2008 (n = 4301). Data collection included: use of cocaine, amphetamines, and opioids (last 30 days) was queried in the following years: 1987/88, 1990/91, 1992/93, 1995/96, 2000/01, 2005/06; survey-based assessment of demographics and psychosocial characteristics; mortality over 18 years. Trajectory analysis identified four groups: Nonusers (n = 3691, 85.8%), Early Occasional Users (n = 340, 7.9%), Persistent Occasional Users (n = 160, 3.7%), and Early Frequent/Later Occasional Users (n = 110, 2.6%). Trajectories conformed to expected patterns regarding demographics, other substance use, family background and education. Adjusting for demographics, baseline health status, health behaviors (alcohol, tobacco), and psychosocial characteristics, Early Frequent/Later Occasional Users had greater all-cause mortality (Hazard Ratio, HR = 4.94, 95% CI = 1.58-15.51, p = 0.006). The study's limitations include the fact that the study was restricted to three common drugs, and trajectory analyses represent statistical approximations rather than identifiable "types". Causal inferences are tentative. Four trajectories describe illicit drug use from young adulthood to middle age. Two trajectories, representing over one third of adult users, continued use into middle age. These persons were more likely to continue harmful risk behaviors such as smoking, and more likely to die. Kertesz S, Khodneva Y, Richman J, Tucker J, Safford M, Jones B, Schumacher J, Pletcher M. Trajectories of drug use and mortality outcomes among adults followed over 18 years. J Gen Intern Med. 2012; e-pub ahead of print.

**Methadone Retention in Treatment is Highly Related to Treatment Satisfaction** Longer tenure in methadone treatment has been associated with positive outcomes such as reductions in drug use and crime, HIV seroconversion, and overdose death. Retention in treatment was examined for 351 opioid-dependent individuals who had been newly admitted to one of six methadone programs in Baltimore, Maryland. Cox proportional hazards regression was used to predict number of days retained in treatment to 90 days from baseline ASI Composite scores and Treatment Motivation scales. A second analysis predicted days in treatment to 365 days using the same baseline variables plus 3-month Motivation scales, Patient Satisfaction scales, and methadone dose in the 248 individuals who had remained in treatment at least 3 months. Analyses held constant gender, race, age, whether participants had a history of regularly smoking cocaine, whether participants were on parole/probation, and program site. Retention at 90 days was predicted by female gender, and greater baseline Treatment Readiness (p = .005) but lower Desire for Help (p = .010). Retention at 365 days was predicted by higher baseline ASI Medical Composite scores (p = .037) and lower Legal Composite scores (p = .039), higher 3-month Treatment Satisfaction scores (p = .008), and higher dose (p = .046). Greater satisfaction with treatment at 3 months was a significant predictor of retention at 12 months, indicating the importance of understanding the role satisfaction plays in determining retention. Greater severity of legal problems was associated with shorter retention, suggesting that program efforts to

increase services to criminal justice patients (e.g., legal counseling) may constitute a useful addition to treatment. Kelly SM, O'Grady KE, Mitchell SG, Brown BS, Schwartz RP. Predictors of methadone treatment retention from a multi-site study: A survival analysis. Drug Alcohol Depend. 2012; 117: 170-175.

**Tobacco Withdrawal Components and Their Relations with Cessation Success** Tobacco withdrawal is a key factor in smoking relapse, but important questions about the withdrawal phenomenon remain. This research was intended to provide information about two core components of withdrawal (negative affect and craving): (1) how various withdrawal symptom profile dimensions (e.g., mean level, volatility, extreme values) differ between negative affect and craving; and (2) how these dimensions relate to cessation outcome. Adult smokers (N = 1,504) in a double-blind randomized placebo-controlled smoking cessation trial provided real-time withdrawal symptom data four times per day for 4 weeks (2 weeks pre-quit and 2 weeks post-quit) via palmtop computers. Cessation outcome was biochemically confirmed 8-week point-prevalence abstinence. Examination of craving and negative affect dimensions following a cessation attempt revealed that craving symptoms differed from negative affect symptoms, with higher means, greater variability, and a greater incidence of extreme peaks. Regression analyses revealed that abstinence was associated with lower mean levels of both craving and negative affect and fewer incidences of extreme craving peaks. In a multivariate model, the increase in mean craving and negative affect scores each uniquely predicted relapse. Real-time reports revealed different patterns of abstinence-related negative affect and craving and that dimensions of both predict cessation outcome, suggesting that negative affect and craving dimensions each has motivational significance. This underscores the complexity of withdrawal as a determinant of relapse and the need to measure its distinct components and dimensions. Piper M, Schlam T, Cook J, Sheffer M, Smith S, Loh W, Bolt D, Kim S, Kaye J, Hefner K, Baker T. Tobacco withdrawal components and their relations with cessation success. Psychopharmacology (Berl). 2011; 216(4): 569-578.

**Mortality among Substance-Using Mothers in California: A 10-Year Prospective Study** The aims of this study were to examine mortality rates and causes of death among a cohort of substance-using mothers and to identify risk factors that predict mortality. This is a prospective study of a cohort of 4,447 substance using mothers (pregnant or parenting) who were enrolled during 2000-02 in 40 drug abuse treatment programs across California. All mothers were assessed at baseline using the Addiction Severity Index. Mortality data were obtained from the National Death Index and causes of death were coded using ICD-10. Standardized mortality ratios (SMR) were calculated relative to women in the general population adjusted for age. Proportional hazard (Cox) regression was used to identify risk factors predicting death. At the end of 2010, 194 deaths were confirmed, corresponding to a crude mortality rate of 4.47 per 1000 person-years and SMR of 8.4 (95% confidence interval: 7.2-9.6). Drug overdose (28.8%), cardiovascular disease (10%), and alcohol or drug disorders (8.9%) were the leading causes of death. Baseline factors associated with higher mortality included older age, being white (relative to African American or Hispanic), heroin, alcohol, cocaine or marijuana (relative to methamphetamine) as the primary drug problem, drug injection and greater severity of employment, medical/health and psychiatric problems. Substance-using mothers have 8.4 times the mortality than that observed among US women of similar age. Greater severity of employment, medical/health and psychiatric problems contributed to the elevated mortality. Hser

Y. Mortality among substance-using mothers in California: A 10-year prospective study. Addiction. 2011; 107: 215-222.

**Physicians in the Substance Abuse Treatment Workforce: Understanding Their Employment within Publicly Funded Treatment Organizations** The employment of physicians by substance abuse treatment organizations is understudied, despite physicians' importance in implementing pharmacotherapy and integrating treatment into the broader system of medical care. Drawing on data collected from 249 publicly funded treatment organizations, this study examined organizational and environmental factors associated with the employment of physicians in these settings. A negative binomial regression model indicated that greater numbers of physicians were employed when organizations offered detoxification services, were embedded in health care settings, and were larger in size. Funding barriers, including the costs of physicians and inadequate reimbursement by funders, were negatively associated with physician employment. Programs unaware that they could use state contract funding to pay for medical staff employed fewer numbers of physicians than programs aware of this type of state policy. Attempts to increase physician employment in substance abuse treatment may require attention to both organizational and environmental factors rather than simply trying to attract individuals to the field. Increasing physician employment may be challenging in the current economic climate. Beth OC. Physicians in the substance abuse treatment workforce: Understanding their employment within publicly funded treatment organizations. J Subst Abuse Treat .2012, Jan.31. [Epub ahead of print].

**Correlates of Participation in Peer Recovery Support Groups** This study explores the correlates of probationers' participation in 12-step programs, voluntary treatment, and mandated treatment, with respect to the geographic location of where the services are being provided as the primary covariate of interest. Data were derived from face to- face interviews with rural and urban probationers (N = 1,464). Results of the three logistic regression models suggested that even when all the covariates are taken into account, urban probationers were significantly more likely to have been involved in 12-step programs, voluntary treatment, and mandated treatment over their lifespan. Despite high levels of self-reported substance use among all participants, treatment services were underused by rural probationers. These data suggest that individuals residing in rural communities may face additional barriers to receiving treatment services and that criminal involvement is associated with participation in peer recovery support groups and treatment. Future studies can investigate criminal involvement as an avenue to enhance recovery and how to overcome treatment barriers in rural areas. Beth, OC. Correlates of participation in peer recovery support groups as well as voluntary and mandated substance abuse treatment among rural and urban probationers. J Subst Abuse Treat. 2012; 42: 95-101.

**Skin and Needle Hygiene Intervention for Injection Drug Users: Results from a Randomized, Controlled Stage I Pilot Trial** A new skin and needle hygiene intervention, designed to reduce high-risk injection practices associated with bacterial and viral infections, was tested in a pilot, randomized controlled trial. Participants included 48 active heroin injectors recruited through street outreach and randomized to either a 2-session intervention or an assessment-only condition (AO) and followed up for 6 months. The primary outcome was skin- and needle-cleaning behavioral skills measured by videotaped demonstration. Secondary outcomes were high-risk injection practices, intramuscular injection, and bacterial infections.

Intervention participants had greater improvements on the skin (d = 1.00) and needle-cleaning demonstrations (d = .52) and larger reductions in high-risk injection practices (d = .32) and intramuscular injection (d = .29), with a lower incidence rate of bacterial infections (hazard ratio = .80), at 6 months compared with AO. The new intervention appears feasible and promising as a brief intervention to reduce bacterial and viral risks associated with drug injection. Phillips K, Stein M, Anderson B, Corsi K. Skin and needle hygiene intervention for injection drug users: Results from a randomized, controlled Stage I pilot trial. J Subst Abuse Treat. 2012; E-pub 001-009.

**Validation of a New Measure for Assessing Motivational Interviewing Skill among Addiction Counselors** Benefits of empirically supported interventions hinge on clinician skill, particularly for motivational interviewing (MI). Existing MI skill assessments are limited with respect to validity (e.g., self-report) and practicality (e.g., coding session tapes). To address these limitations, the authors developed and evaluated two versions of a web-based assessment of MI skills, the Computer Assessment of Simulated Patient Interviews (CASPI). Ninety-six counselors from the community and 24 members of the Motivational Interviewing Network of Trainers (MINT) completed the CASPI (N = 120), in which they verbally responded via microphones to video clips comprising three 9-item vignettes. Three coders used an emergent coding scheme, which was compared with alternative MI skills measures. CASPI demonstrated excellent internal consistency when averaging across two or three vignettes (α's = .86–.89). Intraclass correlations were above .40 for most items. Confirmatory factor analyses supported a correlated three-factor model: MI-consistent, resistance-engendering and global change talk orientation rating. Means and factor loadings were invariant across forms (i.e., the two alternative versions of CASPI), and factor loadings were invariant across subgroup (i.e., community counselor or MINT member). Test–retest reliability was good for MI-consistent and resistance-engendering scores (r = .74 and .80, respectively) but low for change talk orientation (r = .29) unless coder was taken into account (r = .69). CASPI showed excellent construct and criterion-related validity. CASPI represents a promising method of assessing MI skills. Future studies are needed to establish its performance in real-world contexts. Baer JS, Carpenter KM, Beadnell B, Stoner SA, Hangsten Ingalsbe M, Hartzler B, Rosengren DB, Drager Z. Computer Assessment Of Simulated Patient Interviews (CASPI): Psychometric properties of a web-based system for the assessment of motivational interviewing skills. J Stud Alcohol Drugs. 2012; January 154-163.

**Naloxone Can Interact with Psychotropic Medication-Related Obtundation** Buprenorphine is an effective treatment for opiate dependence. Prisoners with histories of opiate dependence who are inducted on buprenorphine prior to release are at decreased risk of post-release relapse and overdose, yet many clinicians are unaware of the risks related to buprenorphine induction for non-opiate tolerant patients, especially those on other psychotropic medications. The authors report a case of probable non-lethal overdose during dose induction of a non-tolerant prisoner and discuss appropriate dosing under similar circumstances. Rich JD, McKenzie M, Dickman S, Bratberg J, Lee JD, Schwartz RP. An adverse reaction to buprenorphine/naloxone induction in prison: A case report. Addictive Disord & Trt. 2012; 10(4): 199-200.

**Disparities in Antiretroviral Treatment: A Comparison of Behaviorally HIV-Infected Youth and Adults in the HIV Research Network** Increasing numbers of youth are becoming HIV infected and need highly active antiretroviral therapy (HAART). The authors hypothesized that behaviorally HIV-infected youth (BIY) ages 18 to 24 years are less likely than adults (25 years or older) to receive HAART and, once initiated, more likely to discontinue their first HAART regimen. This was a longitudinal analysis of treatment-naive patients (age 18 years or older) meeting criteria for HAART and followed at HIV Research Network sites (2002–2008). Time from meeting criteria to HAART initiation and duration on first regimen were assessed using Cox proportional hazards regression. A total of 3,127 (268 youth, 2859 adult) treatment-naive, HIV-infected patients met criteria. BIY were more likely to be black (66.8% vs. 51.1%; $P < 0.01$) and less likely to identify injection drug use HIV risk (1.1% vs 8.8%; $P < 0.01$) than adults 25 years of age or older. Nearly 69% of BIY started HAART versus 79% of adults ($P < 0.001$). Adults 25 to 29 years of age (adjusted hazards ratio [AHR], 1.39; 95% confidence interval [CI], 1.12–1.73) and 50 years of age or older (AHR, 1.24; 95% CI, 1.00–1.54), but not 30 to 49 years (AHR, 1.19; 95% CI, 0.99–1.44) were more likely to initiate HAART than BIY. Attending four or more HIV provider visits within 1 year of meeting criteria was associated with HAART initiation (AHR, 1.91; 1.70–2.14). CD4 200 to 350 versus less than 200 cells/mm3 (AHR, 0.57; 95% CI, 0.52–0.63), and injection drug use (AHR, 0.80; 95% CI, 0.69–0.92) were associated with a lower likelihood of HAART initiation. There were no age-related differences in duration of the first regimen. BIY are less likely to start HAART when meeting treatment criteria. Addressing factors associated with this disparity is critical to improving care for youth. Korthius PT, Agwu AL, Fleishman JA, Sidberry GK, Ellen JM, Gaur AH, Rutstein R, Gebo KA. Disparities in antiretroviral treatment: A comparison of behaviorally HIV-infected youth and adults in the HIV Research Network. J Acquir Immune Defic Syndr. 2011; 58(1): 100-107.

**Long-Term Outcomes Among Drug-Dependent Mothers Treated In Women-Only Versus Mixed-Gender Programs** This study examined the long-term outcomes of women who were pregnant or parenting at admission to women-only (WO; n = 500) versus mixed-gender (MG; a matched sample of 500) substance abuse treatment programs. Administrative records on arrests, incarcerations, mental health services utilization, and drug treatment participation were collected, covering 3 years preadmission and 8 years post admission. Women treated in WO programs had lower levels of arrest; mental health services utilization rates, and drug treatment participation during the first year after drug treatment. No differences were found between the two groups in the long-term trajectories except that the WO program participants had lower incarceration rates during the third year after treatment. The study findings suggest a positive short-term impact of WO versus MG programs with regard to arrest and mental health services utilization. Limited long-term gain is shown in the reductions in post treatment incarceration. The study findings suggest the added value of specialized WO programs and begin to address the gap in knowledge regarding long-term outcomes for substance-abusing women. Hser Y, Evans E, Huang D, Messina N. Long-term outcomes among drug-dependent mothers treated in women-only versus mixed-gender programs. J Subst Abuse Treat. 2011; 115-123.

**Cost-Effectiveness of Long-Term Outpatient Buprenorphine-Naloxone Treatment for Opioid Dependence in Primary Care** Primary care physicians with appropriate training may prescribe buprenorphine-naloxone (bup/nx) to treat opioid dependence in US office-based settings, where many patients prefer to be treated. Bup/nx is off patent but not available as a

generic. The authors evaluated the cost-effectiveness of long-term office-based bup/nx treatment for clinically stable opioid-dependent patients compared to no treatment. A decision analytic model simulated a hypothetical cohort of clinically stable opioid-dependent individuals who have already completed 6 months of office-based bup/nx treatment. Data were from a published cohort study that collected treatment retention, opioid use, and costs for this population, and published quality-of-life weights. Uncertainties in estimated monthly costs and quality-of-life weights were evaluated in probabilistic sensitivity analyses, and the economic value of additional research to reduce these uncertainties was also evaluated. The main outcome measures examined were: Bup/nx, provider, and patient costs in 2010 US dollars, quality-adjusted life years (QALYs), and incremental cost-effectiveness (CE) ratios ($/QALY); costs and QALYs are discounted at 3% annually. In the base case, office-based bup/nx for clinically stable patients has a CE ratio of $35,100/QALY compared to no treatment after 24 months, with 64% probability of being < $100,000/QALY in probabilistic sensitivity analysis. With a 50% bup/nx price reduction the CE ratio is $23,000/QALY with 69% probability of being < $100,000/ QALY. Alternative quality-of-life weights result in CE ratios of $138,000/QALY and $90,600/QALY. The value of research to reduce quality-of-life uncertainties for 24-month results is $6,400 per person eligible for treatment at the current bup/nx price and $5,100 per person with a 50% bup/nx price reduction.The authors conclude that office-based bup/nx for clinically stable patients may be a cost-effective alternative to no treatment at a threshold of $100,000/QALY depending on assumptions about quality-of-life weights. Additional research about quality-of-life benefits and broader health system and societal cost savings of bup/nx therapy is needed. Schackman B, Leff J, Polsky D, Moore B, Fiellin D. Cost-effectiveness of long-term outpatient buprenorphine-naloxone treatment for opioid dependence in primary care. J Gen Intern Med. 2012; 1-8.

**The Source of Methadone in Overdose Deaths in Western Virginia In 2004** Methadone-related overdose deaths increased in the United States by 468% from 1999 to 2005. Current studies associate the nonmedical use of methadone with methadone-related deaths. This study describes medical examiner cases in rural Virginia in 2004 with methadone identified by toxicology and compares cases according to source of methadone. In 2004, all intentional and unintentional poisoning deaths from the office of The Chief Medical Examiner, Western District of Virginia, were reviewed to identify cases in which methadone was a direct or contributing cause of death. The Virginia Prescription Monitoring Program was reviewed for prescription opioids in the name of these identified decedents. Decedent participation in local opioid treatment programs (OTP) was also assessed. The source of methadone in the 61 methadone-related overdose deaths was mostly nonprescribed (67%), although 28% of decedents were prescribed methadone for analgesia. Only 5% of decedents were actively enrolled in an OTP. The majority of deaths were attributed to polysubstance overdose. The majority of methadone overdose deaths in this study were related to illicit methadone use, rather than prescribed or OTP uses. Interventions to decrease methadone-related deaths should focus on reduction of nonprescription use of methadone. Korthius PT. The source of methadone in overdose deaths in Western Virginia in 2004. Journal of Addict Med. 2011; 5(3): 188-202.

**Physician Trust in the Patient: Development and Validation of a New Measure** Mutual trust is an important aspect of the patient-physician relationship with positive consequences for both parties. Previous measures have been limited to patient trust in the physician. The authors set out to develop and validate a measure of physician trust in the patient. They identified candidate items for the scale by content analysis of a previous qualitative study of patient-physician trust and developed and validated a scale among 61 primary care clinicians (50 physicians and 11 non-physicians) with respect to 168 patients as part of a community-based study of prescription opioid use for chronic, nonmalignant pain in HIV-positive adults. Polychoric factor structure analysis using the Pratt D matrix was used to reduce the number of items and describe the factor structure. Construct validity was tested by comparing mean clinician trust scores for patients by clinician and patient behaviors expected to be associated with clinician trust using a generalized linear mixed model. The final 12-item scale had high internal reliability (Cronbach ± =.93) and a distinct 2-factor pattern with the Pratt matrix D. Construct validity was demonstrated with respect to clinician-reported self-behaviors including toxicology screening (P <.001), and refusal to prescribe opioids (P <.001) and with patient behaviors including reporting opioids lost or stolen (P=.008), taking opioids to get high (P <.001), and selling opioids (P<.001). If validated in other populations, this measure of physician trust in the patient will be useful in investigating the antecedents and consequences of mutual trust, and the relationship between mutual trust and processes of care, which can help improve the delivery of clinical care. Thom D, Wong S, Guzman D, Wu A, Penko J, Miaskowski C, Kushel M. Physician trust in the patient: Development and validation of a new measure. Ann Fam Med. 2011; 9(2): 148-154.

**Cultural Competence in Outpatient Substance Abuse Treatment: Measurement and Relationship to Wait Time and Retention** Culturally competent practice is broadly acknowledged to be an important strategy to increase the quality of services for racial/ethnic minorities in substance abuse treatment. However, few empirically derived measures of organizational cultural competence exist, and relatively little is known about how these measures affect treatment outcomes. Using a nationally representative sample of outpatient substance abuse treatment (OSAT) programs, this study used item response theory to create two measures of cultural competence organizational practices and managers'culturally sensitive beliefs and examined their relationship to client wait time and retention using Poisson regression modeling. The most common and precisely measured organizational practices reported by OSAT managers included matching providers and clients based on language/dialect; offering cross-cultural training; and fostering connections with community and faith-based organizations connected to racial and ethnic minority groups. The most culturally sensitive belief among OSAT managers was support for language/ dialect matching for racial and ethnic minority clients. Results of regression modeling indicate that organizational practices were not related to either outcome. However, managers' culturally sensitive beliefs were negatively associated with average wait time ($p < 0.05$), and positively associated with average retention ($p < 0.01$). Managers' culturally sensitive beliefs considered to be influential for effective implementation of culturally competent practices may be particularly relevant in influencing wait time and retention in OSAT organizations that treat Latinos and African American clients. Guerrero EG. Cultural competence in outpatient substance abuse treatment: Measurement and relationship to wait time and retention. Drug Alcohol Depend. 2011; 119 e13-e22.

**Directly Observed Antiretroviral Therapy Eliminates Adverse Effects of Active Drug Use on Adherence** The impact of adherence enhancing interventions on the relationship between active drug use and adherence is largely unknown. The authors conducted a 24-week randomized controlled trial of antiretroviral directly observed therapy (DOT) vs. treatment as usual (TAU) among HIV-infected methadone patients. Their outcome measure was pill count antiretroviral adherence, and their major independent variables were treatment arm (DOT vs. TAU) and active drug use (opiates, cocaine, or both opiates and cocaine). They defined any drug use as >/=1 positive urine toxicology result, and frequent drug use as >/=50% tested urines positive. They used mixed effects linear models to evaluate associations between adherence and drug use, and included a treatment arm-by-drug use interaction term to evaluate whether DOT moderates associations between drug use and adherence. Thirty-nine participants were randomized to DOT and 38 to TAU. The authors observed significant associations between adherence and active drug use, but these were limited to TAU participants. Adherence was worse in TAU participants with any opiate use than in TAU participants without (63% vs. 75%, $p < 0.01$); and worse among those with any polysubstance (both opiate and cocaine) use than without (60% vs. 73%, $p = 0.01$). They also observed significant decreases in adherence among TAU participants with frequent opiate or frequent polysubstance use, compared to no drug use. Among DOT participants, active drug use was not associated with worse adherence. Active opiate or polysubstance use decreases antiretroviral adherence, but the negative impact of drug use on adherence is eliminated by antiretroviral DOT. Arnsten JH. Directly observed antiretroviral therapy eliminates adverse effects of active drug use on adherence. Drug Alcohol Depend. 2012; 120: 174-180.

**Disparities among States in HIV-Related Mortality in Persons with HIV Infection, 37 U.S. STATES, 2001-2007** The objective of this study was to examine interstate variation in US HIV case-fatality rates, and compare them with corresponding conventional HIV death rates. This was a cross-sectional analysis using data on deaths due to HIV infection from the National Vital Statistics System and data on persons 15 years or older living with HIV infection in 2001—2007 in 37 U.S. states from the national HIV/AIDS Reporting System. State rankings by age-adjusted HIV case-fatality rates (with HIV-infected population denominators) were compared with rankings by conventional death rates (with general population denominators). Negative binomial regression determined case-fatality rate ratios (RRs) among states, adjusted for age, sex, race/ethnicity, year, and state-level markers of late HIV diagnosis. Based on 3,096,729 HIV-infected person-years, the overall HIV case-fatality rate was 20.6/1,000 person-years (95% confidence interval [CI], 20.3 – 20.9). Age- adjusted rates by state ranged from 9.6 (95% CI 6.8 – 12.4) in Idaho to 32.9 (95% CI 29.8 – 36.0) in Mississippi, demonstrating significant differences across states, even after adjusting for race/ethnicity ($p < 0.0001$). Many states with low conventional death rates had high case-fatality rates. Nine of the ten states with the highest case-fatality rates were located in the U.S. South. Case-fatality rates complement and are not entirely concordant with conventional death rates. Interstate differences in these rates may reflect differences in secondary and tertiary prevention of HIV-related mortality among infected persons. These data suggest that state-specific contextual barriers to care may impede improvements in quality and disparities of health-care without targeted interventions. Hanna DB. Disparities among states in HIV-related mortality in persons with HIV infection, 37 U.S. STATES, 2001-2007. AIDS. 2011; 25: 1-9.

**Addicts Who Reside in Oxford Houses Commit Less Crime and Reflect Better Cost-Benefit Ratios Compared to Usual Aftercare** The authors used data from a randomized controlled study of Oxford House (OH), a self-run, self-supporting Recovery home, to conduct a cost–benefit analysis of the program. Following substance abuse treatment, individuals that were assigned to an OH condition (n = 68) were compared to individuals assigned to a usual care condition (n = 61). Economic cost measures were derived from length of stay at an Oxford House residence, and derived from self-reported measures of inpatient and outpatient treatment utilization. Economic benefit measures were derived from self-reported information on monthly income, days participating in illegal activities, binary responses of alcohol and drug use, and incarceration. Results suggest that OH compared quite favorably to usual care: the net benefit of an OH stay was estimated to be roughly $29,000 per person on average. Bootstrapped standard errors suggested that the net benefit was statistically significant. Costs were incrementally higher under OH, but the benefits in terms of reduced illegal activity, incarceration and substance use substantially outweighed the costs. The positive net benefit for Oxford House is primarily driven by a large difference in illegal activity between OH and usual care participants. Using sensitivity analyses, under more conservative assumptions the authors still arrived at a net benefit favorable to OH of $17,830 per person. LoSasso, AT, Byro, E, Jason, LA, Ferrari, JR, Olson, B. Benefits and costs associated with mutual-help community-based recovery homes: The Oxford House model. Eval Program Plann. 2012; 35: 47-53.

**HIV-Related Research in Correctional Populations: Now Is the Time** The incarcerated population has increased to unprecedented levels following the 1970 US declaration of war on illicit drug use. A substantial proportion of people with or at risk for HIV infection, including those with substance use and mental health disorders, have become incarcerated. The overlapping epidemics of incarceration and HIV present a need for academic medical centers to collaborate with the criminal justice system to improve the health of incarcerated populations. With coordinated collaboration and new programmatic initiatives it is possible to reduce HIV-associated risk behaviors and the likelihood of acquisition and transmission of HIV. Centers for AIDS Research (CFAR), funded by the National Institutes of Health, have proactively responded to this need through Collaboration on HIV in Corrections (CHIC) to improve the diagnosis, treatment, linkage to care, and prevention of HIV. This collaboration serves as a model for aligning academic expertise with criminal justice to confront this challenge to individual and public health. This is especially relevant given recent evidence of the effectiveness of antiretroviral therapy in reducing HIV transmission. Rich JD, Wohl DA, Beckwith CG, Spaulding AC, Lepp NE, Baillargeon J, Gardner A, Avery A, Altice FL, Springer S, the Centers for AIDS Research—Collaboration on HIV in Corrections (CFAR-CHIC) Working Group. HIV-related research in correctional populations: Now is the time. Curr HIV/AIDS Rep. 2011; 8(4): 288-296.

**Addicts with High Criminal Recidivism Improve Best when in Treatment for Longer Periods of Time** High-risk offenders treated by California's Proposition 36 court-supervised drug treatment initiative account for a disproportionate number of re-arrests (Hawken 2008) undermining the many successes of the program, yet little is known about their characteristics, treatment experiences, or factors that influence re-arrest. To better understand this group, self-reported and administrative data were analyzed on 78 high-risk (five or more convictions in the previous 5 years) and 1,009 low-risk offenders enrolled during 2004. At intake, high-risk

offenders were younger, more were male, and more had prior contact with psychiatric and criminal justice systems. Treatment received and the proportion recidivated during the 30-months after treatment assessment were similar across groups, but high-risk offenders had a greater number of re-arrests. The number of re-arrests was increased by high-risk classification, but decreased by receipt of more treatment services and longer treatment length. Moreover, the number of re-arrests was highest among high-risk offenders with shorter treatment lengths, whereas it was similar to that among low-risk offenders if treatment length was longer. To reduce recidivism among high-risk offenders in court-supervised drug treatment, consideration of psychiatric problems and criminal history is needed, as is receipt of sufficient treatment. Evans E, Huang D, Hser Y. High-risk offenders participating in court-supervised substance abuse treatment characteristics, treatment received, and factors associated with recidivism. J Behav Health Serv Res. 2011; 38(4): 510-525.

**Drug-Abusing Offenders with Comorbid Mental Disorders: Problem Severity, Treatment Participation, and Recidivism** This study examined problem severity, treatment participation, and recidivism among 1,016 offenders with co-occurring mental disorders who participated in California's Proposition 36. Participants were assessed using the Addiction Severity Index (ASI) at baseline, and their records on mental health diagnoses, drug treatment participation, and arrests were also obtained. Participants' co-occurring disorder (COD) severity was classified as mild or severe based on specific mental health diagnoses. Predictors of recidivism were examined among mild- COD and severe-COD participants separately using ordinal logistic regression. Results indicate that although previous arrests, education, and treatment retention length are predictors of recidivism generally, gender, age, primary drug, ASI drug severity score, and treatment modality are differentially important depending on COD status. These results underscore the need for COD-focused intervention strategies among offenders, taking into consideration the severity of their COD status. Hser Y. Drug-abusing offenders with co morbid mental disorders: Problem severity, treatment participation, and recidivism. J Subst Abuse Treat. 2012; Feb. 1. [Epub ahead of print]

**Costs of Addressing Heroin Addiction in Malaysia and 32 Comparable Countries Worldwide** The objective of this study was to develop and apply new costing methodologies to estimate costs of opioid dependence treatment in countries worldwide. The micro-costing methodology used was developed and data collected during randomized controlled trial (RCT) involving 126 patients (July 2003-May 2005) in Malaysia. Gross-costing methodology was developed to estimate costs of treatment replication in 32 countries with data collected from publicly available sources. Fixed, variable, and societal cost components of Malaysian RCT micro-costed and analytical framework were created and employed for gross-costing in 32 countries selected by three criteria relative to Malaysia: major heroin problem, geographic proximity, and comparable gross domestic product (GDP) per capita. Medication, and urine and blood testing accounted for the greatest percentage of total costs for both naltrexone (29-53 percent) and buprenorphine (33-72 percent) interventions. In 13 countries, buprenorphine treatment could be provided for under $2,000 per patient. For all countries except United Kingdom and Singapore, incremental costs per person were below $1,000 when comparing buprenorphine to naltrexone. An estimated 100 percent of opiate users in Cambodia and Lao People's Democratic Republic could be treated for $8 and $30 million, respectively. The authors concluded that buprenorphine treatment can be provided at low cost in countries across the

world. This study's new costing methodologies provide tools for health systems worldwide to determine the feasibility and cost of similar interventions. Ruger J, Chawarski M, Mazlan M, Luekens C, Ng N, Schottenfeld R. Costs Of Addressing Heroin Addiction in Malaysia and 32 comparable countries worldwide. Health Serv Res. 2012; 47(2): 865-887.

**Improving Substance Abuse Data Systems to Measure Waiting Time to Treatment** Robust data measurement systems assess health care performance and monitor population-level treatment trends. A key challenge in the assessment of substance abuse treatment is the development of systems to accurately monitor service delivery indicators. Wait time to treatment, as defined by the days between first request for service and first treatment, is an important measure of organizational process and delivery of care. The Network for the Improvement of Addiction Treatment (NIATx) emphasizes wait time as a primary outcome in their study of 201 addiction treatment agencies in the USA. This article describes the changes made in five state data systems to monitor wait times and outlines lessons learned that could be applied to other health data tracking systems. Hoffman K, Quanbeck A, Ford J, Wrede F, Wright D, Lambert-Wacey D, Chvojka P, Hanchett A, McCarty, D. Improving substance abuse data systems to measure waiting time to treatment: Lessons learned from a quality improvement initiative. Health Informatics J. 2011; 17: 256-265.

**Treatment Reengagement Intervention for Syringe Exchangers** Poor sustained treatment engagement limits the effectiveness of all modalities of substance abuse treatment. This study evaluated the efficacy of a novel treatment reengagement intervention for a subset of syringe-exchange program (SEP) participants (N = 113) that had enrolled in treatment as part of a 4-month clinical trial (M. Kidorf et al., 2009). Three reengagement conditions for participants leaving treatment were compared. Motivational referral condition (MRC) participants (n = 31) could attend group sessions that focused on renewing treatment interest. MRC plus incentive (MRC + I) participants (n = 49) could receive modest monetary incentives for attending these sessions and reenrolling in treatment. Standard referral condition participants (n = 33) could not attend groups or receive incentives. Across a 1-year observation window, almost all study participants (86%) were discharged from treatment. MRC + I participants attended more group sessions than MRC participants and were considerably more likely to reenroll in treatment than participants in the other study conditions. Reengagement strategies can further enhance the public health benefits of SEPs by increasing rates of treatment participation over time. Kidorf M, King VL, Peirce J, Kolodner K, Brooner RK. Treatment reengagement intervention for syringe exchangers. J Subst Abuse Treat. 2011; 41: 415-421.

**Lack of Sustained Improvement in Adherence or Viral Load Following a Directly Observed Antiretroviral Therapy Intervention** Methadone clinic–based directly observed antiretroviral therapy (DOT) has been shown to be more efficacious for improving adherence and suppressing human immunodeficiency virus (HIV) load than antiretroviral self-administration. The authors sought to determine whether the beneficial effects of DOT remain after DOT is discontinued. They conducted a post-trial cohort study of 65 HIV-infected opioid-dependent adults who had completed a 24-week randomized controlled trial of methadone clinic–based DOT versus treatment as usual (TAU). For 12 months after DOT discontinuation, they assessed antiretroviral adherence using monthly pill counts and electronic monitors. They also assessed viral load at 3, 6, and 12 months after DOT ended. They examined differences

between DOT and TAU in (1) adherence, (2) viral load, and (3) proportion of participants with viral load of 75 copies/Mr. At trial end, adherence was higher among DOT participants than among TAU participants (86% and 54%, respectively; P < .001), and more DOT participants than TAU participants had viral loads of <75 copies/mL (71% and 44%, respectively; P = .03). However, after DOT ended, differences in adherence diminished by 1 month (55% for DOT vs 48% for TAU; P = .33) and extinguished completely by 3 months (49% for DOT vs 50% for TAU; P = .94). Differences in viral load between DOT and TAU disappeared by 3 months after the intervention, and the proportion of DOT participants with undetectable viral load decreased steadily after DOT was stopped until there was no difference (36% for DOT and 34% for TAU; P = .92). Because the benefits of DOT for adherence and viral load among HIV-infected methadone patients cease after DOT is stopped, methadone-based DOT should be considered a long-term intervention. Arnsten JH. Lack of sustained improvement in adherence or viral load following a directly observed antiretroviral therapy intervention. Clin Infect Dis. 2011; 53(9): 936-943.

**Therapeutic Substance Abuse Treatment for Incarcerated Women** The purpose of this qualitative systematic review was to explicate attributes of optimal therapeutic strategies for treating incarcerated women who have a history of substance abuse. An expansive search of electronic databases for qualitative research reports relating to substance abuse treatment for incarcerated women was conducted. Nine qualitative research reports comprised the sample for this review. Findings from these reports were extracted, placed into a data analysis matrix, coded, and categorized. Memos were written and strategies for treating incarcerated women with alcohol problems were identified. Therapeutic effects of treatment programs for incarcerated women with substance abuse problems appear to be enhanced when trust-based relationships are established, individualized and just care is provided, and treatment facilities are separate from the general prison environment. Finfgeld-Connett D. Therapeutic substance abuse treatment for incarcerated women. Clinical Nursing Research. 2011; 20(4): 462-481.

**Issues in Defining and Applying Evidence-Based Practices Criteria for Treatment of Criminal-Justice Involved Clients** Evidence-based practice (EBP) applies the principles and techniques of evidence-based decision making to interventions intended to improve, or ameliorate, the social or clinical problems of affected individuals, including offenders with drug abuse problems. This article provides a general overview of EBP, particularly as it applies to treatment and other interventions for offenders with problems involving drugs (including alcohol). The discussion includes a definition of EBP, notes the implications of using EBPs to make policy and clinical decisions, lists the various efforts by government and academic organizations to identify practices that can be considered evidence-based, describes the criteria used by such organizations to evaluate programs as being evidence-based, raises some cautions about the use of EBPs, and ends with some challenges in disseminating and implementing EBPs. Prendergast ML. Issues in defining and applying evidence-based practices criteria for treatment of criminal-justice involved clients. J Psychoactive Drugs. 2011; 43(Sup1): 10-18.

**Race/Ethnic Differences in Adult Mortality: The Role of Perceived Stress and Health Behaviors** The authors examine the role of perceived stress and health behaviors (i.e., cigarette smoking, alcohol consumption, physical inactivity, sleep duration) in shaping differential mortality among whites, blacks, and Hispanics. They use data from the 1990 National Health

Interview Survey (N=38,891), a nationally representative sample of United States adults, to model prospective mortality through 2006. The authors' first aim examines whether unhealthy behaviors and perceived stress mediate race/ethnic disparities in mortality. The black disadvantage in mortality, relative to whites, closes after adjusting for socioeconomic status (SES), but re-emerges after adjusting for the lower smoking levels among blacks. After adjusting for SES, Hispanics have slightly lower mortality than whites; that advantage increases after adjusting for the greater physical inactivity among Hispanics, but closes after adjusting for their lower smoking levels. Perceived stress, sleep duration, and alcohol consumption do not mediate race/ethnic disparities in mortality. Their second aim tests competing hypotheses about race/ethnic differences in the relationships among unhealthy behaviors, perceived stress, and mortality. The social vulnerability hypothesis predicts that unhealthy behaviors and high stress levels will be more harmful for race/ethnic minorities. In contrast, the Blaxter (1990) hypothesis predicts that unhealthy lifestyles will be less harmful for disadvantaged groups. Consistent with the social vulnerability perspective, smoking is more harmful for blacks than for whites. But consistent with the Blaxter hypothesis, compared to whites, current smoking has a weaker relationship with mortality for Hispanics, and low or high levels of alcohol consumption, high levels of physical inactivity, and short or long sleep hours have weaker relationships with mortality for blacks. Krueger PM, Saint Onge JM, Chang, VW. Race/ethnic differences in adult mortality: The role of perceived stress and health behaviors. Soc Sci Med. 2011; 73: 1312-1322.

**The DSM Guided Cannabis Screen (DSM-G-CS): Description, Reliability, Factor Structure and Empirical Scoring With a Clinical Sample** Clinicians need cannabis-specific diagnostic screens compatible with DSM-IV-TR and proposed DSM-5. A clinical sample (n=174) completed the DSM-Guided-Cannabis Screen (DSM-G-CS) 21 and 11 criteria versions and three drug comparison measures. DSM-G-CS descriptive statistics, reliabilities, three factor analyses, and eight ROC and discriminant analyses evaluated construct validity and empirical scoring. DSM-GCS reliabilities are .88 (21-items) and .85 (11-criteria). Factor analyses (FA) with varimax rotation derived six and three factors explaining 62% to 60% of variances for the DSM-G-CS 21 and 11 respectively, with >/=.400 loadings supporting retention of all items. Cannabis withdrawal subscale reliability .952 (10-items) and FA supported one factor composite item. ROC and discriminant analyses supports DSM-G-CS 1.5 to 2.5 scoring cutoffs as empirically sound, based upon sensitivity, specificity maximums, accuracy probabilities, confidence levels and correctly classified percentages, optimal with Marijuana Screening Inventory (MSI) comparisons. Results support DSM-G-CS construct validity, empirical scoring and compatibility with DSM-IV-TR cannabis abuse or dependence and proposed DSM-5 cannabis use disorder diagnostic models. Clinically, DSM-G-CS scores of two to three (or more) suggest probable cannabis-use disorder, deserving assessment to determine diagnostic accuracy. Alexander D, Leung P. The DSM Guided Cannabis Screen (DSM-G-CS): description, reliability, factor structure and empirical scoring with a clinical sample. Addict Behav. 2011; 36: 1095-1100.

**Women Tend to Recover from Heroin Addiction Quicker than Men** This study examines 30-year trajectories of heroin and other drug use among men and women who were in methadone maintenance treatment in California in the late1970s and interviewed in 1978–1981. Nearly half (N = 428; 46.8%) of the original study sample (N = 914) was deceased. Of the remaining 486 subjects, 343 (44.3% female) completed a follow-up interview in 2005–2009 (70.6% of those not

deceased). Average age at follow-up was 58.3 (SD = 4.9) years for males and 55.0 (SD = 4.1) years for females. Longitudinal data was obtained on their drug use, treatment participation, and criminal justice status over the follow-up period. Trajectory group modeling was used to identify distinctive trajectory groups based on monthly averages of heroin and other drug use per year; group differences were examined. Four heroin and five alcohol and other drug (AOD) trajectory groups were identified. A greater proportion of women (60%) were in the "rapid decrease" heroin group (odds of use less than 10% by 10 years following initiation of use) as compared with the other groups. More rapid decrease of heroin use was associated with increases in AOD use, whereas a gradual decrease in heroin use was associated with a gradual decrease in AOD use. More school problems and earlier age at onset of heroin use and first arrest were associated with more persistent heroin use. Heroin-use trajectories were linked with changes in AOD use. Childhood antecedents of heroin-use trajectories were identified as well as gender differences. Grella CE, Lovinger, K. 30-year trajectories of heroin and other drug use among men and women sampled from methadone treatment in California. Drug Alcohol Depend. 2012; 118: 251-258.

**There are System Barriers which Delay Methadone Admission for Some Types of Patients that Could be Corrected** Waiting lists for methadone treatment have existed in many U.S. communities, but little is known nationally about what patient and service system factors are related to admission delays that stem from program capacity shortfalls. Using a combination of national data sources, this study examined patterns in capacity-related admission delays to outpatient methadone treatment in 40 U.S. metropolitan areas (N = 28,920). Patient characteristics associated with admission delays included racial/ethnic minority status, lower education, criminal justice referral, prior treatment experience, secondary cocaine or alcohol use, and co-occurring psychiatric problems. Injection drug users experienced fewer delays, as did self-pay patients and referrals from health care and addiction treatment providers. Higher community-level utilization of methadone treatment was associated with delay, whereas delays were less common in communities with higher utilization of alternative modalities. These findings highlight potential disparities in timely admission to outpatient methadone treatment. Implications for improving treatment access and service system monitoring are discussed. Gryczynski J, Schwartz RP, Salkever DS, Gwin MS, Jaffe JH. Patterns in admission delays to outpatient methadone treatment in the United States. J Subst Abuse Treat. 2012; 41: 431-439.

**Governing Boards Influence Treatment Policies and Practices** Boards of directors are the ultimate governing authorities for most organizations providing substance abuse treatment. A governing board may establish policies, monitor and improve operations, and represent a treatment organization to the public. This article explores alternative configurations of governing boards in a national sample of 500 substance abuse treatment centers. The study proceeds from the premise that boards may be configured with varying levels of engagement in five aspects of internal management and external connections in treatment center operating environments. Based on interviews with treatment center administrative directors, four clusters emerge, describing boards that are (a) active and balanced across internal and external domains, (b) active boundary spanners concentrating primarily on external relationships, (c) focused primarily on internal organizational management, and (d) relatively inactive. In post hoc analysis, we found that placement in these clusters is associated with treatment center attributes such as rate of growth and financial results, use of evidence-based practices, and provision of integrated care.

Fields D, Blum TC, Roman PM. An exploratory study of alternative configurations of governing boards of substance abuse treatment centers. J Subst Abuse Treat. 2012; 41: 156-168.

**Oxford Houses are More Engaging and Supportive than Therapeutic Communities** This study compared the social climate of peer run homes for recovering substance abusers called Oxford House (OH) to that of a staffed residential therapeutic community (TC). Residents of OHs (N = 70) and the TC (N = 62) completed the Community Oriented Programs Environment Scales. OHs structurally differ on two primary dimensions from TCs in that they tend to be smaller and are self-run rather than professionally run. Findings indicated significantly higher Involvement, Support, Practical Orientation, Spontaneity, Autonomy, Order and Organization, and Program Clarity scores among the OH compared to TC residents. Additional analyses found the OH condition was higher Support, Personal Problem Orientation, and Order and Organization scores among women compared to men residents. These results suggested that these smaller OH self-run environments created a more involving and supportive social milieu than a larger staff run TC. These findings are interpreted within Moos' (2007) four theoretical ingredients (i.e., social control, social learning, behavioral economics, and stress and coping), which help account for effective substance abuse treatment environments. Harvey R, Jason L.. Contrasting social climates of small peer-run versus a larger staff-run substance abuse recovery setting. Am J Community Psychol. 2011; 48: 365-372.

**Contingency Management Incentivization Improved Methadone Retention in China**
Methadone maintenance treatment has been made available in China in response to the rapid spread of human immunodeficiency virus (HIV), but high rates of dropout and relapse are problematic. The aim of this study was to apply and test if a contingency management (or motivational incentives) intervention can improve treatment retention and reduce drug use. The study design comprised random assignment to usual care with ($n$ = 160) or without ($n$ = 159) incentives during a 12-week trial. Incentives participants earned draws for a chance to win prizes on two separate tracks targeting opiate-negative urine sample or consecutive attendance; the number of draws increased with continuous abstinence or attendance. The study setting was community-based methadone maintenance clinics in Shanghai and Kunming. The sample was 23.8% female, mean age was 38, mean years of drug use was 9.4 and 57.8% had injected drugs in the past 30 days. Measurements collected were treatment retention and negative drug urine. Relative to the treatment-as usual (control) group, better retention was observed among the incentive group in Kunming (75% versus 44%), but no difference was found in Shanghai (90% versus 86%). Submission of negative urine samples was more common among the incentive group than the usual care (74% versus 68% in Shanghai, 27% versus 18% in Kunming), as was the longest duration of sustained abstinence (7.7 weeks versus 6.5 in Shanghai, 2.5 versus 1.6 in Kunming). The average total prize amount was 371 Yuan (or $55) per participant (527 for Shanghai versus 216 in Kunming). Contingency management improves treatment retention and drug abstinence in methadone maintenance treatment clinics in China, although there can be considerable site differences in magnitude of effects. Hser Y, Li J, Jiang H, Zhang R, Du J, Zhang C, Zhang B, Evans E, Wu F, Chang Y, Peng C, Huang D, Stitzer M, Roll J, Zhao M. Effects of a randomized contingency management intervention on opiate abstinence and retention in methadone maintenance treatment in China. Addiction. 2011; 106: 1801-1809.

**Organizational Characteristics that Foster Early Adoption of Cultural and Linguistic Competence in Outpatient Substance Abuse Treatment** Recent years have seen an increased interest in developing culturally and linguistically responsive systems of care in substance abuse treatment in the United States. This study examines the extent to which external and internal organizational pressures contributed to the degree of adoption of culturally and linguistically responsive practices in the nation's outpatient substance abuse treatment system early in the period of development of this system of care. Findings show that a higher degree of adoption of culturally competent practices was most likely in treatment programs with high dependence on external funding and regulation. Internally, programs with a larger number of professionals were associated with the lowest degree of adoption, while managers' cultural sensitivity contributed significantly to a high degree of adoption of these responsive practices. Considering the passage of recent legislation enforcing the use of cultural and linguistic competence in health care, implications of these baseline findings on early adoption patterns are discussed for future research and health care policy evaluation. Guerrero EG. Organizational characteristics that foster early adoption of cultural and linguistic competence in outpatient substance abuse treatment in the United States. Eval Program Plann. 2012; 35: 9-15.

**Learning Collaboratives Can Enhance Implementation of EBPs** Local governments play an important role in improving substance abuse and mental health services. The structure of the local learning collaborative requires careful attention to old relationships and challenges local governmental leaders to help move participants from a competitive to collaborative environment. This study describes one county's experience applying the NIATx process improvement model via a local learning collaborative. Local substance abuse and mental health agencies participated in two local learning collaboratives designed to improve client retention in substance abuse treatment and client access to mental health services. Results of changes implemented at the provider level on access and retention are outlined. The process of implementing evidence-based practices by using the Plan-Do-Study-Act rapid-cycle change is a powerful combination for change at the local level. Key lessons include: creating a clear plan and shared vision, recognizing that one size does not fit all, using data can help fuel participant engagement, a long collaborative may benefit from breaking it into smaller segments, and paying providers to offset costs of participation enhances their engagement. The experience gained in Onondaga County, New York, offers insights that serve as a foundation for using the local learning collaborative in other community-based organizations. Roosa M, Scripa JS, Zastowny TR, Ford JH. Using a Niatx based local learning collaborative for performance improvement. Eval Program Plann. 2011; 34: 390-398.

**History of the TCU Institute of Behavioral Research Addiction Health Services Research** For more than 40 years the Texas Institute of Behavioral Research (IBR) has given special attention to assessment and evaluation of drug user populations, addiction treatment services and various cognitive and behavioral interventions. Emphasis has been on studies in real-world settings and the use of multivariate methodologies to address evaluation issues within the context of longitudinal natural designs. Historically, its program of addiction treatment research may be divided into three sequential epochs—the first era dealt mainly with client assessment and its role in treatment outcome and evaluation (1969–89), the second focused upon modeling the treatment process and the importance of conceptual frameworks (1989–2009) in explaining the relationships among treatment environment, client attributes, treatment process and outcome, and

the third (and current) era has expanded into studying tactical deployment of innovations and implementation. Recent projects focus upon adapting and implementing innovations for improving early engagement in adolescent residential treatment settings and drug-dependent criminal justice populations. Related issues include the spread of human immunodeficiency virus/acquired immune deficiency syndrome and other infectious diseases, organizational and systems functioning, treatment costs and process related to implementation of evidence-based practices. Simpson DD, Joe GW, Dansereau DF, Flynn PM. Addiction treatment outcomes, process and change: Texas Institute of Behavioral Research At Texas Christian University. Addiction. 2012; 106: 1733-1740.

## CTN-RELATED RESEARCH

**Injection Behaviors Among Injection Drug Users In Treatment: The Role Of Hepatitis C Awareness** Injection drug use (IDU) is a primary vector for blood-borne infections. Awareness of Hepatitis C virus (HCV) infection status may affect risky injection behaviors. This study determines the prevalence of risky injection practices and examines associations between awareness of positive HCV status and risky injection behaviors. The authors surveyed individuals seeking treatment for substance use at 12 community treatment programs as part of a national HIV screening trial conducted within the National Drug Abuse Treatment Clinical Trials Network. Participants reported socio-demographic characteristics, substance use, risk behaviors, and HCV status. They used multivariable logistic regression to test associations between participant characteristics and syringe/needle sharing. The 1281 participants included 244 (19.0%) individuals who reported injecting drugs in the past 6months and 37.7% of IDUs reported being HCV positive. During the six months preceding baseline assessment, the majority of IDUs reported obtaining sterile syringes from pharmacies (51.6%) or syringe exchange programs (25.0%), but fewer than half of IDUs always used a sterile syringe (46.9%). More than one-third (38.5%) shared syringe/needles with another injector in the past 6months. Awareness of positive HCV vs. negative/unknown status was associated with increased recent syringe/needle sharing (aOR 2.37, 95% CI 1.15, 4.88) in multivariable analysis. Risky injection behaviors remain prevalent and awareness of HCV infection was associated with increased risky injection behaviors. New approaches are needed to broadly implement HCV prevention interventions for IDUs seeking addiction treatment. Korthuis PT, Feaster DJ, Gomez ZL, Das M, Tross S, Wiest K, Douaihy A, Mandler RN, Sorensen JL, Colfax G, McCarty D, Cohen SE, Penn PE, Lape D, Metsch LR. Injection behaviors among injection drug users in treatment: The role of hepatitis C awareness. Addict Behav. 2012 Apr; 37(4): 552-555. Epub 2011 Dec 14.

**Attention-Deficit/Hyperactivity Disorder (ADHD) Symptoms, Craving To Smoke, And Tobacco Withdrawal Symptoms In Adult Smokers With ADHD** Tobacco withdrawal symptoms may be confounded with attention-deficit/hyperactivity disorder (ADHD) symptoms among smokers with ADHD. The objectives of this study were 1) to assess overlap between ADHD symptoms and tobacco/nicotine withdrawal symptoms and craving; (2) to assess the relationship between craving or withdrawal symptoms and the effect of osmotic-release oral system methylphenidate (OROS-MPH) on ADHD symptoms; (3) to assess the association of ADHD symptoms, craving, and withdrawal symptoms with abstinence. The authors employed a secondary analysis of a randomized, placebo controlled smoking cessation trial assessing the efficacy of OROS-MPH taken in addition to nicotine patch among individuals with ADHD. ADHD symptoms, withdrawal symptoms, and craving were assessed at baseline and 2, 4 and 6 weeks after a target quit day. Withdrawal symptoms and craving showed limited and modest overlap with ADHD symptoms prior to abstinence but more extensive and stronger correlation after quit day. Compared to placebo, OROS-MPH reduced ADHD symptoms; this effect was attenuated by controlling for withdrawal symptoms, but not by craving. Craving, but not ADHD symptoms and withdrawal symptoms, was associated with abstinence during the trial. When treating smokers with ADHD (1) craving, rather than tobacco withdrawal symptoms or ADHD symptoms may be the more effective therapeutic smoking cessation targets; (2) careful distinction of craving, withdrawal symptoms, and ADHD symptoms when assessing withdrawal phenomena is needed. Berlin I, Hu MC, Covey LS, Winhusen T. Attention-deficit/hyperactivity

disorder (ADHD) symptoms, craving to smoke, and tobacco withdrawal symptoms in adult smokers with ADHD. Drug Alcohol Depend. 2012 Feb 22. [Epub ahead of print]

**Alcohol And Drug Dependence Symptom Items As Brief Screeners For Substance Use Disorders: Results From The Clinical Trials Network** The aim of this study was to address an urgent need for screening of substance use problems in medical settings, the authors examined substance-specific dependence criteria as potential brief screeners for the detection of patients with a substance use disorder (SUD). The study sample included 920 opioid-dependent adults who were recruited from outpatient treatment settings at 11 programs in 10 U.S. cities and who completed intake assessments of SUDs for a multisite study of the National Drug Abuse Treatment Clinical Trials Network (CTN003). Data were analyzed by factor analysis, item response theory (IRT), sensitivity, and specificity procedures. Across all substances (alcohol, amphetamines, cannabis, cocaine, sedatives), withdrawal was among the least prevalent symptoms, while taking large amounts and inability to cut down were among the most prevalent symptoms. Items closely related to the latent trait of a SUD showed good-to-high values of area under the receiver operating characteristic curve in identifying cases of a SUD; IRT-defined severe and less discriminative items exhibited low sensitivity in identifying cases of a SUD (withdrawal for all substances; time using for alcohol and sedatives; giving up activities for sedatives). Study results suggest that withdrawal and time using are much less reliable indicators for a SUD than taking larger amounts than intended and inability to cut down and that the latter two items should be studied further for consideration in developing a simplified tool for screening patients for SUDs in medical settings. These findings have implications for the use of common health indicators in electronic health records systems to improve patient care. Wu LT, Blazer DG, Woody GE, Burchett B, Yang C, Pan JJ, Ling W. Alcohol and drug dependence symptom items as brief screeners for substance use disorders: Results from the Clinical Trials Network. J Psychiatr Res. 2011 Dec 26. [Epub ahead of print]

**Comparing Buprenorphine Induction Experience With Heroin And Prescription Opioid Users** Prescription opioid (PO)-dependent treatment presentations are becoming increasingly common; however, most research on the treatment of opioid-dependent populations has been conducted in heroin users. The aim of this secondary data analysis was to compare the buprenorphine induction experience of 167 heroin and 61 PO users. Results demonstrate that although the groups differed on some baseline characteristics, many of the key induction experience variables were comparable between the groups. Heroin users were found to have significantly higher preinduction Clinical Opiate Withdrawal Scale (COWS) scores ($p = .014$) and postinduction COWS score ($p = .008$) compared with the PO users. No differences between groups were found for self-reported craving and withdrawal scores, mean buprenorphine dose on Day 1, or retention at the end of the first week. The findings of this study suggest that existing buprenorphine induction practices developed for heroin users appear to be equally effective with PO users. Nielsen S, Hillhouse M, Mooney L, Fahey J, Ling W. Comparing buprenorphine induction experience with heroin and prescription opioid users. J Subst Abuse Treat. 2012 Jan 31. [Epub ahead of print].

**Electronic Health Records: Essential Tools In Integrating Substance Abuse Treatment With Primary Care** While substance use problems are considered to be common in medical settings, they are not systematically assessed and diagnosed for treatment management. Research data suggest that the majority of individuals with a substance use disorder either do not use treatment or delay treatment-seeking for over a decade. The separation of substance abuse services from mainstream medical care and a lack of preventive services for substance abuse in primary care can contribute to under-detection of substance use problems. When fully enacted in 2014, the Patient Protection and Affordable Care Act 2010 will address these barriers by supporting preventive services for substance abuse (screening, counseling) and integration of substance abuse care with primary care. One key factor that can help to achieve this goal is to incorporate the standardized screeners or common data elements for substance use and related disorders into the electronic health records (EHR) system in the health care setting. Incentives for care providers to adopt an EHR system for meaningful use are part of the Health Information Technology for Economic and Clinical Health Act 2009. This commentary focuses on recent evidence about routine screening and intervention for alcohol/drug use and related disorders in primary care. Federal efforts in developing common data elements for use as screeners for substance use and related disorders are described. A pressing need for empirical data on screening, brief intervention, and referral to treatment (SBIRT) for drug-related disorders to inform SBIRT and related EHR efforts is highlighted. Tai B, Wu LT, Clark HW. Electronic health records: essential tools in integrating substance abuse treatment with primary care. Subst Abuse Rehabil. 2012 Feb: 3(1): 1–8.

**Support for EBS Increases with Education, Licensure, and Tenure** The National Drug Abuse Treatment Clinical Trials Network (CTN) is an alliance of drug abuse treatment programs and research centers testing new interventions and implementation factors for treating alcohol and drug use disorders. A workforce survey distributed to those providing direct services in 295 treatment units in the CTN obtained responses from 1750 individuals with a job title of counselor ($n$ = 1395) or counselor supervisor ($n$ = 355). A secondary analysis compares and describes both groups. Supervisors were more likely to be licensed or certified. Master's degrees were more common among counselors in outpatient and methadone programs. Counselors in residential settings tended to be on the job fewer years. Finally, higher education was associated with greater familiarity with and acceptance of evidence-based practices. Riechmann T, Farentinos C, Tillotson CJ, Kocarnik J, McCarty D. The substance abuse counseling workforce: Education, preparation, and certification. Subst Abus. 2012; 32: 180-190.

**Helping Alliance, Retention, and Treatment Outcomes: A Secondary Analysis From the NIDA Clinical Trials Network Women and Trauma Study** The authors examined the association between the therapeutic alliance and treatment outcomes among 223 women with posttraumatic stress disorder (PTSD) and substance use disorders who participated in a multisite clinical trial of group treatments for trauma and addictions in the United States throughout 2004 and 2005. General linear models indicated that women who received Seeking Safety, a cognitive-behavioral treatment, had significantly higher alliance ratings than those in Women's Health Education, a control group. Alliance was related to significant decreases in PTSD symptoms and higher attendance in both interventions. Alliance was not related to substance use outcomes. Implications and limitations of the findings are discussed. Ruglass LM, Miele GM, Hien DA, Campbell AN, Hu MC, Caldeira N, Jiang H, Litt L, Killeen T, Hatch-Maillette M,

Najavits L, Brown C, Robinson JA, Brigham GS, Nunes EV. Helping alliance, retention, and treatment outcomes: A secondary analysis from the NIDA Clinical Trials Network Women and Trauma Study. Subst Use Misuse. 2012 Apr 4. [Epub ahead of print].

**Tobacco Dependence Counseling In A Randomized Multisite Clinical Trial**
Pharmacotherapy trials for treating tobacco dependence would benefit from behavioral interventions providing treatment consistent with clinical practice guidelines but not directing participants to treatments not evaluated in the trial. The Smoke Free and Living It© behavioral intervention manual includes participant and interventionist guides and is designed to provide both practical counseling and intra-treatment support. The authors utilized this intervention manual in a multicenter, randomized clinical trial of smokers with attention deficit hyperactivity disorder. In this study, they evaluated how the interventional manual performed in a "train-the-trainer" model requiring uniform counseling across 6 sites and 15 interventionists. They analyzed the skill-adherence of the interventionists and the intervention-adherence of the participants. The 255 randomized participants completed 9.3±2.8 sessions (mean±SD), with 157 participants (61.6%) completing all 11 of the sessions and 221 (86.7%) completing at least 6 of the 11 sessions. Of the 163 sessions for which the study interventionists were evaluated, 156 (95.7%) were rated as adherent to protocol and "meeting expectations" on at least 6 of 7 established criteria, illustrating that fidelity can be maintained with minimal supervision. The self-help and interventionists guides of the Smoke Free and Living It manual can thus be used to provide behavioral intervention with a high rate of adherence by both the interventionists and the participants. This manual meets the requirements of the United States Public Health Service Clinical Practice Guideline, can be adapted to specific research protocols, and provides a useful option for behavioral intervention during clinical trials for smoking cessation. Croghan IT, Trautman JA, Winhusen T, Ebbert JO, Kropp FB, Schroeder DR, Hurt RD. Tobacco dependence counseling in a randomized multisite clinical trial. Contemp Clin Trials. 2012 Mar 3. [Epub ahead of print].

**Attendance And Substance Use Outcomes For The Seeking Safety Program: Sometimes Less Is More** This study uses data from the largest effectiveness trial to date on treatment of co-occurring posttraumatic stress and substance use disorders, using advances in statistical methodology for modeling treatment attendance and membership turnover in rolling groups. Women receiving outpatient substance abuse treatment (N = 353) were randomized to 12 sessions of Seeking Safety or a health education control condition. Assessments were completed at baseline and at 1 week, 3, 6, and 12 months posttreatment. Outcome measures were alcohol and cocaine use in the prior 30 days captured using the Addiction Severity Index. Latent class pattern mixture modeling (LCPMM) was used to estimate attendance patterns and to test for treatment effects within and across latent attendance patterns and group membership turnover. Across LCPMM analyses for alcohol and cocaine use, similar treatment attendance patterns emerged: Completers never decreased below an 80% probability of attendance, droppers never exceeded a 41% probability of attendance, and titrators demonstrated a 50% to 80% probability of attendance. Among completers, there were significant decreases in alcohol use from baseline to 1-week posttreatment, followed by nonsignificant increases in alcohol during follow-up. No differences between treatment conditions were detected. Titrators in Seeking Safety had lower rates of alcohol use from 1-week through 12-month follow-up compared with control participants. Droppers had nonsignificant increases in alcohol during both study phases. Cocaine

use findings were similar but did not reach significance levels. The impact of client self-modulation of treatment dosage and group membership composition may influence behavioral treatment outcomes among this population. Hien DA, Morgan-Lopez AA, Campbell AN, Saavedra LM, Wu E, Cohen L, Ruglass L, Nunes EV. Attendance and substance use outcomes for the Seeking Safety program: Sometimes less is more. J Consult Clin Psychol. 2012 Feb; 80(1): 29-42. Epub 2011 Dec 19.

**Missing Data in Substance Abuse Treatment Research: Current Methods and Modern Approaches** Two common procedures for the treatment of missing information, listwise deletion and positive urine analysis (UA) imputation (e.g., if the participant fails to provide urine for analysis, then score the UA positive), may result in significant biases during the interpretation of treatment effects. To compare these approaches and to offer a possible alternative, these two procedures were compared to the multiple imputation (MI) procedure with publicly available data from a recent clinical trial. Listwise deletion, single imputation (i.e., positive UA imputation), and MI missing data procedures were used to comparatively examine the effect of two different buprenorphine/naloxone tapering schedules (7- or 28-days) for opioid addiction on the likelihood of a positive UA (Clinical Trial Network 0003; Ling et al., 2009). The listwise deletion of missing data resulted in a nonsignificant effect for the taper while the positive UA imputation procedure resulted in a significant effect, replicating the original findings by Ling et al. (2009). Although the MI procedure also resulted in a significant effect, the effect size was meaningfully smaller and the standard errors meaningfully larger when compared to the positive UA procedure. This study demonstrates that the researcher can obtain markedly different results depending on how the missing data are handled. Missing data theory suggests that listwise deletion and single imputation procedures should not be used to account for missing information, and that MI has advantages with respect to internal and external validity when the assumption of missing at random can be reasonably supported. (PsycINFO Database Record (c) 2012 APA, all rights reserved). McPherson S, Barbosa-Leiker C, Burns GL, Howell D, Roll J. Missing data in substance abuse treatment research: Current methods and modern approaches. Exp Clin Psychopharmacol. 2012 Feb 13. [Epub ahead of print]

## INTRAMURAL RESEARCH

### Cellular Neurobiology Research Branch
### Behavioral Neurophysiology Science Section

**The Impact Of Orbitofrontal Dysfunction On Cocaine Addiction** Cocaine addiction is characterized by poor judgment and maladaptive decision-making. Here IRP scientists review evidence implicating the orbitofrontal cortex in such behavior. This evidence suggests that cocaine-induced changes in orbitofrontal cortex disrupt the representation of states and transition functions that form the basis of flexible and adaptive 'model-based' behavioral control. By impairing this function, cocaine exposure leads to an overemphasis on less flexible, maladaptive 'model-free' control systems. The authors propose that such an effect accounts for the complex pattern of maladaptive behaviors associated with cocaine addiction. Lucantonio F, Stalnaker TA, Shaham Y, Niv, Y, Schoenbaum G. The impact of orbitofrontal dysfunction on cocaine addiction. Nat. Neurosci. 2012 Jan 22; 15(3): 358-366.

### Molecular Neuropsychiatry Research Branch

**Involvement Of Dopamine Receptors In Binge Methamphetamine-Induced Activation Of Endoplasmic Reticulum And Mitochondrial Stress Pathways** Single large doses of methamphetamine (METH) cause endoplasmic reticulum (ER) stress and mitochondrial dysfunctions in rodent striata. The dopamine D(1) receptor appears to be involved in these METH-mediated stresses. The purpose of this study was to investigate if dopamine D(1) and D(2) receptors are involved in ER and mitochondrial stresses caused by single-day METH binges in the rat striatum. Male Sprague-Dawley rats received 4 injections of 10 mg/kg of METH alone or in combination with a putative D(1) or D(2) receptor antagonist, SCH23390 or raclopride, respectively, given 30 min prior to each METH injection. Rats were euthanized at various timepoints afterwards. Striatal tissues were used in quantitative RT-PCR and western blot analyses. The authors found that binge METH injections caused increased expression of the pro-survival genes, BiP/GRP-78 and P58(IPK), in a SCH23390-sensitive manner. METH also caused up-regulation of ER-stress genes, Atf2, Atf3, Atf4, CHOP/Gadd153 and Gadd34. The expression of heat shock proteins (HSPs) was increased after METH injections. SCH23390 completely blocked induction in all analyzed ER stress-related proteins that included ATF3, ATF4, CHOP/Gadd153, HSPs and caspase-12. The dopamine D(2)-like antagonist, raclopride, exerted small to moderate inhibitory influence on some METH-induced changes in ER stress proteins. Importantly, METH caused decreases in the mitochondrial anti-apoptotic protein, Bcl-2, but increases in the pro-apoptotic proteins, Bax, Bad and cytochrome c, in a SCH23390-sensitive fashion. In contrast, raclopride provided only small inhibition of METH-induced changes in mitochondrial proteins. These findings indicate that METH-induced activation of striatal ER and mitochondrial stress pathways might be more related to activation of SCH23390-sensitive receptors. Beauvais G, Atwell K, Jayanthi S, Ladenheim B, Cadet JL. PLoS One. 2011; 6(12): e28946. Epub 2011 Dec 13.

**Sex-Specific Changes In Gene Expression And Behavior Induced By Chronic Toxoplasma Infection In Mice** There is growing evidence that Toxoplasma gondii modifies the behavior of its intermediate hosts. IRP scientists investigated the molecular basis of these infection-induced behavioral changes, followed by five related behavioral tests to assess the extent of biological relevance. Gene expression signatures were generated in the frontal cortex of male and female mice during the latent stage of infection. Theye found marked sex-dependent expression differences in mice. In female mice, Toxoplasma infection altered the expression of genes involved in the development of the forebrain, neurogenesis, and sensory and motor coordination (i.e. downregulation of fatty acid-binding protein 7 and eyes absent homolog 1, upregulation of semaphorin 7A). In male mice, infection led mainly to modulation of genes associated with olfactory function (i.e. downregulation of a number of olfactory receptors and dopamine receptor D4, upregulation of slit homolog 1). Although infection appears to affect the olfactory function in male mice, it is the female but not male mice that exhibited attraction to cat odor. In contrast, infected male mice showed a deficit in social transmission of food preference. In contrast to males, infected females displayed locomotor hyperactivity in open field. General olfaction and sensorimotor gating were normal in both male and female infection. These results indicate that the sex of the host plays a major role in determining variable brain and behavior changes following Toxoplasma infection. These observations are consistent with heterogeneity of neuropsychiatric outcomes of the infection in humans. Xiao J, Kannan G, Jones-Brando L, Brannock C, Krasnova IN, Cadet JL, Pletnikov M, Yolken RH. Neuroscience. 2012 Mar 29; 206: 39-48. Epub 2012 Jan 3.

**Glua3-Deficiency In Mice Is Associated With Increased Social And Aggressive Behavior And Elevated Dopamine In Striatum** Glutamate signaling has been implicated in the regulation of social behavior. AMPA-glutamate receptors are assembled from four subunits (GluA1-4) of mainly GluA1/2 and GluA2/3 tetramers that form ion channels of distinct functional properties. Mice lacking GluA1 showed a reduced anxiety and male aggression. To understand the role of GluA3 in modulating social behavior, IRP researchers investigated GluA3-deficient mice (Gria3-/Y) on C57BL/6J background. Compared to wild type (WT) littermates (n=14), Gria3-/Y mice (n=13) showed an increase in isolation-induced male aggression (p=0.011) in home cage resident-intruder test; an increase in sociability (p=0.01), and increase in male-male social interactions in neutral arena (p=0.005); an increase in peripheral activities in open field test (p=0.037) with normal anxiety levels in elevated plus maze and light-dark box; and minor deficits in motor and balance function in accelerating rotarod test (p=0.016) with normal grip strength. Gria3-/Y mice showed no significant deficit in spatial memory function in Morris-water maze and Y-maze tests, and normal levels of testosterone. Increased dopamine concentrations in stratum (p=0.034) and reduced serotonin turnover in olfactory bulb (p=0.002) were documented in Gria3-/Y mice. These results support a role of GluA3 in the modulation of social behavior through brain dopamine and/or serotonin signaling and different AMPA receptor subunits affect social behavior through distinct mechanisms. Adamczyk A, Mejias R, Takamiya K, Yocum J, Krasnova IN, Calderon J, Cadet JL, Huganir RL, Pletnikov MV, Wang T. Behav Brain Res. 2012 Apr 1; 229(1): 265-272. Epub 2012 Jan 21.

**Chemical Biology Research Branch**

**The Neuropharmacology Of Prolactin Secretion Elicited By 3,4-Methylenedioxymeth-Amphetamine ("Ecstasy"): A Concurrent Microdialysis And Plasma Analysis Study** 3,4-methylenedioxymethamphetamine (MDMA) is a substituted phenethylamine that is widely abused as the street drug "ecstasy". Racemic MDMA (S,R(+/-)-MDMA) and its stereoisomers elicit complex spectrums of psychobiological, neurochemical, and hormonal effects. In this regard, recent findings demonstrated that S,R(+/-)-MDMA and its stereoisomer R(-)-MDMA elicit increases in striatal extracellular serotonin levels and plasma levels of the hormone prolactin in rhesus monkeys. In the present mechanistic study, IRP scientists evaluated the role of the serotonin transporter and the 5-HT(2A) receptor in S,R(+/-)-MDMA- and R(-)-MDMA-elicited prolactin secretion in rhesus monkeys through concurrent microdialysis and plasma analysis determinations and drug interaction experiments. Concurrent neurochemical and hormone determinations showed a strong positive temporal correlation between serotonin release and prolactin secretion. Consistent with their distinct mechanisms of action and previous studies showing that the serotonin transporter inhibitor fluoxetine attenuates the behavioral and neurochemical effects of S,R(+/-)-MDMA, pretreatment with fluoxetine attenuated serotonin release elicited by either S,R(+/-)-MDMA or R(-)-MDMA. As hypothesized, at a dose that had no significant effects on circulating prolactin levels when administered alone, fluoxetine also attenuated prolactin secretion elicited by S,R(+/-)-MDMA. In contrast, combined pretreatment with both fluoxetine and the selective 5-HT(2A) receptor antagonist M100907 was required to attenuate prolactin secretion elicited by R(-)-MDMA, suggesting that this stereoisomer of S,R(+/-)-MDMA elicits prolactin secretion through both serotonin release and direct agonism of 5-HT(2A) receptors. Accordingly, these findings inform our understanding of the neuropharmacology of both S,R(+/-)-MDMA and R(-)-MDMA and the regulation of prolactin secretion. Murnane KS, Kimmel HL, Rice KC, Howell LL. Horm Behav. 2012 Feb; 61(2): 181-190. Epub 2011 Dec 14.

**Probes For Narcotic Receptor Mediated Phenomena. 44. Synthesis Of An N-Substituted 4-Hydroxy-5-(3-Hydroxyphenyl)Morphan With High Affinity And Selective M-Antagonist Activity** A simple three-step synthesis of 5-(3-hydroxyphenyl)-2-methyl-2-azabicyclo [3.3.1]nonan-4-ol (3a) was achieved using an osmium tetroxide mediated oxidation of the known intermediate 6. A pyrrolidine-ring variant of 3a (3-(7-(hydroxymethyl)-6-methyl-6-azabicyclo [3.2.1]octan-1-yl)phenol (5)) was isolated when other routes were used. The epimeric hydroxy analogue 4a was synthesized by simple inversion of the stereochemistry at C-4. Both N-methyl (3a and 4a) and N-phenethyl (3b and 4b) derivatives were synthesized. The compounds were examined for their opioid receptor affinity and the N-phenethyl analogue 3b was found to have relatively weak affinity for the μ-opioid receptor (K(i) = 74 nM). However, the N-phenethyl analogue of the C-4 epimer, 4b, had about 15 fold higher affinity than 3b and was selective for the μ-opioid receptor (K(i) = 4.6 nM). Compound 4b was a moderately potent μ-opioid antagonist (K(e) = 12 nM), as determined by [(35)S]GTP-γ-S assays. Compounds 3b and 4b were energy minimized at the level of B3LYP/6-31G*, and then overlaid onto the 5-phenylmorphan, the (1R,5R,9S)-(-)-enantiomer of 2b (Fig. 1) with the α or β-OH group at the C-9 position. The spatial orientation of the hydroxyl moiety in 3b, 4b, 2a, and 2b is proposed to be the structural requirement for high μ-opioid receptor binding affinity and their agonist or antagonist activity. The modest change in spatial position of the hydroxyl moiety, and not the N-

substituent, induced the change from potent agonist to an antagonist of moderate potency. Iyer MR, Lee YS, Deschamps JR, Dersch CM, Rothman RB, Jacobson AE, Rice KC . Eur J Med Chem. 2012 Apr; 50: 44-54. Epub 2012 Jan 20.

**Configurational Reassignment and Improved Preparation of the Competitive IL-6 Receptor Antagonist 20R,21R-Epoxyresibufogenin-3-formate** 20R,21R-Epoxyresibufogenin-3-formate (1) and 20S,21S-epoxyresibufogenin-3-formate (2) were synthesized from commercial resibufogenin (3) using known procedures. The major product (1) was dextrorotatory, as was the major product from the reported synthesis of epoxyresibufogenin-3-formate; however, the literature (+)-compound was assigned the 20S,21S-configuration on the basis of NMR data. IRP scientists have now unequivocally determined, using single-crystal X-ray structure analyses of the major and minor products of the synthesis and of their derivatives, that the major product from the synthesis was (+)-20R,21R-epoxyresibufogenin-3-formate (1). The auithors' minor synthetic product was determined to have the (-)-20S,21S-configuration (2). The (+)-20R,21R-compound 1 has been found to have high affinity for the IL-6 receptor and to act as an IL-6 antagonist. A greatly improved synthesis of 1 was achieved through oxidation of preformed resibufogenin-3-formate. This has enabled us to prepare, from the very expensive commercial resibufogenin, considerably larger quantities of 1, the only known nonpeptide small-molecule IL-6 antagonist. Boos TL , Cheng K , Greiner E , Deschamps JR , Jacobson AE , Rice KC . J Nat Prod. 2012 Feb 23. [Epub ahead of print].

**Effects Of The GABA(B) Receptor-Positive Modulators CGP7930 And Rac-BHFF In Baclofen- And In GHB-Discriminating Pigeons** In vivo effects of GABA(B) receptor-positive modulators suggest them to have therapeutic potential to treat central nervous system disorders such as anxiety and drug abuse. Although these effects are thought to be mediated by positive modulation of GABA(B) receptors, such modulation has been examined primarily in vitro. This study further examined the in vivo properties of the GABA(B) receptor-positive modulators, 2,6-di-tert-butyl-4-(3-hydroxy-2,2-dimethylpropyl) phenol (CGP7930) and (R,S)-5,7-di-tert-butyl-3-hydroxy-3-trifluoromethyl-3H-benzofuran-2-one (rac-BHFF). In pigeons discriminating baclofen from saline, γ-hydroxybutyrate (GHB) produced 100% baclofen-appropriate responding, and the GABA(B) antagonist 3-aminopropyl(dimethoxymethyl) phosphinic acid (CGP35348) blocked the effects of both drugs. CGP7930 and rac-BHFF produced at most 41% and 74% baclofen-appropriate responding, respectively, and enhanced the discriminative stimulus effects of baclofen, but not of GHB. In pigeons discriminating GHB from saline, CGP7930 and rac-BHFF produced at most 1% and 49% GHB-appropriate responding, respectively, and enhanced the effects of baclofen, but not of GHB. Enhancement of the discriminative stimulus effects of baclofen by rac-BHFF and CGP7930 is further evidence of their effectiveness as GABA(B) receptor-positive modulators in vivo. Further, lack of complete substitution of the positive modulators rac-BHFF and CGP7930 for baclofen and GHB suggests that their discriminative stimulus effects differ from those of GABA(B) receptor agonists. Finally, together with converging evidence that the GABA(B) receptor populations mediating the effects of baclofen and GHB are not identical, the present findings suggest that these populations differ in their susceptibility to positive modulatory effects. Such differences could allow for more selective therapeutic targeting of the GABA(B) system. Koek W, France CP, Cheng K, Rice KC. J Pharmacol Exp Ther. 2012 Feb 7. [Epub ahead of print].

**Integrative Neuroscience Branch**
**Cellular Pathobiology Section**

**Compromising Sigma-1 Receptors At The ER Renders Cytotoxicity To Physiologically Relevant Concentrations Of Dopamine In A NF-Kb/Bcl-2-Dependent Mechanism: Potential Relevance To Parkinson's Disease** The endoplasmic reticulum (ER) chaperone sigma-1 receptor (Sig-1R) is cytoprotective against ER stress-induced apoptosis. The level of Sig-1Rs in the brain was reported to be lower in the early Parkinsonian patients. Because dopamine (DA) toxicity is well-known to be involved in the etiology of Parkinson's disease, IRP scientists tested in this study if a relationship might exist between Sig-1Rs and DA-induced cytotoxicity in a cellular model by using CHO cells. DA in physiological concentrations (e.g., lower than 10 μM) does not cause apoptosis. However, the same concentrations of DA cause apoptosis in Sig-1R knockdown CHO cells. In search for a mechanistic explanation, the authors found that unfolded protein response is not involved. Rather, the level of protective protein Bcl-2 is critically involved in this DA/Sig-1R knockdown-induced apoptosis. Specifically, the DA/Sig-1R knockdown causes a synergistic proteasomal conversion of NF-κB p105 to the active form of p50 which is known to downregulate the transcription of Bcl-2. Importantly, the DA/Sig-1R knockdown-induced apoptosis is blocked by the overexpression of Bcl-2. These results therefore indicate that DA is involved in the activation of NF-κB and suggest that endogenous Sig-1Rs are tonically inhibiting the proteasomal conversion/activation of NF-κB caused by physiologically relevant concentrations of DA which would otherwise cause apoptosis. Thus, Sig-1Rs and associated ligands may represent new therapeutic targets for the treatment of Parkinsonism. Mori T, Hayashi T, Su TP. Compromising sigma-1 receptors at the ER renders cytotoxicity to physiologically relevant concentrations of dopamine in a NF-kB/Bcl-2-dependent mechanism: Potential relevance to Parkinson's disease. J Pharmacol Exp Ther 2012 March 7; DOI:10.1124/jpet.111.190868I.

**Molecular Neurobiology Branch**

**Knocking Out The Dopamine Reuptake Transporter (DAT) Does Not Change The Baseline Brain Arachidonic Acid Signal In The Mouse** Dopamine transporter (DAT) homozygous knockout (DAT(-/-)) mice have a 10-fold higher extracellular DA concentration in the caudate-putamen and nucleus accumbens than do wildtype (DAT(+/+)) mice, but show reduced presynaptic DA synthesis and fewer postsynaptic D(2) receptors. One aspect of neurotransmission involves DA binding to postsynaptic D(2)-like receptors coupled to cytosolic phospholipase A(2) (cPLA(2)), which releases the second messenger, arachidonic acid (AA), from synaptic membrane phospholipid. IRP researchers hypothesized that tonic overactivation of D(2)-like receptors in DAT(-/-) mice due to the excess DA would not increase brain AA signaling, because of compensatory downregulation of postsynaptic DA signaling mechanisms. [1-(14)C]AA was infused intravenously for 3 min in unanesthetized DAT(+/+), heterozygous (DAT(+/-)), and DAT(-/-) mice. AA incorporation coefficients k* and rates J(in), markers of AA metabolism and signaling, were imaged in 83 brain regions using quantitative autoradiography; brain cPLA(2)-IV activity also was measured. Neither k* nor J(in) for AA in any brain region, or brain cPLA(2)-IV activity, differed significantly among DAT(-/-), DAT(+/-), and DAT(+/+) mice. These results differ from reported increases in k* and J(in) for AA, and in brain cPLA(2)

expression, in serotonin reuptake transporter (5-HTT) knockout mice, and suggest that postsynaptic dopaminergic neurotransmission mechanisms involving AA are downregulated despite elevated DA in DAT(-/-) mice. Ramadan E, Chang L, Chen M, Ma K, Hall FS, Uhl GR, Rapoport SI, Basselin M. Int J Neurosci. 2012 Mar 1. PMID: 22376027

**Mouse Models For Studying Genetic Influences On Factors Determining Smoking Cessation Success In Humans** Humans differ in their ability to quit using addictive substances, including nicotine, the major psychoactive ingredient in tobacco. For tobacco smoking, a substantial body of evidence, largely derived from twin studies, indicates that approximately half of these individual differences in ability to quit are heritable genetic influences that likely overlap with those for other addictive substances. Both twin and molecular genetic studies support overlapping influences on nicotine addiction vulnerability and smoking cessation success, although there is little formal analysis of the twin data that support this important point. None of the current datasets provides clarity concerning which heritable factors might provide robust dimensions around which individuals differ in ability to quit smoking. One approach to this problem is to test mice with genetic variations in genes that contain human variants that alter quit success. This review considers which features of quit success should be included in a comprehensive approach to elucidate the genetics of quit success, and how those features may be modeled in mice. Hall FS, Markou A, Levin ED, Uhl GR. Ann N Y Acad Sci. 2012 Feb; 1248: 39-70. doi: 10.1111/j.1749-6632.2011.06415.x. PMID: 22304675

**Pretreatment With Nomifensine Or Nomifensine Analogue 4-Phenyl-1,2,3,4-Tetrahydroisoquinoline Augments Methamphetamine-Induced Stereotypical Behavior In Mice** Nomifensine is a dopamine/norepinephrine reuptake inhibitor. Nomifensine and some of its structural analogues produce behavioral effects indicative of indirect dopaminergic agonist properties, such as hyperlocomotion. By contrast, the deaminated and demethylated nomifensine analogue 4-phenyl-1,2,3,4-tetrahydroisoquinoline (PTIQ) is reported to have amphetamine-antagonistic properties, as demonstrated by inhibition of methamphetamine (METH)-induced dopamine release in the nucleus accumbens and METH-induced hyperlocomotion in rats. In the present study, IRP scientists examined the effect of PTIQ (10mg/kg, i.p.) and nomifensine (3mg/kg, i.p.) on METH (5 or 10mg/kg, i.p.)-induced stereotypical behavior in mice in order to determine whether PTIQ and nomifensine inhibit and augment, respectively, METH-induced stereotypical behavior. Unexpectedly, their observations demonstrated that both PTIQ and nomifensine significantly augmented METH-induced stereotypical behavior and locomotion in mice. This augmentation is likely the result of additive effects on dopaminergic function by METH in combination with PTIQ or nomifensine. These results suggest that, contrary to some reports, PTIQ may display dopaminergic agonist properties in mice. Kitanaka J, Kitanaka N, Hall FS, Uhl GR, Asano H, Chatani R, Hayata S, Yokoyama H, Tanaka K, Nishiyama N, Takemura M. Brain Res. 2012 Feb 23; 1439: 15-26. Epub 2011 Dec 31. PMID: 22265332

**Active Behaviours Produced By Antidepressants And Opioids In The Mouse Tail Suspension Test** Most classical preclinical tests to predict antidepressant activity were initially developed to detect compounds that influenced noradrenergic and/or serotonergic activity, in accordance with the monoaminergic hypothesis of depression. However, central opioid systems are also known to influence the pathophysiology of depression. While the tail suspension test (TST) is very sensitive to several types of antidepressant, the traditional form of scoring the TST

does not distinguish between different modes of action. The present study was designed to compare the behavioural effects of classical noradrenergic and/or serotonergic antidepressants in the TST with those of opioids. IRP researchers developed a sampling technique to differentiate between behaviours in the TST, namely, curling, swinging and immobility. Antidepressants that inhibit noradrenaline and/or serotonin re-uptake (imipramine, venlafaxine, duloxetine, desipramine and citalopram) decreased the immobility of mice, increasing their swinging but with no effect on their curling behaviour. No differences were observed between antidepressants that act on noradrenergic or serotoninergic transmission. While opioid compounds also decreased the immobility of the mice [morphine, codeine, levorphanol, (-)-methadone, (±)-tramadol and (+)-tramadol], they selectively increased curling behaviour. Blocking opioid receptors with naloxone prevented the antidepressant-like effect of codeine, and μ-opioid receptor knockout decreased normal curling behaviour and blocked (±)-tramadol-induced curling, further demonstrating the reliability and validity of this approach. These results show that at least two behaviourally distinct processes occur in the TST, highlighting the antidepressant-like effects of opioids evident in this test. Furthermore, these data suggest that swinging and curling behaviours are mediated by enhanced monoamine and opioid neurotransmission, respectively. Berrocoso E, Ikeda K, Sora I, Uhl GR, Sánchez-Blázquez P, Mico JA.Int J Neuropsychopharmacol. 2012 Jan 5: 1-12. PMID: 22217458

**A Single Administration Of Methamphetamine To Mice Early In The Light Period Decreases Running Wheel Activity Observed During The Dark Period** Repeated intermittent administration of amphetamines acutely increases appetitive and consummatory aspects of motivated behaviors as well as general activity and exploratory behavior, including voluntary running wheel activity. Subsequently, if the drug is withdrawn, the frequency of these behaviors decreases, which is thought to be indicative of dysphoric symptoms associated with amphetamine withdrawal. Such decreases may be observed after chronic treatment or even after single drug administrations. In the present study, the effect of acute methamphetamine (METH) on running wheel activity, horizontal locomotion, appetitive behavior (food access), and consummatory behavior (food and water intake) was investigated in mice. A multi-configuration behavior apparatus designed to monitor the five behaviors was developed, where combined measures were recorded simultaneously. In the first experiment, naïve male ICR mice showed gradually increasing running wheel activity over three consecutive days after exposure to a running wheel, while mice without a running wheel showed gradually decreasing horizontal locomotion, consistent with running wheel activity being a positively motivated form of natural motor activity. In experiment 2, increased horizontal locomotion and food access, and decreased food intake, were observed for the initial 3h after acute METH challenge. Subsequently, during the dark phase period decreased running wheel activity and horizontal locomotion were observed. The reductions in running wheel activity and horizontal locomotion may be indicative of reduced dopaminergic function, although it remains to be seen if these changes may be more pronounced after more prolonged METH treatments. Kitanaka N, Kitanaka J, Hall FS, Uhl GR, Watabe K, Kubo H, Takahashi H, Tatsuta T, Morita Y, Takemura M. Brain Res. 2012 Jan 6;1429:155-63. Epub 2011 Oct 26. PMID: 22079320

**Meta-Analysis And Genome-Wide Interpretation Of Genetic Susceptibility To Drug Addiction** Classical genetic studies provide strong evidence for heritable contributions to susceptibility to developing dependence on addictive substances. Candidate gene and genome-wide association studies (GWAS) have sought genes, chromosomal regions and allelic variants likely to contribute to susceptibility to drug addiction. Here, IRP scientists performed a meta-analysis of addiction candidate gene association studies and GWAS to investigate possible functional mechanisms associated with addiction susceptibility. From meta-data retrieved from 212 publications on candidate gene association studies and 5 GWAS reports, they linked a total of 843 haplotypes to addiction susceptibility. The authors mapped the SNPs in these haplotypes to functional and regulatory elements in the genome and estimated the magnitude of the contributions of different molecular mechanisms to their effects on addiction susceptibility. In addition to SNPs in coding regions, these data suggest that haplotypes in gene regulatory regions may also contribute to addiction susceptibility. When the authors compared the lists of genes identified by association studies and those identified by molecular biological studies of drug-regulated genes, we observed significantly higher participation in the same gene interaction networks than expected by chance, despite little overlap between the two gene lists. These results appear to offer new insights into the genetic factors underlying drug addiction. Li CY, Zhou WZ, Zhang PW, Johnson C, Wei L, Uhl GR. BMC Genomics. 2011 Oct 15; 12: 508. PMID: 21999673

**Quantitative Detection of μ Opioid Receptor: Western Blot Analyses Using μ Opioid Receptor Knockout Mice** Increasing evidence suggests that Âμ opioid receptor (MOP) expression is altered during the development of and withdrawal from substance dependence. Although anti-MOP antibodies have been hypothesized to be useful for estimating MOP expression levels, inconsistent MOP molecular weights (MWs) have been reported in studies using anti-MOP antibodies. In the present study, IRP investigators generated a new anti-MOP antibody (N38) against the 1-38 amino acid sequence of the mouse MOP N-terminus and conducted Western blot analysis with wildtype and MOP knockout brain lysates to determine the MWs of intrinsic MOP. The N38 antibody detected migrating bands with relative MWs of 60-67 kDa in the plasma membrane fraction isolated from wildtype brain, but not from the MOP knockout brain. These migrating bands exhibited semi-linear density in the range of 3-30 Âμg membrane proteins/lane. The N38 antibody may be useful for quantitatively detecting MOP. Kasai S, Yamamoto H, Kamegaya E, Uhl GR, Sora I, Watanabe M, Ikeda K. Curr Neuropharmacol. 2011 Mar;9(1):219-22. PMID:21886594

**Effects of MDMA on Extracellular Dopamine and Serotonin Levels in Mice Lacking Dopamine and/or Serotonin Transporters** 3,4-Methylendioxymethamphetamine (MDMA) has both stimulatory and hallucinogenic properties which make its psychoactive effects unique and different from those of typical psychostimulant and hallucinogenic agents. The present study investigated the effects of MDMA on extracellular dopamine (DA(ex)) and serotonin (5-HT(ex)) levels in the striatum and prefrontal cortex (PFC) using in vivo microdialysis techniques in mice lacking DA transporters (DAT) and/or 5-HT transporters (SERT). subcutaneous injection of MDMA (3, 10 mg/kg) significantly increased striatal DA(ex) in wild-type mice, SERT knockout mice, and DAT knockout mice, but not in DAT/SERT double-knockout mice. The MDMA-induced increase in striatal DA(ex) in SERT knockout mice was significantly less than in wildtype mice. In the PFC, MDMA dose-dependently increased DA(ex) levels in wildtype, DAT

knockout, SERT knockout and DAT/SERT double-knockout mice to a similar extent. In contrast, MDMA markedly increased 5-HT(ex) in wildtype and DAT knockout mice and slightly increased 5-HT(ex) in SERT-KO and DAT/SERT double-knockout mice. The results confirm that MDMA acts at both DAT and SERT and increases DA(ex) and 5-HT(ex).
Hagino Y, Takamatsu Y, Yamamoto H, Iwamura T, Murphy DL, Uhl GR, Sora I, Ikeda K. Curr Neuropharmacol. 2011 Mar; 9(1): 91-95. PMID: 21886569

**Genomic Regions Identified By Overlapping Clusters Of Nominally-Positive SNPs From Genome-Wide Studies Of Alcohol And Illegal Substance Dependence** Declaring "replication" from results of genome wide association (GWA) studies is straightforward when major gene effects provide genome-wide significance for association of the same allele of the same SNP in each of multiple independent samples. However, such unambiguous replication is unlikely when phenotypes display polygenic genetic architecture, allelic heterogeneity, locus heterogeneity and when different samples display linkage disequilibria with different fine structures. The authors seek chromosomal regions that are tagged by clustered SNPs that display nominally-significant association in each of several independent samples. This approach provides one "nontemplate" approach to identifying overall replication of groups of GWA results in the face of difficult genetic architectures. The authors apply this strategy to 1 M SNP GWA results for dependence on: a) alcohol (including many individuals with dependence on other addictive substances) and b) at least one illegal substance (including many individuals dependent on alcohol). This approach provides high confidence in rejecting the null hypothesis that chance alone accounts for the extent to which clustered, nominally-significant SNPs from samples of the same racial/ethnic background identify the same sets of chromosomal regions. It identifies several genes that are also reported in other independent alcohol-dependence GWA datasets. There is more modest confidence in: a) identification of individual chromosomal regions and genes that are not also identified by data from other independent samples, b) the more modest overlap between results from samples of different racial/ethnic backgrounds and c) the extent to which any gene not identified herein is excluded, since the power of each of these individual samples is modest. Nevertheless, the strong overlap identified among the samples with similar racial/ethnic backgrounds supports contributions to individual differences in vulnerability to addictions that come from newer allelic variants that are common in subsets of current humans.
Johnson C, Drgon T, Walther D, Uhl GR. PLoS One. 2011; 6(7): e19210. Epub 2011 Jul 27. PMID: 21818250

**Effects Of Neurotensin Gene Knockout In Mice On The Behavioral Effects Of Cocaine** The neuropeptide neurotensin (NT), which has been implicated in the modulation of dopamine signaling, is expressed in a subset of dopamine neurons and antagonism of the NT receptor has been reported to reduce psychostimulant-induced behavior. Gene knockout (KO) of the neurotensin/neuromedin N precursor provides an approach to delineating possible roles of endogenous NT in psychostimulant-induced responses. Involvement of NT in cocaine responses was examined by comparing acute and conditioned locomotor responses, conditioned place preference, and sensitization in wild-type (WT), heterozygous, and homozygous NT KO mice. NT KO mice did not differ from their WT or heterozygous littermates in either baseline or acute cocaine-stimulated locomotor activity. The locomotor stimulant effects of cocaine were slightly prolonged in these mice under some, but not all, experimental conditions. The rewarding effects of cocaine as assessed in the conditioned place preference and conditioned locomotion

paradigms were also similar between genotypes at all cocaine doses tested. These results suggest that endogenous NT is not involved in cocaine-mediated behaviors in most circumstances, but under some conditions, a slight prolongation of the effects of cocaine was observed in the absence of endogenous NT. Hall FS, Centeno M, Perona MT, Adair J, Dobner PR, Uhl GR. Psychopharmacology (Berl). 2012 Jan; 219(1): 35-45. Epub 2011 Jul 1. PMID: 21720755

**Menthol Preference Among Smokers: Association With TRPA1 Variants** Preference for smoking menthol cigarettes differs from individual to individual and population to population in ways that may provide higher levels of nicotine intake and contribute to smoking's morbidity and mortality. Menthol acts at sites that include the transient receptor potential (TRP) A1 channel that is expressed by nociceptors in the lung and airways, suggesting that individual and population differences in TRPA1 sequences might contribute to observed differences in menthol preference among smokers. IRP scientists have thus sought association between menthol preference and common variants in the TRPA1 gene in heavier and lighter European-American smokers. Smokers were recruited for studies of smoking cessation in North Carolina and of substance abuse genetics in Maryland. A common TRPA1 haplotype is defined by 1 missense and 10 intronic single nucleotide polymorphisms that display significant ($.006 < p < .05$; $\chi(2)$) association with preference for mentholated cigarettes in heavy smokers (odds ratio ca. 1.3). There are smaller trends in the same direction in lighter smokers. This TRPA1 haplotype provides a novel biological basis for individual differences in menthol preference and possibly for actions of other agents that act at TRPA1. Uhl GR, Walther D, Behm FM, Rose JE. Nicotine Tob Res. 2011 Dec; 13(12): 1311-1135. Epub 2011 Jun 30. PMID: 21719896

**Decreased Response To Social Defeat Stress In M-Opioid-Receptor Knockout Mice**
Substantial evidence exists that opioid systems are involved in stress response and that changes in opioid systems in response to stressors affect both reward and analgesia. Reportedly, mice suffering chronic social defeat stress subsequently show aversion to social contact with unfamiliar mice. To further examine the role of opioid systems in stress response, the behavioral and neurochemical effects of chronic social defeat stress (psychosocial stress) were evaluated in μ-opioid-receptor knockout (MOR-KO) mice. Aversion to social contact was induced by chronic social defeat stress in wild-type mice but was reduced in MOR-KO mice. Moreover, basal expression of brain-derived neurotrophic factor (BDNF) mRNA in MOR-KO mice hippocampi was significantly lower than in wild-type mice. Psychosocial stress significantly decreased BDNF mRNA expression in wild-type mice but did not affect BDNF expression in MOR-KO mice; no difference in basal levels of plasma corticosterone was observed. These results suggest that the μ-opioid receptor is involved in the behavioral sequelae of psychosocial stress and consequent regulation of BDNF expression in the hippocampus, and may play an important role in psychiatric disorders for which stress is an important predisposing or precipitating factor, such as depression, posttraumatic stress disorder, and social anxiety disorder. Komatsu H, Ohara A, Sasaki K, Abe H, Hattori H, Hall FS, Uhl GR, Sora I.Pharmacol Biochem Behav. 2011 Oct; 99(4): 676-682. Epub 2011 Jun 15. PMID: 21703297

**CHRNA3 Rs1051730 Genotype And Short-Term Smoking Cessation** The rs1051730 genetic variant within the CHRNA5-A3-B4 gene cluster is associated with heaviness of smoking and has recently been reported to be associated with likelihood of stopping smoking. IRP scientists investigated the potential association of rs1051730 genotype with reduced likelihood of smoking

cessation in 2 cohorts of treatment-seeking smokers in primary care in the United Kingdom. Data were drawn from 2 clinical trials on which DNA was available. One sample was a randomized placebo-controlled trial of nicotine transdermal patch and the other sample an open-label trial where all participants received nicotine transdermal patch. Smoking status was biochemically verified. Logistic regression was used to assess evidence for association in each sample, and data were combined within a meta-analysis. There was evidence of association of rs1051730 genotype with short-term (4-week) cessation in our open-label trial sample but not our placebo-controlled trial sample. When combined in a meta-analysis, this effect remained. There was no evidence of association at later follow-up intervals. Adjustment for cigarette consumption and tobacco dependence did not alter these results substantially. These data, taken together with previous recent studies, provide some support for a weak association between this variant and short-term smoking cessation in treatment-seeking smokers, which does not seem to operate only among those receiving nicotine replacement therapy. Moreover, the rs1051730 variant may not merely operate as a marker for dependence or heaviness of smoking. Munafò MR, Johnstone EC, Walther D, Uhl GR, Murphy MF, Aveyard P. Nicotine Tob Res. 2011 Oct; 13(10): 982-988. Epub 2011 Jun 20. PMID: 21690317

**Histamine H3 Receptor Agonists Decrease Hypothalamic Histamine Levels And Increase Stereotypical Biting In Mice Challenged With Methamphetamine** The effects of the histamine H(3) receptor agonists (R)-α-methylhistamine, imetit and immepip on methamphetamine (METH)-induced stereotypical behavior were examined in mice. The administration of METH (10 mg/kg, i.p.) to male ddY mice induced behaviors including persistent locomotion and stereotypical behaviors, which were classified into four categories: stereotypical head-bobbing (1.9%), circling (1.7%), sniffing (14.3%), and biting (82.1%). Pretreatment with (R)-α-methylhistamine (3 and 10 mg/kg, i.p.) significantly decreased stereotypical sniffing, but increased stereotypical biting induced by METH, in a dose-dependent manner. This effect of (R)-α-methylhistamine on behavior was mimicked by imetit or immepip (brain-penetrating selective histamine H(3) receptor agonists; 10 mg/kg, i.p. for each drug). Hypothalamic histamine levels 1 h after METH challenge were significantly increased in mice pretreated with saline. These increases in histamine levels were significantly decreased by pretreatment with histamine H(3) receptor agonists, effects which would appear to underlie the shift from METH-induced stereotypical sniffing to biting. Kitanaka J, Kitanaka N, Hall FS, Uhl GR, Tatsuta T, Morita Y, Tanaka K, Nishiyama N, Takemura M. Neurochem Res. 2011 Oct; 36(10): 1824-1833. Epub 2011 May 15. PMID: 21573995

**Behavioral Neuroscience Branch**
**Behavioral Neuroscience Section**

**Satiating Effects Of Cocaine Are Controlled By Dopamine Actions In The Nucleus Accumbens Core** Intravenous cocaine intake in laboratory animals is characterized by periods of apparent drug satiety between regularly spaced earned injections. The reinforcing properties of cocaine are linked primarily to dopaminergic neurotransmission in the shell and not the core of nucleus accumbens. To determine whether the satiating effects of cocaine are similarly mediated, IRP scientists perfused dopamine receptor agonists into the core or the shell during intravenous cocaine self-administrations by rats. Neither D1-type (SKF38393) nor D2-type

(quinpirole) agonist was effective when given alone. However, a combination of the two agonists perfused into the core but not the shell significantly increased the time between cocaine self-injections, decreasing the amount of earned intake. Together with previous findings, the current data suggest that the satiating and reinforcing effects of cocaine are mediated by different ventral striatal output neurons. Suto N, Wise RA. Satiating effects of cocaine are controlled by dopamine actions in the nucleus accumbens core. J Neurosci. 2011 Dec 7; 31(49): 17917-17922.

**Preclinical Pharmacology Section**

**Cannabinoid Receptor Stimulation Increases Motivation For Nicotine And Nicotine Seeking** The cannabinoid system appears to play a critical facilitative role in mediating the reinforcing effects of nicotine and relapse to nicotine-seeking behaviour in abstinent subjects based on the actions of cannabinoid (CB) receptor antagonists. However, the effects of CB receptor stimulation on nicotine self-administration and reinstatement have not been systematically studied. Here, IRP investigators studied the effects of WIN 55,212-2, a CB1/2 agonist, on intravenous nicotine self-administration under fixed-ratio (FR) and progressive-ratio (PR) schedules of reinforcement in rats. The effects of WIN 55,212-2 on responding for food under similar schedules were also studied. In addition, the effects of WIN 55,212-2 on nicotine- and cue-induced reinstatement of nicotine seeking were also studied, as well as the effects of WIN 55,212-2 on nicotine discrimination. WIN 55,212-2 decreased nicotine self-administration under the FR schedule. However, co-administration of WIN 55,212-2 with nicotine decreased responding for food, which suggests that this effect was non-selective. In contrast, WIN 55,212-2 increased both nicotine self-administration and responding for food under the PR schedule, produced dose-dependent reinstatement of nicotine seeking, and enhanced the reinstatement effects of nicotine-associated cues. Some of these effects were reversed by the CB1 antagonist rimonabant, but not by the CB2 antagonist AM630. In the drug discrimination tests between saline and 0.4 mg/kg nicotine, WIN 55,212-2 produced no nicotine-like discriminative effects but significantly potentiated discriminative stimulus effects of nicotine at the low dose through a CB1-receptor-dependent mechanism. These findings indicate that cannabinoid CB1-receptor stimulation increases the reinforcing effects of nicotine and precipitates relapse to nicotine-seeking behaviour in abstinent subjects. Thus, modulating CB1-receptor signalling might have therapeutic value for treating nicotine dependence. Gamaleddin I, Wertheim C, Zhu AZ, Coen KM, Vemuri K, Makryannis A, Goldberg SR, Le Foll B. Addiction Biology, 2012 Jan; 17(1): 47-61.

**Modification Of Pharmacokinetic And Abuse-Related Effects Of Cocaine By Human-Derived Cocaine Hydrolase In Monkeys** Although substantial research effort has focused on developing pharmacological treatments for cocaine abuse, no effective medications have been developed. Recent studies show that enzymes that metabolize cocaine in the periphery, forestalling its entry into the brain, can prevent cocaine toxicity and its behavioral effects in rodents. Here IRP scientists report on effects of one such enzyme (Albu-CocH) on the pharmacokinetic and behavioral effects of cocaine in squirrel monkeys. Albu-CocH was developed from successive mutations of human butyrylcholinesterase (BChE) and has 1000-fold greater catalytic activity against cocaine than naturally occurring BChE. Pharmacokinetic studies

showed that Albu-CocH (5mg/kg) had a half-life of 56.6 hours in squirrel monkeys. In these studies, plasma levels of cocaine following i.v. 1mg/kg cocaine were reduced 2 hours after administration of Albu-CocH, whereas plasma levels of the cocaine metabolite ecgonine methyl ester were increased. These effects were still evident 72 hours following Albu-CocH administration. In behavioral experiments in monkeys, pre-treatment with 5mg/kg Albu-CocH dramatically decreased self-administration of a reinforcing dose of i.v. cocaine (30 µg/kg/injection) for over 24 hours. Pre-treatment with 5mg/kg Albu-CocH also attenuated the reinstatement of extinguished cocaine self-administration by an i.v. priming injection of cocaine (0.1 or 0.3mg/kg) and, in separate studies, attenuated the discriminative-stimulus effects of cocaine. The ability of Albu-CocH to attenuate the abuse-related effects of cocaine in squirrel monkeys indicates that further investigation of BChE mutants as potential treatment for cocaine abuse and toxicity is warranted. Schindler CW, Justinova Z, Lafleur D, Woods D, Roschke V, Hallak H, Sklair-Tavron L, Redhi GH, Yasar S, Bergman J, Goldberg SR. Addiction Biology, 2012 Jan 20. doi: 10.1111/j.1369-1600.2011.00424.x. [Epub ahead of print] PMID: 22264200

**Accelerating Cocaine Metabolism As An Approach To The Treatment Of Cocaine Abuse And Toxicity** One pharmacokinetic approach to the treatment of cocaine abuse and toxicity involves the development of compounds that can be safely administered to humans and that accelerate the metabolism of cocaine to inactive components. Catalytic antibodies have been developed and shown to accelerate cocaine metabolism, but their catalytic efficiency for cocaine is relatively low. Mutations of human butyrylcholinesterase and a bacterial cocaine esterase found in the soil of coca plants have also been developed. These compounds accelerate cocaine metabolism and antagonize the behavioral and toxic effects of cocaine in animal models. Of these two approaches, the human butyrylcholinesterase mutants show the most immediate promise as they would not be expected to evoke an immune response in humans. Schindler CW, Goldberg SR. Future Medicinal Chemistry. 2012 Feb; 4(2):163-175.

## PROGRAM ACTIVITIES

### New NIDA RFAs

On April 24, 2012, NIDA issued an RFA entitled **FY13 NIDA Avant-Garde Award Program for HIV/AIDS Research (DP1) RFA-DA-13-002**. The NIDA Avant-Garde Award Program for HIV/AIDS Research supports individual scientists of exceptional creativity who propose high-impact research that will open new areas of HIV/AIDS research and/or lead to new avenues for prevention and treatment of HIV/AIDS among drug abusers. Open date: December 17, 2012. Application due date: January 17, 2013, by 5:00 PM local time of applicant organization. AIDS application due date: Not applicable.

### New NIDA Program Announcements

On March 21, 2012, NIDA issued a PAS entitled **Strategic Alliances for Medications Development to Treat Substance Use Disorders (R01) PAS-12-122.** The purpose of this Funding Opportunity Announcement (FOA) is to help support the efforts of individual grantees to meet the objectives of developing medications for the treatment of Substance Use Disorders (SUDs) by leveraging the strengths of two or more organizations toward a common goal of medications development. Open date(s): July 7, 2012; November 7, 2012; June 17, 2013; November 4, 2013; February 24, 2014; November 4, 2014. Application due date: August 7, 2012; December 7, 2012; July 17, 2012; December 4, 2013; March 24, 2014; December 4, 2014; by 5:00 PM local time of applicant organization. AIDS application due date: same as Application due date.

On March 23, 2012, NIDA issued a PA entitled **Technology-Based Interventions to Promote Engagement in Care and Treatment Adherence for Substance Abusing Populations with HIV (R01) PA-12-117; (R34) PA-12-118.** The purpose of this FOA is to encourage pilot and preliminary research on (1) organizational and/or systems-level interventions that may optimize access, utilization, delivery, quality, and/or cost of treatment services for drug, tobacco, or alcohol abuse or dependence through the use of evidence-based practices; (2) organizational and/or systems-specific adaptations to existing evidence-based practices necessary to facilitate their implementation in these new contexts; and (3) novel service delivery models to be pilot tested in preparation for larger-scale effectiveness trials. Open date: April 7, 2012. Application due date: standard dates apply. AIDS application due date: standard dates apply.

On April 23, 2012, NIDA issued a PA entitled **Pilot and Feasibility Studies in Preparation for Drug and Alcohol Abuse Prevention Trials (R34) PA-12-171.** This FOA for R34 applications seeks to support: (a) pilot and/or feasibility testing of new, revised, or adapted preventive intervention approaches targeting the initiation of drug and alcohol use, the progression to abuse or dependence, and the acquisition or transmission of HIV infection among diverse populations and settings; and (b) pre-trial feasibility testing for prevention services and systems research. Open date: May 16, 2012. Application due date: Standard dates apply. AIDS application due date: Standard dates apply.

On April 24, 2012, NIDA issued a PA entitled Pre-Application for the **FY13 NIDA Avant-Garde Award Program for HIV/AIDS Research (X02) PAR-12-164.** The NIDA Avant-Garde Award Program for HIV/AIDS Research supports individual scientists of exceptional creativity who propose high-impact research that will open new areas of HIV/AIDS research and/or lead to new avenues for prevention and treatment of HIV/AIDS among drug abusers. Open date: September 3, 2012. Application due date: October 3, 2012, by 5:00 PM local time of applicant organization. AIDS application due date: Not applicable.

**New FOAs Issued by the NIH Roadmap**

On February 16, 2012, the NIH Common Fund issued a Roadmap PA entitled **Assays for High Throughput Screening (HTS) to Discover Chemical Probes in the Molecular Libraries Probe Production Centers Network (MLPCN) (X01) PAR-12-108.** The purpose of this FOA is to encourage the investigators to form collaborations with the Molecular Libraries Probe Production Centers Network (MLPCN) to implement HTS-ready assays for the discovery and development of small molecule chemical probes. Open date: March 16, 2012. Application due date(s): April 16, 2012; August 15, 2012; by 5:00 PM local time of applicant organization. AIDS application due date: Not Applicable.

On March 19, 2012, the NIH Common Fund issued a Roadmap PA entitled **Use-Oriented Basic Research: Change Mechanisms of Behavioral Social Interventions (Admin Supp) PA-12-119.** The purpose of this FOA is to solicit administrative supplement applications to study possible mechanisms of action of behavioral or social interventions, with the ultimate aim of informing the simplification or other modifications of behavioral or social interventions to improve use in target settings and by target interventionists. Open date: April 15, 2012. Application due date: May 15, 2012 by 5:00 PM local time of applicant organization. AIDS application due date: Not Applicable.

**New Administrative Supplement Program Announcements Issued by NIH**

On February 13, 2012, NIDA, in collaboration with numerous other NIH components, issued an administrative supplement entitled **Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Parent Admin Supp) PA-12-100**. The Office of Research on Women's Health (ORWH), participating Institutes and Centers (ICs) of the National Institutes of Health (NIH), and the Office of Dietary Supplements (ODS) announce the continuation of the program for administrative supplements to research grants to support individuals with high potential to re-enter an active research career after an interruption for family responsibilities or other qualifying circumstances. The purpose of these supplements is to encourage such individuals to re-enter research careers within the missions of all the program areas of NIH. Open date(s): Due dates may vary by awarding IC. Application due date(s): Due dates may vary by awarding IC. AIDS application date: Not applicable

On April 6, 2012, NIDA, in collaboration with numerous other NIH components, issued an administrative supplement entitled **Research Supplements to Promote Diversity in Health-**

**Related Research (Admin Supp) PA-12-149.** The National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) hereby notify Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) holding specific types of NIH research grants, listed in the full Funding Opportunity Announcement (FOA) that funds are available for administrative supplements to improve the diversity of the research workforce by supporting and recruiting students, postdoctorates, and eligible investigators from groups that have been shown to be underrepresented in health-related research. Open date(s): Due dates may vary by awarding IC. Application due date(s): Due dates may vary by awarding IC. AIDS application date: Not applicable.

On April 6, 2012, NIDA, in collaboration with numerous other NIH components, issued an administrative supplement entitled **Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers (Admin Supp) PA-12-150.** The Office of Research on Women's Health (ORWH), participating Institutes and Centers (ICs) of the National Institutes of Health (NIH), and the Office of Dietary Supplements (ODS) announce the continuation of the program for administrative supplements to research grants to support individuals with high potential to re-enter an active research career after an interruption for family responsibilities or other qualifying circumstances. The purpose of these supplements is to encourage such individuals to re-enter research careers within the missions of all the program areas of NIH. Open date(S): Due dates may vary by awarding IC. Application due date(s): Due dates may vary by awarding IC. AIDS application date: Not applicable.

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

On February 21, 2012, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **NIH Blueprint for Neuroscience Research Grand Challenge: Discovering Novel Drugs for Disorders of the Nervous System (U01) RFA-NS-13-003.** The National Institutes of Health (NIH) announces a unique opportunity for investigators working with small molecule compounds to gain access to a robust 'virtual pharma' network to discover neurotherapeutic drugs. Successful applicants to this FOA will become collaborative participants in this network, receiving both funding and no-cost access to contracted drug discovery services that are not typically available to the academic research community. Open Date: September 8, 2012. Application due date: October 8, 2012, by 5:00 PM local time of applicant organization. AIDS application date: Not Applicable.

On February 29, 2012, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Small Business Alzheimer's Disease Research (SBBR [R34/R44]) RFA-OD-12-003; (STTR [R41/R42]) RFA-OD-12-004**. The purpose of this funding opportunity announcement is to solicit Small Business Innovation Research (SBIR) and Small Business Technology Transfer Research (STTR) applications from eligible small business concerns in the area of Alzheimer's disease. Open Date: March 30, 2012. Application due date: April 30, 2012, by 5:00 PM local time of applicant organization. AIDS application due date: Not applicable.

On April 20, 2012, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Clinical Sequencing Exploratory Research (U01) RFA-HG-12-009.** Applications submitted in response to this FOA will address critical questions about the application of genomic sequencing to clinical care of individual patients, from generation of genomic sequence data, to interpretation and translation of the data for the physician, to communication to the patient, including an examination of the ethical, legal and psychosocial implications of bringing broad genomic data into the clinic. Open date: June 26, 2012. Application due date: July 26, 2012, by 5:00 PM local time of applicant organization. AIDS application due date: Not applicable

**New PAs Issued with Other NIH/HHS Components in which NIDA is a Participant**

On February 23, 2012, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Research on the Health of LGBTI Populations (R01) PA-12-111; (R03) PA-12-112; (R21) PA-12-113.** The National Institutes of Health (NIH) is committed to supporting research that will increase scientific understanding of the health status of various population groups and improve the effectiveness of health interventions and services for individuals within those groups. This Funding Opportunity Announcement (FOA) highlights a particular community: lesbian, gay, bisexual, transgender, intersex, and related populations (designated here as LGBTI populations).Open Date: May 5, 2012. Application due dates(s): Standard dates apply. AIDS application due date(s): Standard dates apply.

On March 19, 2012, NIDA issued a PA entitled **Pilot Health Services and Economic Research on the Treatment of Drug, Alcohol, and Tobacco Abuse (R34) PA-12-130.** This Funding Opportunity Announcement (FOA) issued by the National Institute on Drug Abuse (NIDA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) encourages pilot and preliminary research on (1) organizational and/or systems-level interventions that may optimize access, utilization, delivery, quality, and/or cost of treatment services for drug, tobacco, or alcohol abuse or dependence through the use of evidence-based practices; (2) organizational and/or systems-specific adaptations to existing evidence-based practices necessary to facilitate their implementation in these new contexts; and (3) novel service delivery models to be pilot tested in preparation for larger-scale effectiveness trials. Open date: May 16, 2012. Application due date(s): standard dates apply. AIDS application due date: standard dates apply.

On March 19, 2012, NIDA issued a PA entitled **Health Services and Economic Research on the Prevention and Treatment of Drug, Alcohol, and Tobacco Abuse (R01) PA-12-127; (R21) PA-12-128; (R03) PA-12-129 .** This Funding Opportunity Announcement (FOA) issued by the National Institute on Drug Abuse (NIDA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) encourages Research Project Grant (R01), Exploratory/ Developmental (R21), and Small Grant (R03) applications on health services and economic research to improve the quality of prevention, treatment, and recovery support services for drug, alcohol and tobacco abuse. Such research projects might emphasize any of the following subjects: (1) clinical quality improvement; (2) organization and delivery of services; (3) implementation research; (4) economic and cost studies; or (5) development or improvement of research methodology, analytic approaches, and measurement instrumentation used in the study

of drug, alcohol, and tobacco prevention, treatment, and recovery services. Open date: May 16, 2012. Application due date(s): standard dates apply. AIDS application due date: standard dates apply.

On March 30, 2012, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Senior Scientist Research Award (K05) PA-12-148.** The purpose of the Senior Scientist Research (K05) is intended to provide protected time for outstanding senior scientists who have demonstrated a sustained high level of productivity conducting biomedical research relevant to the scientific mission of the appropriate institute to focus on their research and to provide mentoring of new investigators. Open Date: May 12, 2012. Application due date(s): Standard dates apply. AIDS application due date(s): Standard dates apply.

On April 24, 2012, NIDA, in collaboration with numerous other NIH components, issued a PAR entitled **Multidisciplinary Studies of HIV/AIDS and Aging (R21) PAR-12-174; (R01) PAR-12-175; (R03) PAR-12-176.** This FOA invites applications proposing to study HIV infection, HIV-associated conditions, HIV treatment, and/or biobehavioral or social factors associated with HIV/AIDS in the context of aging and/or in older adults. Research approaches of interest include clinical translational, observational, and intervention studies in domestic and international settings. Open date: July 7, 2012. Application due date(s): August 7, 2012; December 7, 2012; April 9, 2013; August 7, 2013; December 6, 2013; April 9, 2014; August 7, 2014; December 9, 2014; April 7, 2015, by 5:00 PM local time of applicant organization. AIDS application due date: Not applicable.

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

On February 13, 2012, NIDA, in collaboration with numerous other NIH components and with the FDA Center for Tobacco Products, issued a Notice of Intent entitled **Notice of Intent to Publish a Request for Applications for Centers of Excellence for Research Relevant to the Family Smoking Prevention and Tobacco Control Act (P50) NOT-DA-12-007**. This Notice is provided to allow prospective applicants sufficient time to develop essential collaborations and plans prior to submitting an application in response to the published FOA. Projects resulting from this FOA are expected to serve the FDA by generating relevant findings and data needed to inform the regulation of the manufacture, distribution, and marketing of tobacco products to protect public health. Consistent with the FDA CTP mission, this FOA seeks research centers that address such topics as: the diversity of tobacco products, reducing addiction, reducing toxicity and carcinogenicity, adverse health consequences, communications, marketing of tobacco products, and economics and policies. Estimated publication date of announcement: Spring 2012. First estimated application due date: Fall 2012. Earliest estimated start date: July 2013.

On January 20, 2012, NIDA, in collaboration with numerous other NIH components and with the FDA Center for Tobacco Products, issued a Notice of Intent entitled **Administrative Supplements to NIH-funded Program Projects/Center Grants (with FDA) (P01, P50, and P60) NOT-CA-12-007.** The administrative supplements program and other FDA-NIH initiatives (for details, see http://cancercontrol.cancer.gov/nih-fda) are intended to provide a rapid mechanism for the FDA to promote research and generate findings needed to inform the

development of regulations pertaining to the manufacture, distribution, and marketing of tobacco products. Consistent with the FDA CTP mission, this Notice seeks administrative supplements that expand, enhance, or facilitate research relevant to these issues. Receipt date: April 6, 2012. Earliest anticipated start date: September 2012.

## Other Program Activities

### CTN Update

A total of 47 protocols have been initiated since 2001, including multi-site clinical trials (33), multi-site surveys (3), studies in special populations (5), and secondary analyses of data across various trials (6). In addition, 27 ancillary studies have been supported by CTN and non-CTN funds. Over 14,000 participants have been enrolled in CTN studies.

Information on protocols can be found at: http://ww2.drugabuse.gov/ctn/researchstudies.php.

## EXTRAMURAL POLICY AND REVIEW ACTIVITIES

**Receipt, Referral, and Review**

NIDA received 1,422 applications, including both primary and dual assignments, for which the Office of Extramural Affairs (OEA) managed the programmatic referral process during this Council cycle. Of these, NIDA received the primary assignment on 882 applications.

OEA arranged and managed 15 grant review meetings in which 194 applications were evaluated. OEA's reviews included applications in a chartered, standing review committee and Special Emphasis Panels (SEPs). In addition, OEA staff arranged and managed 6 review meetings dealing either with contract proposals or contract concepts.

NIDA has one standing chartered committee, NIDA-K, which reviewed Career Development applications and Institutional Training Grant applications (T32). There were also 14 Special Emphasis Panels to review grant applications for a variety of reasons:

- Conflicts with the chartered committee
- Behavioral Science Track Award for Rapid Transition (B/START)
- Imaging Science Track Award for Research Transition (I/START)
- Diversity-Promoting Institutions Drug Abuse Research Program (DIDARP) (R24)
- Conference Grants (R13)
- Cutting-Edge Basic Research Awards (CEBRA) (R21)
- Mechanism For Time-Sensitive Drug Abuse Research (R01)
- Collaborative Clinical Trials In Drug Abuse (Collaborative R01)
- Grand Opportunity In Medications Development For Substance-Related Disorders (U01)
- Center Grants (P50, P30)
- Loan Repayment Program
- Requests for Applications (RFAs)

OEA managed the following RFA reviews:

| | |
|---|---|
| DA12-008 | Integration of Drug Abuse Prevention and Treatment In Primary Care Settings (R01) |
| DA12-010 | 2012 NIDA Translational Avant-Garde Award for Medication Development for the Treatment of Substance Use Disorders (DP1) |

Completed contract-related review activity from the Contracts Review Branch since the last Council includes:

SBIR Phase II

| | |
|---|---|
| N44DA-12-1206 | Rapid Portable Devices to Measure Drug Uses |
| N44DA-12-5567 | E-Technology Tools for Extending the Reach of Prevention Interventions in Rural and Remote Locations |

Contract Reviews (R&D and non-R&D)

NO1DA-12-5570 State and Local Planning and Information Development

Concept Reviews (R&D and non-R&D)

N01DA-12-8905 Pharmacokinetic and Pharmacodynamic Studies for Medications Development
N01DA-12-2229 Data, Statistics, and Information Technology Support for NIDA
N01DA-12-2230 Clinical Trials Research Coordination Center

## CTN-Related Review Activities

The Data and Safety Monitoring Board(s) met:

- January 30, 2012 to discuss protocol CTN 0053, Achieving Cannabis Cessation-Evaluating N-Acetylcysteine Treatment (ACCENT)
- February 9, 2012 to discuss protocol CTN 0051, Extended-Release Naltrexone vs. Buprenorphine for Opioid Treatment (X:BOT)
- February 21, 2012 to discuss protocol CTN 0048, Cocaine Use Reduction with Buprenorphine (CURB)
- March 29, 2012 to discuss protocol CTN 0047, Screening, Motivational Assessment, Referral, and Treatment in Emergency Departments (SMART-ED)

## Certificates of Confidentiality

Between December 29, 2011 and April 4, 2012, OEA, processed 48 Certificate of Confidentiality applications, including 7 amendments for either extension of expiration date or protocol change.

## Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued to provide open forums for discussions and presentations that included presentations about Certificates of Confidentiality, by Dr. Mark Green, NIDA and the NIH Peer Review Appeals Process, by Dr. Teri Levitin, NIDA.

## CONGRESSIONAL AFFAIRS SECTION
**(Prepared April 26, 2012)**

## APPROPRIATIONS/BUDGET

In the President's Fiscal Year 2013 budget, the request for NIH is $30.62 billion, identical to the enacted level in FY 2012 of 30.62 billion. For NIDA, the Fiscal Year 2013 request is $1.054 billion, compared to an enacted level in FY 2012 of $1.052 billion.

## CONGRESSIONAL BRIEFINGS/MEETINGS OF INTEREST

### Friends of NIDA Coalition Hosts Congressional Briefing on Developing Medications to Treat Addiction

On March 1, the FoN organized a briefing on the Hill focused on the development of new medications to treat addictions and the challenges in getting such medications FDA-approved and marketed (see Developing Medications to Treat Addiction: Challenges for Science, Policy, and Practice). We have made great strides in advancing the science needed to develop medications, and we have promising new approaches already in clinical trials—vaccines and an implantable form of buprenorphine are just two examples. But in the past few years some of the largest pharmaceutical companies have reduced or completely eliminated their research and development in this area. After discussing the current and future directions of the science behind drug treatments for addiction, we had a round-table discussion on the reasons for the present state of affairs in the pharmaceutical industry and what the future may hold. With Dr. Volkow at this briefing were Dr. Phil Skolnick, Director of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse; Dr. David Gastfriend of Alkermes, Inc., the maker of Vivitrol (the depot injection of naltrexone); and Shaun Thaxter of Reckitt Benckiser Pharmaceuticals, Inc., maker of Suboxone. Past collaboration between NIDA and drug companies were instrumental in making drugs like Vivitrol and Suboxone a reality. Although the market for addiction medications presents unique challenges to drug companies, NIDA remains committed to creating new opportunities to engage the pharmaceutical industry in addiction treatment research.

### Member Meetings

Dr. Volkow had a few meetings recently with members of Congress:

- 3/7/12 with John Sullivan (R-OK). Mr. Sullivan was interested in discussing new and interesting research information from NIDA's treatment and medications research portfolios.
- 3/8/12 with John Larson (D-CT). Mr. Larson was interested in discussing evidence based prevention approaches focused on youth.
- 4/11/12 with Harold Rogers (R-KY). As part of the Prescription Drug Abuse Summit, Mr. Rogers wanted to thank Dr. Volkow for her participation, and to discuss prescription drug abuse issues. He also addressed the pending reorganization of alcohol and drug abuse and addiction research at the NIH.

- 4/12/12 with Mary Bono Mack (R-CA) (at the Prescription Drug Summit, as part of a larger discussion) to discuss prescription drug issues.

## FEDERAL REGULATIONS / INVESTIGATIONS / REPORTS REQUESTED BY CONGRESS

**Drug Prevention and Treatment Programs** – On December 12, 2011, GAO notified the Secretary of HHS that they are initiating a review of drug prevention and treatment programs within HHS. The review is in response to a request by the Senate Caucus on International Narcotics Control. Following are the key questions/objectives of the review: (1) To what extent do federal agencies fund drug prevention and treatment programs? (2) To what extent do federal agencies evaluate the drug prevention and treatment programs they fund? HHS agencies involved in the review include the Centers for Disease Control and Prevention (CDC), the Health Resources and Services Administration (HRSA), the Indian Health Service (IHS), the National Institutes of Health (NIH), and the Substance Abuse and Mental Health Services Administration (SAMHSA). Work began on this review in January 2012.

**National Drug Control Strategy** – On February 9, 2012, GAO notified the Secretary of HHS that they were initiating a review of the National Drug Control Strategy. The review is in response to a request by the Senate Caucus on International Narcotics Control. Following are the key questions/objectives of the review: (1) To what extent has the 2010 National Drug Control Strategy been implemented, and how does the Office on National Drug Control Prevention (ONDCP) assess the effectiveness of the Strategy in preventing and reducing drug use? (2) To what extent does ONDCP have metrics in place to assess drug treatment and prevention programs? (3) What does the available research suggest about the effect of societal factors, such as state laws allowing the use of marijuana for medical purposes, the drug legalization movement, and pro-drug media, on youth drug use? HHS agencies involved in the review include SAMHSA, NIH, and CDC. In addition, GAO plans to contact several federal agencies that engage in drug control activities in order to obtain information and perspectives on the status and implementation of the national drug control strategy and performance metrics to assess drug prevention and treatment programs. Work began on this review in February 2012.

**Inmate Reentry Programs** - On March 5, 2012 GAO notified the Secretary of HHS that in response to a Congressional mandate, they were initiating a review of Inmate Reentry Programs. This will focus on: 1) What federal programs exist to support former inmates' reentry into society; 2) To what extent is there duplication of efforts; 3) what efforts the Federal Interagency Reentry Council and key agencies have taken to reduce duplication and provide effective coordination; and 4) what do federal agencies know about the effectiveness of programs to help former inmates re-enter society. Within HHS, participating agencies include ACF, SAMHSA, IHS and NIH. The DOJ will also be consulted. NIDA, NIMH, and NIAAA are participating from NIH. Work began on this review in April, 2012.

## BILLS OF INTEREST

**H.R. 866 –** On March 1, 2011, Representative Ed Whitfield (R-TN) introduced the National All Schedules Prescription Electronic Reporting Reauthorization Act of 2011, to amend and reauthorize the controlled substance monitoring program under section 3990 of the Public Health Service Act. The bill was referred to the House Energy and Commerce Committee, Subcommittee on Health.

**H.R. 1065 –** On March 14, 2011, Representative Vern Buchanan (R-FL) introduced the Pill Mill Crackdown Act of 2011, to amend the Controlled Substances Act to provide for increased penalties for operators of pill mills, and for other purposes. The bill was referred to the House Committees on the Judiciary and Energy and Commerce Subcommittee on Health. See S. 1760.

**H.R. 1562** – On April 14, 2011, Representative Lucille Roybal-Allard (D-CA) introduced the Sober Truth on Preventing Underage Drinking Reauthorization Act, to provide for programs and activities with respect to the prevention of underage drinking. The bill was referred to the House Committee on Energy and Commerce, Subcommittee on Health. See also S. 854.

**H.R. 1729** – On May 4, 2011, Representative Dutch Ruppersberger (R-MD) introduced the Opiate Addiction Treatment Act of 2011, to amend the Controlled Substances Act to authorize certain practitioners other than physicians to dispense certain narcotic drugs in schedule III, IV, and V for maintenance treatment or detoxification treatment without obtaining annually a separate registration for that purpose. The bill was referred to the House Energy and Commerce (Subcommittee on Health) and Judiciary Committees (Subcommittee on Crime, Terrorism and Homeland Security).

**H.R. 1925** - On March 8, 2011, Representative Nick Rahall (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2011, to focus on consumer and practitioner education, opioid treatment programs, prescription monitoring programs, and mortality reporting. The bill was referred to the House Judiciary Committee (Subcommittee on Crime, Terrorism and Homeland Security) and Energy and Commerce Committee (Subcommittee on Health). See also S. 507.

**H.R. 1983** – On May 2, 2011, Representative Barney Frank (D-MA) introduced the States' Medical Marijuana Patient Protection Act, to provide for the rescheduling of marijuana and for the medical use of marijuana in accordance with the laws of the various States. The bill was referred to the Committee on Energy and Commerce, Subcommittee on Health.

**H.R. 2119** – On June 3, 2011, Representative Mary Bono Mack (R-CA) introduced the Ryan Creedon Act of 2011, to amend the Controlled Substances Act to require practitioners to obtain particular training or special certification, approved by the Attorney General, on addiction to and abuse of controlled substances and appropriate and safe use of controlled substances. The bill was referred to the House Judiciary Committee (Subcommittee on Crime, Terrorism and Homeland Security) and House Energy and Commerce Committee (Subcommittee on Health).

**H.R. 2306 –** On June 23, 2011, Representative Barney Frank (D-MA) introduced the Ending Federal Marijuana Prohibition Act of 2011, to limit the application of Federal laws to the distribution and consumption of marijuana. The bill was referred to the House Judiciary Committee (Subcommittee on Crime, Terrorism and Homeland Security) and the Energy and Commerce Committee (Subcommittee on Health).

**H.R. 2334** – On June 23, 2011, Representative Jim Moran (D-VA) introduced the Comprehensive Problem Gambling Act of 2011, to include in SAMHSA programs activities to research, prevent and treat the harmful consequences of pathological and other problem gambling, and for other purposes. The bill was referred to the House Energy and Commerce Committee, Subcommittee on Health.

**H.R. 2376** -- On June 24, 2011, Representative Diana DeGette (D-CO) introduced the Stem Cell Research Advancement Act of 2011. Similar to legislation Representative DeGette introduced in the 111th Congress, H.R. 2376 would amend the Public Health Service Act to provide for human stem cell research, including human embryonic stem cell research. The bill would establish criteria for the use of human embryonic stem cells in research; require the Secretary of HHS to maintain and update guidelines applicable to the conduct and support of embryonic stem cell research; prohibit funding for human cloning; and require that a section on stem cells be added to the NIH Biennial Report. H.R. 2376 was referred to the House Committee on Energy and Commerce, Subcommittee on Health.

**H.R. 2689** – On July 28, 2011, Representative Gwen Moore (D-WI) introduced the SAFE Teen Act, to amend the Safe and Drug Free Schools and Communities Act to authorize the use of grant funds for violence prevention and other purposes. The bill was referred to the House Committee on Education and the Workforce, Subcommittee on Early Childhood, Elementary, and Secondary Education. See also S. 1447.

**H.R. 3433 –** On November 16, 2011, Representative James Lankford (R-OK) introduced H.R. 3433, the Grant Reform and New Transparency Act of 2011. The bill would amend title 31, United States Code, to provide transparency and require certain standards in the award of federal grants, and for other purposes. Among the provisions in the bill are requirements for posting grant award information for each competitive grant awarded by a federal agency on a public web site. Specifically, the bill would require the posting of the full grant application, award decision documentation and rankings, justification for deviating from rankings, and disclosure of information on individuals who served as peer reviewers on the grant. In addition, the bill would require the posting of grant performance information within 60 days after the end of the period for completion of the grant. The bill was reported out of committee (Oversight and Government Reform) on November 17 and awaits further action.

**H.R. 3699 –** On December 16, 2011, Representatives Darrell Issa (R-CA) and Carolyn Maloney (D-NY) introduced H.R. 3699, the Research Works Act, which would prohibit any Federal agency, including NIH, from requiring that investigators make any research paper arising from research funds publicly accessible via the Internet without the prior consent of the publisher. The bill would also prevent government agencies from including in its grant and contract agreements a prospective requirement that the results of the research be made publicly available

on the Internet. The bill would effectively prevent NIH from posting peer-reviewed papers arising from NIH funds to PubMed Central as required by Division G, Title II, Section 218 of P.L. 110-161. The bill was referred to the House Committee on Oversight and Government Reform.

**NOTE:** On February 27, 2012, Representatives Darrell Issa (R-CA) and Carolyn Maloney (D-NY) submitted identical statements supporting continued dialogue about open access publishing and intellectual property, and expressions by each of their intent to stop pursuing legislative action on this bill.

**H.R. 4292** – On March 28, Representative Harold Rogers (D-KY) introduced the ID MEDS Act (Interstate Drug Monitoring Efficiency and Data Sharing Act of 2012), to direct the Attorney General to establish uniform standards for the exchange of controlled substance and prescription information for the purpose of preventing diversion, fraud, and abuse of controlled substances and other prescription drugs. The bill was referred to the Committee on Energy and Commerce. See also S. 2254.

**S. 507 –** On March 8, 2011, Senator John Rockefeller (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2011, to focus on consumer and practitioner education, opioid treatment programs, prescription monitoring programs, and mortality reporting. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also H.R. 1925.

**S. 660 –** On March 29, 2011, Senator Jon Kyle (R-AZ) introduced the Preserving Access to Targeted, Individualized, and Effective New Treatments and Services (PATIENTS) Act of 2011. S. 660 states that notwithstanding any other provisions of law, the Secretary of Health and Human Services (HHS) shall not use data obtained from the conduct of Comparative Effectiveness Research (CER), including such research that is conducted or supported using funds appropriated under the American Recovery and Reinvestment Act of 2009 or authorized or appropriated under the Patient Protection and Affordable Care Act, to deny or delay coverage of an item or service under a Federal health care program. In addition, the bill would require the Secretary of HHS to ensure that CER conducted or supported by the Federal government accounts for factors contributing to differences in treatment response and treatment preferences of patients, including patient-reported outcomes, genomics of personalized medicine, the unique needs of health disparity populations, and indirect patient benefits. The bill was referred to the Committee on Health, Education, Labor and Pensions.

**S. 854** – On April 14, 2011, Senator Frank Lautenberg (D-NJ) introduced the Sober Truth on Preventing Underage Drinking Reauthorization Act, to provide for programs and activities with respect to the prevention of underage drinking. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also H.R. 1562.

**S. 882 –** On May 4, 2011, Senator Sherrod Brown (D-OH) introduced the STOP Act, to prevent misuse, overutilization, and trafficking of prescription drugs by limiting access to such drugs for Medicare and Medicaid beneficiaries who have been identified as high-risk prescription drug users. The bill was referred to the Committee on Finance.

**S. 1231** – On June 20, 2011, Senator Patrick Leahy (D-VT) introduced the Second Chance Reauthorization Act of 2011. First passed in 2007, the Second Chance Act provides resources to states, local governments and nonprofit organization to improve outcomes for people returning to communities from prisons and jails. The bill was reported out of Committee on July 21 and placed on the Senate calendar.

**S. 1234** – On June 20, 2011, Senator Charles Grassley (R-IA) introduced the Partners for Stable Families and Foster Youth Affected by Methamphetamine or Other Substance Abuse Act, to amend the Social Security Act to reauthorize grants to assist children affected by methamphetamine or other substance use under the promoting safe and stable families program. The bill was referred to the Committee on Finance.

**S. 1447** – On July 28, 2011, Senator Mike Crapo (R-ID) introduced the SAFE Teen Act, to amend the Safe and Drug Free Schools and Communities Act to authorize the use of grant funds for violence prevention and other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also H.R. 2689.

**S. 1760** -- On October 20, 2011, Senator Joe Manchin (D-WV) introduced the Pill Mill Crackdown Act of 2011, to amend the Controlled Substances Act to provide for increased penalties for operators of pill mills, and for other purposes. The bill was referred to the Judiciary Committee. See H.R. 1065.

**S. 2254** - On March 29, Senator Rob Portman (R-OH) introduced the ID MEDS Act (Interstate Drug Monitoring Efficiency and Data Sharing Act of 2012), to direct the Attorney General to establish uniform standards for the exchange of controlled substance and prescription information for the purpose of preventing diversion, fraud, and abuse of controlled substances and other prescription drugs. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also H.R. 4292.

**S. 2262** – On March 29, Senator Tim Johnson (D-SD) introduced the Advancing FASD Research, Prevention and Services Act, to amend the Public Health Service Act to reauthorize and extend the Fetal Alcohol Syndrome prevention and services program, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

# INTERNATIONAL ACTIVITIES

## Binational Agreements

### *NIDA Participates in Italian National School on Addiction*

Building on the 2011 Binational Agreement between NIDA and the Italian Department for Anti-drug Policies (DAP), NIDA staff and grantees taught a module of the National School on Addiction, which was held March 12-13, 2012, in Italy. IRP Director Antonello Bonci, M.D., and Giovanni Serpelloni, M.D., DAP, opened the school with a discussion of research opportunities available through the Binational Agreement. NIDA Director Nora Volkow, M.D., addressed participants by video. Dr. Bonci and Marilyn A. Huestis, Ph.D., IRP, reported on advances in clinical and preclinical neuroscience research conducted by NIDA. Dr. Huestis also discussed acute and chronic cannabis smoking and approaches to differentiating new drug use from residual drug excretion. DESPR Director Wilson Compton, M.D., reviewed the Screening, Brief Intervention, and Referral to Treatment (SBIRT) protocol and methods to evaluate the effectiveness of prevention programs. Markus A. Hellig, M.D., Ph.D., clinical director of both the NIDA intramural and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) intramural clinical research programs, outlined pharmacogenetic approaches to addiction treatment for alcohol abuse. The four grantee speakers included: 1) A. Thomas McLellan, Ph.D., University of Pennsylvania, who discussed evidence-based policies and strategies; 2) Walter Ling, M.D., University of California, Los Angeles, who discussed the NIDA Clinical Trials Network (CTN) and the CTN protocol to reduce cocaine use with buprenorphine (CURB); 3) Robert Schwartz, M.D., Friends Research Institute, who reported on the effectiveness of opiate substitution treatments and strategies to manage non-compliant patients; and 4) David Gastfriend, M.D., Alkermes, who summarized strategies for matching patients to treatments. Participation by U.S. scientists in Italian training programs such as the National School on Addiction was a priority established by the Binational Agreement.

## Research Results

### *InWomen Working Group Publishes Journal Supplement*

The International Women's and Children's Health and Gender Research Group (InWomen), a multidisciplinary research group organized through the IP's NIDA International Virtual Collaboratory (NIVC) has published a supplement to *Substance Abuse and Rehabilitation* (2012; 3[S1]) to focus research attention on women who use substances, their diversity, the contextual factors affecting their lives, their needs, the treatment barriers they face, and next steps with regard to interventions and treatment. The open access supplement is available online at http://www.dovepress.com/substance-abuse-and-rehabilitation-i631-j98. The collection of seven papers includes work focusing on: 1) long-term, residential substance abuse treatment for Israeli women; 2) methadone treatment for Iranian women; 3) HIV prevention interventions targeted at women who have been victims of intimate partner violence; 4) substance abuse treatment needs of lesbian, bisexual, and transgender women; 5) the impact of criminal justice system involvement on interventions for drug-using women in South Africa; 6) the Maternal Opioid Treatment Human Experimental Research (MOTHER) study comparing the efficacy of buprenorphine versus methadone for detoxification of pregnant women addicted to opiods; and 7) the GENACIS multisite international study of alcohol abuse. Authors are InWomen members,

and several were speakers at the 2011 InWomen satellite to the NIDA International Forum and the College on Problems of Drug Dependence. The InWomen group is chaired by NIDA grantee Wendee Wechsberg, Ph.D., RTI International, who also wrote the introduction to the supplement.

***Former Humphrey Fellow Finds Georgian Drug Treatment Reduces HIV Risk Behaviors***

The first behavioral treatment randomized clinical trial in the Republic of Georgia found that the use of tailored behavioral therapy paired with naltrexone is both feasible and efficacious for treating drug use and reducing HIV drug-risk behavior in Georgian men. Writing in *Drug and Alcohol Dependence* (January 1, 2012; 120[1]:14-21), former NIDA Hubert H. Humphrey Fellow David Otiashvili, M.D., and colleagues describe a 22-week comprehensive intervention that aimed at engaging, retaining, and treating opioid-injecting men in the Republic of Georgia. The research was supported by a NIDA grant to Hendree E. Jones, Ph.D., RTI International.

***Former INVEST/CTN Fellow Finds Buprenorphine Induction Effective for Prescription Opioid Users***

Research published by 2010–2011 INVEST/CTN Fellow Suzanne Nielsen, Ph.D., University of Sydney, Australia, suggests that existing buprenorphine induction practices developed for heroin users appear to be equally effective in treating prescription opioid users. Writing in the *Journal of Substance Abuse Treatment* (published online January 31, 2012; http://dx.doi.org/10.1016/j.jsat.2011.12.009), Dr. Nielsen and her colleagues conducted a secondary data analysis to compare the buprenorphine induction experiences of 167 heroin and 61 prescription opioid users. Participants in both groups reported similar withdrawal and craving scores and also ended up on comparable doses of buprenorphine, important information for clinicians as they see more prescription opioid-dependent patients. The research was supported by Dr. Nielsen's INVEST/CTN fellowship and a NIDA grant to Walter Ling, M.D., University of California, Los Angeles.

***Journal Articles by INVEST/CTN Fellow Assess Diagnostic Criteria***

INVEST/CTN Fellow Cécile Denis, Ph.D., University of Bordeaux, France, has published articles in *Drug and Alcohol Dependence* (April 1, 2012; 122[1-2]:22-27) and *Substance Use and Misuse* (2012 Mar;47[4]:356-63) that assess diagnostic criteria. Writing in *Drug and Alcohol Dependence*, Dr. Denis and her colleagues conclude that the four possible sets of diagnostic criteria for pathological gambling they assessed were all reliable and valid, and did not appear to alter the meanings of the diagnoses of pathological gambling from those in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The work was done in response to proposals to include pathological gambling in the Substance-Related Disorders section of the forthcoming fifth edition of the DSM. Writing in *Substance Use and Misuse*, Dr. Denis and her colleagues examined the validity of 1,848 self-reported uses of drugs determined within an Addiction Severity Index (ASI) interview in comparison with urinalysis results among in-treatment, drug-dependent subjects in France. Dr. Denis spent her INVEST/CTN fellowship working with John Cacciola, Ph.D., and Charles O'Brien, M.D., Ph.D., University of Pennsylvania, where she compared diagnostic severity measures proposed for DSM-5 with ASI scores to test the 1) feasibility of combining the two measures in the clinical evaluation of patients, and 2) sensitivity of the diagnostic-specific severity measure against the ASI measures of substance use disorder severity over time.

## Fellowships

### *IP Fellows Attend Orientation at NIDA Headquarters*

In February, NIDA IP welcomed 27 fellows from as many nations as part of a 3-day orientation. IP Director Steven W. Gust, Ph.D., and Associate Director Dale Weiss hosted the Hubert H. Humphrey Fellows from Virginia Commonwealth University and Johns Hopkins University as well as NIDA INVEST and INVEST/CTN fellows. The fellows met with representatives of the NIDA divisions about their offices' international research priorities, resources and collaboration and training tools, and opportunities for collaborative international research. NIDA staff who participated included: Richard Denisco, M.D., Peter Hartsock, Ph.D., and Richard Jenkins, Ph.D., DESPR; Diane Lawrence, Ph.D., and Katherine Davenny, Ph.D., ARP; and Brian Marquis, Geoffrey Laredo, M.P.A., and Susan Weiss, Ph.D., OSPC. Shana Potash, National Library of Medicine, briefed the fellows on online resources available to international users, and James Herrington, Ph.D., M.P.H., Fogarty International Center, discussed the center's research training and funding programs. The orientation also featured a networking session with researchers and students at the University of Maryland Center for Addictions Personality and Emotion Research (CAPER). CAPER students and researchers gave talks on such topics as self-regulatory mechanisms in risk taking, meditative therapies for managing addiction, and behavioral activation treatment. Four NIDA fellows described the state of drug abuse in their countries and the research they are currently undertaking: Maria de L. Garcia-Anaya, M.D., Ph.D., Mexico; Saeed Momtazi, M.D., Iran; Eugene Dordoye, MBChB, MGCPsych, Ghana; and Tin Moe Aung, MBBS, Burma (Myanmar).

### *Mexican Scientist Awarded New Prevention Fellowship*

Argentina Elisa N. Servin Aguirre, M.D., has been named the first U.S.–Mexico Drug Abuse Prevention Research Fellow. The new fellowship is a collaborative effort between NIDA and the National Institute of Psychiatry Ramón de la Fuente Muñiz, along with participation from the National Commission Against Addictions (CONADIC) and the Society for Prevention Research. Dr. Servin Aguirre will work in the United States for 12 months to develop, implement, and assess HIV prevention efforts among vulnerable populations in Mexico. She will conduct a series of secondary data analyses to characterize female sex workers who inject drugs (FSW-IDUs) and are living with dependent children in Tijuana and Ciudad Juarez, and identify correlates of living with dependent children that could predispose them to health and social harms. Dr. Servin Aguirre will also describe patterns and correlates of intergenerational sex work and drug use among FSW-IDUs in Tijuana and Ciudad Juarez. Her mentors are Steffanie A. Strathdee, Ph.D., and Jay G. Silverman, Ph.D., both at the University of California, San Diego (UCSD). Dr. Strathdee is the associate dean of global health sciences, Harold Simon Professor, and chief of the Division of Global Public Health in the Department of Medicine at the UCSD School of Medicine. Dr. Silverman is professor of medicine and global public health at UCSD.

### *New INVEST Fellow Investigates Cognitive Enhancer*

New INVEST Drug Abuse Research Fellow Sujung Yoon, M.D., Ph.D., South Korea, will spend 12 months under the mentorship of Perry F. Renshaw, M.D., Ph.D., M.B.A., University of Utah, to focus on the application of multinuclear magnetic resonance spectroscopy markers of brain health in response to treatment. Dr. Yoon and Dr. Renshaw have already been working together evaluating the effects of citicoline and, based on their findings in methamphetamine-dependent adolescents, plan to spend the next year assessing the effects of citicoline as a cognitive enhancer

for patients with methamphetamine dependence. Dr. Yoon will focus specifically on the application of multinuclear magnetic resonance spectroscopy markers of brain health in response to treatment.

***Brazilian Scientist Named ISAJE/WHO Young Scholar***

Gabriel Andreuccetti, a Ph.D. candidate in epidemiology at the University of São Paolo Medical School, Brazil, has received the 2011 International Society of Addiction Journal Editors (ISAJE)/World Health Organization Young Scholars Award. He received the award for his paper, "Reducing the Legal Blood Alcohol Concentration Limit for Driving in Developing Countries: A Time for Change? Results and Implications Derived From a Time-Series Analysis (2001–10) conducted in Brazil," in *Addiction* (2011 Dec;106[12]:2124-31). In Brazil, a 2008 law lowered the blood alcohol concentration limit for drivers from 0.06 to 0.02. Assessing the impact of the new law on the prevalence and severity of traffic accidents, Mr. Andreuccetti concluded that significant reductions in traffic injury and fatality rates were reported in the Brazilian state of São Paolo after the new law was enacted. The runner-up for the award was Hui Cheng, a research associate at the Institute of Mental Health, Peking University, China, for her paper "Harsh Physical Punishment as a Specific Childhood Adversity Linked to Adult Drinking Consequences: Evidence From China" also published in *Addiction* (2010 Dec;105[12]:2097-2105).

***Former Humphrey Fellow Leads Methadone Maintenance Treatment in Bangladesh***

Munir Ahmed, M.D., a 2008-2009 NIDA Hubert H. Humphrey Drug Abuse Research Fellow at Virginia Commonwealth University, is now Officer-In-Charge for the Joint United Nations Programme for HIV/AIDS (UNAIDS) in Dhaka, Bangladesh. He started the country's first methadone maintenance treatment program and directs efforts to reduce stigma and discrimination against drug users. During 2012, a pilot methadone program in government health care settings will be replicated with nongovernmental organizations. Dr. Ahmed reports that HIV prevalence among Bangladeshi injection drug users has been 5.3 percent for about a decade.

**CTN INVEST Fellows**

Since 2008, NIDA's International Program and the Clinical Trials Network (CTN) jointly offer fellowships to non-U.S. scientists. The international researcher works with a CTN mentor affiliated with one of the 13 CTN Nodes. Fellows may conduct their research in any aspect of the CTN research agenda on drug abuse and addiction, such as intervention research, clinical trials methodology, or drug abuse treatment, as well as HIV/AIDS prevention. To date, seven scientists have completed their fellowships and have successfully continued their research in their countries; seven are currently working on their projects.

Current fellows visited the NIH and NIDA from February 1-3, 2012. They met with NIDA staff on Friday, February 3, 2012. The current fellows are:
Cecile Denis (France, University of Pennsylvania)
Sergii Dvoriak (Ukraine, University of Pennsylvania)
Maria Garcia-Anya (Mexico, University of Miami and Columbia University)
Effat M. Khoei (Iran, Medical University of South Carolina)
Xuyi Wang (China, University of California, Los Angeles)
Gabriel Thorens, guest (Switzerland, New York University)

## International Visitors

As part of the Research Council of Norway's (RCN) visit to NIH the delegation from Norway visited NIDA on February 14, 2012. The purpose of the visit was to meet to discuss how the RCN and NIDA can cooperate in order to better facilitate increased US-Norway research collaboration within biomedical science. The Norway delegation was chaired by Ole Andreassen, Chair, Mental Health Program, Research Council of Norway and Professor, University of Norway.

On March 12, 2012, Jorg Morland, M.D., Ph.D. Professor, University of Oslo and Director, Division for Forensic Medicine and Drug Abuse Research, Norwegian Institute for Public Health visited NIDA to give a presentation titled, "Impairment Based Legislative Limits for Driving Under the Influence of Non-alcohol Drugs in Norway".

## Other International Activities

Dr. Wilson M. Compton, Director, DESPR, presented at an international forum on new approaches to jurisprudence at the National Autonomous University of Mexico, Mexico City, April 24, 2012.

Dr. Wilson M. Compton presented a plenary on the "Drug Abuse Outcomes" as the Italian Government Outcomes Meeting, Rome, Italy March 24, 2012. Dr. Compton also presented on "Screening and Brief Intervention, or Referral to Treatment (SBIRT)" as part of a webinar training organized with the Italian Government, March 12, 2012.

Dr. Peter Hartsock, DESPR, participated in the NIMH "Grand Challenges in Global Mental Health" meeting on "Integration and Implementation in Research, Policy, and Practice held April 2-3, 2912, in Bethesda, MD. He presented on current NIDA activities which parallel supplement those being planning by NIMH.

Dr. Peter Hartsock participated in a meeting, sponsored by the Inter-American Development Bank and the U.S. Global Ambassador for Women's Issues, dealing with violence and human trafficking held February 23, 2012 in Washington, D.C. He presented on current and planned activities by NIDA dealing with drug and human trafficking.

Dr. Peter Hartsock participated in the Presidential Bilateral Commission on the U.S. and Russia's Health Task Force meeting to refine recommendations on strategic resource allocation to enable better U.S.-Russia cooperation in health held March 23, 2012 in Washington, D.C.

Dr. Ivan Montoya, DPMCDA, was invited to give a lecture at the University of Granada in Granada (Spain) about the Advances in the Pharmacological Treatment of Substance Use Disorders on March 26$^{th}$ and 28$^{th}$, 2012.

Dr. Ivan Montoya participated in a Forum organized by the World Psychiatric Association about Globalization and Drug Addiction Treatment that took place on March 28th, 2012, in Tarragona, Spain.

Dr. Ivan Montoya was invited by the Caixa of Catalunya to give a lecture for health care providers about the New Research of Pharmacotherapies for Nicotine Dependence. The lecture took place in Tarragona (Spain) on March 29th, 2012.

Dr. Ivan Montoya gave the closing lecture at the annual meeting of the Society on Alcohol and Drug Abuse of Spain entitled "Advances in the Development of Biologics to Treat Addictions". The conference took place in Tarragona, Spain on March 30, 2012.

Dr. Vishnudutt Purohit, DBNBR, was an invited speaker for three lectures at the Gachon University of Medicine and Sciences, Incheon, Korea: Role of Cannabinoids in Fatty Liver, Lee Gil Ya Cancer and Diabetes Institute in Gachon University, March 30, 2012; Molecular Pathogenesis in Alcohol- and Tobacco-Associated Hepatocellular Carcinoma, Gachon International Symposium on Gastroenterology, Gachon University Gil Hospital, March 31, 2012; Cannabinoid System and Liver Inflammation, The Catholic University of Korea, Gachon, April 3, 2012.

**14th Society for Research on Adolescence (SRA) Biennial Meeting**, Vancouver, BC Canada, March 8 - March 10, 2012. NIDA's Child and Adolescent Workgroup members participated in workshops to provide an interactive discussion on career paths and NIH grant opportunities for early stage investigators. Speakers presented on current NIH and NIDA grant mechanisms available for emerging scholars, successful strategies for research grant review, and NIDA research priorities in developmental research for domestic and international researchers. The sessions were organized in collaboration with other federal colleagues and included NIDA staff: Cheryl Anne Boyce, DCNBR; Aria Crump, DESPR; Kathy Etz, DESPR; and Jacqueline Lloyd, DESPR; Mariela Shirley, NIAAA; LeShawndra Price, NIMH; and Anna Riley, CSR/NIH. The program sessions were very successful and participants benefitted from the opportunity to interact with program staff for individualized feedback on their grant applications. Dr. Cheryl Anne Boyce (DCNBR) also served as discussant on two paper symposia: "Mediators and Moderators of Exposure to Community Violence" and "The Use of Growth Mixture Modeling to Examine Trajectories of Clustered Psychosocial Difficulties Among Diverse Adolescents."

## MEETINGS/CONFERENCES

On April 12, 2012, NIDA, FDA, and CDC held a meeting titled **Role of Naloxone in Opioid Overdose Fatality Prevention** to discuss whether naloxone should be made more widely available to trained individuals who are not part of the healthcare system to reduce opioid overdose fatalities. Participants included academic, government and industry experts and patient advocates. Among the topics discussed were: populations at risk; successful public health interventions for preventing and treating opioid overdose; issues related to product development; and the social and legal aspects of wider naloxone availability.

Dr. Nora Volkow gave a keynote address titled "It's *Not* What the Doctor Ordered" at the inaugural **National Prescription Drug Abuse Summit** in Orlando, FL. This summit held April 10-12, 2012 brought together state and national leaders, including the Surgeon General, law enforcement officials, medical professionals, community advocates, treatment experts, educators and others to share strategies to combat this devastating problem. NIDA also showcased resources for healthcare professionals and teens; including NIDA's PEERx, an online peer-to-peer initiative that educates teens and helps them spread the word about the dangers of prescription drug abuse.

On April 19-22, 2012, NIDA participated in the **Blending Conference on SBIRT** at the **ASAM Annual Meeting** held in Atlanta, GA. The Blending Initiative meeting provided a forum to discuss emerging research findings and their implications in clinical practice. Workshops were offered on a variety of topics including: making Motivational Interviewing accessible to primary care: new approaches to pharmacotherapy for SUD; Screening, Brief Intervention, Referral to Treatment (SBIRT); and HIV testing and intervention in integrated treatment settings.

The National Institute on Drug Abuse (NIDA) held a research track at the **American Psychiatric Association (APA) Annual Meeting** in Philadelphia, Pennsylvania, May 5-9, 2012. NIDA participated in a number of sessions on topics unique to addiction science. Topics included: Assessment of Substance Use Disorder (SUD) Patient Outcomes Based on Longitudinal Registry/EMR Data; Social Stress and Drug Addiction in Preclinical & Clinical Studies: Sex/Gender Matters in Effects on Brain and Behavior and Treatment Implications; Neurobehavioral and Pharmacological Approaches to Target Cognitive Remediation in Drug Addiction; and Dys-connectivity of the Brain in Addiction and Pain. A special performance of NIDA's ***Addiction Performance Project***, with a dramatic reading by a professional actor and chaired by NIDA Director, Dr. Nora Volkow, was also featured at this year's meeting.

NIDA, in conjunction with NIAAA, NICHD, NIMH and NINDS, hosted the third installment of the **"Addressing Health Disparities through Neuroscience" Seminar Series** on April 12, 2012 in Bethesda, Maryland. The seminar featured speakers Drs. Evan Kharasch (Washington University - St. Louis) and David Flockhart (Indiana University School of Medicine), whose talks were centered on personalized medicine. Flair Lindsey, Program Analyst, Special Populations Office, represented NIDA on the seminar series' planning committee.

The **National CTN Steering Committee Meetings** were held April 17-19, 2012 in Atlanta, Georgia in conjunction with the ASAM Pre-conference session entitled "Accelerating Knowledge Exchange in Substance Abuse Treatment" (mini-blending meeting). The following meetings convened:

CTP and PI Caucuses
Executive Committee
Research Utilization Committee
Research Development Committee
Node Coordinator Workgroup
International Forum and Poster Session with Invest Fellows
Steering Committee
Psychopharmacotherapy Special Interest Group
Blending Products
CTN 0037, STRIDE
CTN 0044, Web-based TES
CTN 0047, SMART-ED
CTN 0048, CURB
CTN 0050, START Follow-up

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Ana Anders, M.S.W., Public Health Analyst, Special Populations Office, participated in the National Hispanic Science Network Steering Committee meeting on January 19- 21, 2012 in New Orleans, Louisiana.

Dr. Cathrine Sasek, Science Policy Branch, OSPC, presented an overview of NIDA's Science Education Drug Abuse Partnership Award program at the NIH SciEd 2012 Annual Conference for NIH Science Education Projects on Monday, May 14, 2012 in Washington, D.C.

Dr. Ruben Baler, Science Policy Branch, OSPC, gave a lecture on the "Neuroscience of Addiction" for Health Providers and Youth Advocates on January 27th, 2012, at the Unity Health Care Cardozo Clinic, Washington D.C.

Dr. Baler lectured on the Neuroscience of Addiction to freshman students in the Drug Awareness class on February 7th, 2012, at the GW School of Public Health, Mt. Vernon Campus.

Dr. Baler led a workshop entitled: "Where do addictions come from?" on February 9th, 2012, at the CADCA 2012 Forum, National Harbor, Maryland.

Dr. Baler presented a lecture focused on the pharmacology of synthetic drugs at the DEA Museum lecture series "Deadly Chemistry: The Rise of Synthetic Drugs" on March 13th, 2012, in Arlington, Virginia.

Dr. Cora Lee Wetherington and Dr. Samia Noursi, DBNBR chaired a symposium "Social Stress and Drug Addiction in Preclinical and Clinical Studies: Sex/Gender Matters in Effects on Brain and Behavior and Treatment Implications," at the American Psychiatric Association Annual

Meeting, Philadelphia, May 5, 2012. The panel included presentations by Michael Nader, Ph.D. (Wake Forest University School of Medicine), Sari Izenwasser, Ph.D. (University of Miami Miller School of Medicine), Colleen Hanlon, Ph.D. (Medical University of South Carolina), and Sudie Back, Ph.D. (Medical University of South Carolina). Rajita Sinha, Ph.D. (Yale University School of Medicine) served as the discussant.

Dr. Cora Lee Wetherington served as a poster judge at the 2012 Women's Health Congress in Washington, DC, March 16-18, 2012.

Dr. Cora Lee Wetherington gave the keynote address at the annual Women's Health Research Day at the University of Illinois – Chicago, March 29, 2012.

Dr. Jerry Frankenheim, DBNBR, organized and chaired a session on January 23, 2012 at the 45th Winter Conference on Brain Research, Snowbird, Utah. "Neurotensin: Self-Control Neuropeptide and Drug Discovery Target?" presenters were Glen Hanson, Mona Boules, Ricardo Cáceda, and George Uhl.

Dr. John Satterlee, DBNBR**,** attended an NIEHS sponsored minisymposium: Epigenetics, Chromatin Biology, Development, and Disease held in Raleigh, NC, on January 10, 2012.

Dr. John Satterlee attended the 19th Conference on Retroviruses and Opportunistic Infections in Seattle, WA, March 5-8, 2012.

Dr. David Thomas, DBNBR, presented a webinar titled "The NIH Pain Consortium's Centers of Excellence in Pain Education" to the Clinical & Translational Science Awards Pain Researchers Interest Group on March 19th, 2012.

Dr. David Thomas made a presentation titled "The NIH Pain Consortium's Centers of Excellence in Pain Education" to the Office of National Drug Control Policy on March 6th, 2012.

David Thomas made a presentation and participated in a workshop with the National Center for Medical Rehabilitation Research Advisory Board on May 3rd, 2012.

Drs. Cathrine Sasek, OSPC, and Roger Sorensen and Dave Thomas, DBNBR, participated in Brain Awareness Week activities at Walter Reed Medical Center on March 14-15, 2012.

Dr. Rao Rapaka, DBNBR, was a co-organizer for a symposium entitled "Spice and bath salts-An emerging health risk in the United States" at the 18th scientific conference of the Society on Neuroimmune Pharmacology (SNIP), Honolulu, Hawaii April 28, 2012. Dr. Rapaka also co-organized a symposium at the University of Hawaii on April 30, 2012 entitled "Critical Areas of Research: Drugs of Abuse". Dr. Rapaka could not attend these two symposia and the co-organizers were involved in conducting these two symposia.

Dr. Harold Gordon, DCNBR, participated as NIDA's "sleep" representative in the semi-annual meeting of the National Sleep Awareness Roundtable on March 1, 2012 in Washington, DC.

Dr. Yu (Woody) Lin, DCNBR, organized and moderated a workshop session entitled "NIH Pain Research: Optimizing Funding through Grant Writing" at the 28th annual conference of American Academy of Pain Medicine on February 23- 26, 2012 in Palm Springs, California.

Dr. Yu (Woody) Lin organized and moderated a workshop session entitled **"**Acupuncture for Chronic Low Back Pain: Clinical Evidence, the Science, and the Challenge**"** at the 28th annual conference of American Academy of Pain Medicine on February 23-26, 2012 in Palm Springs, California.

Dr. James Bjork, DCNBR, organized and served as a discussant for a symposium session entitled **"**Dys-connectivity of the Brain in Addiction and Pain**"** that was chaired by Dr. Joseph Frascella of DCNBR at the 165th annual meeting of the American Psychiatric Association on May 7, 2012 in Philadelphia, PA.

Dr. Cheryl Anne Boyce, DCNBR, participated in the Institute of Medicine Science of Research on Families meeting conducted on February 8, 2012 in Washington, DC. The meeting convened a key group of those developing and working with large scale family surveys at the federal level together with researchers from a range of backgrounds focusing on family measurement building upon the recent workshop report released in the spring and co-sponsored by OBSSR, ACF, and NIDA's Child and Adolescent Workgroup entitled *Toward an Integrated Science of Research on Families.*

Dr. Cheryl Anne Boyce organized and presented at the webinar, Research Career Training for the University of North Carolina at Chapel Hill Center for Developmental Science on February 13, 2012. Dr. Karen Sirocco (DCNBR/NIDA), Dr. Mariela Shirley (NIAAA), and Ms. Erica Wells (NIDA/GMB) served as the discussant panel for the session. The Center serves as an inter-institutional and interdisciplinary institute of advanced study in human development to training and research across disciplines and across the six regional participating universities (UNC-Chapel Hill, UNC-Greensboro, North Carolina Central University, North Carolina State University, Duke University, and Meredith College).

Dr. Cheryl Anne Boyce attended the President's Advisory Council on HIV/AIPDS (PACHA) Full Council meeting on February 28, 2012 in Washington, DC at the Eisenhower Executive Office Building. *HHS Secretary* Kathleen *Sebelius gave opening remarks to the participants for this* special session to highlight issues related to Women and HIV.

Dr. Cheryl Anne Boyce served as the invited plenary luncheon speaker on "Federal Funding" at the Building Careers for Research in Child Maltreatment and Intimate Partner Violence: Early Career Scholar Interdisciplinary Training Program on March 12, 2012 at Washington University in St. Louis, Missouri. This NIH OppNet funded training program is a collaborative effort between the Centers for Disease Control and Prevention (CDC) funded, Brown Center for Violence and Injury Prevention, the Injury Research Center at the Medical College in Wisconsin, and University of North Carolina Injury Prevention Research Center; as well as colleagues at the Colorado School of Public Health, University of Colorado Anschutz Medical Campus, and the Society for the Advancement of Violence and Injury Research.

On March 27, 2012, Dr. Cheryl Anne Boyce (DCNBR) participated in the Federal Expert panel for the Development of the Frameworks meeting for the identification of research gaps of relevance to ACYF populations to inform an ACYF research agenda.

Dr. Cheryl Anne Boyce of DCNBR organized and chaired a workshop entitled, "Research on Child Neglect: Data to Inform Prevention" on April 19, 2012 at the 18th National Conference on Child Abuse and Neglect held in conjunction with the DHHS Children's Bureau's Centennial Celebration Year in Washington, DC. Drs. Cathy Widom (John Jay College of Criminal Justice), Penelope Trickett (USC) and Melissa Jonson-Reid (Washington University at St. Louis) presented their latest research on child neglect for the workshop participants.

Dr. Cheryl Anne Boyce served as an invited speaker for the Latina Researchers Conference: Increasing the Pipeline for Future Scholars sponsored by the Robert Wood Johnson Foundation on "Opportunities and Challenges to Obtaining NIH Funding" on April 28, 2012. The meeting was held at the John Jay College of Criminal Justice in New York, NY. The mission of the conference was to examine the barriers and opportunities for advancement in research and academic positions.

Dr. Cheryl Anne Boyce served on the planning committee for the meeting, *Neuroscience and Child Maltreatment* which convened an expert panel focused on neuroscience and child maltreatment in Washington, DC on May 3-4, 2012. This is an initiative of the Office of the Commissioner, Administration on Children, Youth and Families (ACYF), DHHS and co-sponsored by partners from NIDA, the Robert Wood Johnson Foundation, the *Eunice Shriver* National Institute on Child Health and Human Development (NICHD), and the National Institute on Mental Health (NIMH).

Drs. Will Aklin, DCNBR, and Ivan Montoya, DPMCDA, co-chaired a symposium at the American Psychiatric Association on May 6, 2012 entitled, Neurobehavioral and Pharmacological Approaches to Target Cognitive Remediation in Drug Addiction. The overarching goal of the symposium was to provide an overview of currently funded NIDA studies that incorporated preliminary evidence of cognitive remediation into clinical trials with pharmacological and/or behavioral interventions to improve treatment efficacy, retention, relapse prevention, and long-term treatment outcome. Each presentation focused on proposed mechanisms and neurophysiologic substrates underlying cognitive deficits in drug users. The presenters included, Advisory Council member, Caryn Lerman (UPenn), A. Eden Evins (Mass General), Joseph Newman (Wisconsin), Joy Schmitz (UT Medical School), and Morris Bell (Yale).

Wilson M. Compton, M.D., M.P.E., Director, DESPR, continues to participate in the White House Office of National Drug Control Policy Interagency Workgroup on a continuing basis.

Wilson M. Compton, M.D., M.P.E. continues to participate in two interagency workgroups for the Department of Health and Human Services: The Behavioral Health Coordinating Committee (particularly the Prescription Drug Abuse Subcommittee) and the Tobacco Control Steering Committee (including co-chairing the Data/Research Subcommittee) on a continuing basis. As

part of these efforts, Dr. Compton chaired a panel at a meeting jointly sponsored by FDA, NIDA and CDC on the potential for expanded access to naloxone for opioid overdose prevention.

Wilson M. Compton, M.D., M.P.E. continues to participate in the NIH Opportunity Network for Basic Behavioral and Social Science Research (OppNet) as a member of the Steering Committee and as an alternate for the Coordinating Committee on a continuing basis.

Wilson M. Compton, M.D., M.P.E. continues to participate in the DSM-V Task Force and DSM-V Substance Use Disorders Workgroup meetings on a continuing basis. At part of this effort, Dr. Compton co-chaired and presented in a panel on DSM-5 at the Joint Meeting on Adolescent Treatment Effectiveness, Washington, D.C., April 11, 2012.

Wilson M. Compton, M.D., M.P.E. co-chaired two panels and presented a plenary lecture and presented in a panel at the American Society of Addiction Medicine, Atlanta, Georgia, April 19-20, 2012.

Wilson M. Compton, M.D., M.P.E. presented a Grand Rounds on "Embedding Addictions in General Medicine" at the University of Arkansas Medical Sciences Department of Psychiatry, April 5, 2012.

Wilson M. Compton, M.D., M.P.E. participated as an expert panelist in the Betty Ford Institute Foundation's Consensus Conference on Recovery Support Services, Palm Springs, California, February 21-23, 2012. Dr Harold Perl organized and chaired an invited panel titled, "Targeted Contingency Management and Skillful Motivational Interviewing: 2 Evidence-Based Methods to Reduce Substance Abuse Problems in Your Caseload", and presented a session in that panel titled, "NIDA's Clinical Trials Network: Science, Practice & Reality", at the 18th National TASC Conference on Drugs, Crime and Reentry on March 22nd, 2012, in Baltimore, MD.

Dr. Elizabeth Robertson, DESPR, organized a panel on "Taking Evidence-Based Prevention to Scale – Pennsylvania's Model," for the Community Anti-Drug Coalitions of America (CADCA) National Forum, held in National Harbor, MD, in February 2012.

Dr. Elizabeth Robertson was a discussant on a panel at the Advancing Transdisciplinary Translation for Prevention of High Risk Behaviors meeting sponsored by the Research Triangle Institute in Durham, North Carolina on April 24-25, 2012.

The staff of the Prevention Research Branch hosted a day long technical assistance meeting for faculty from the University of Alabama at the Neuroscience Center in Bethesda, MD on March 29, 2012.

Dr. Jacqueline Lloyd presented on a NIH panel titled "Research Opportunities at NIH" at the Society for Social Work Research (SSWR) 16th Annual conference in Washington DC on January 12, 2012.

Dr. Jacqueline Lloyd participated on an a panel at the Networking Meeting for Federal Funders, Social Work Deans and Directors, Associate Deans of Research and SSWR Board Members at

the Society for Social Work Research (SSWR) 16th Annual conference in Washington DC on January 12, 2012.

Drs. Jacqueline Lloyd and Belinda Sims, DESPR, organized and co-chaired a session titled "The Role of Cultural Adaptation in Dissemination and Implementation Research" at the 5th Annual NIH Conference on the Science of Dissemination and Implementation Research: Research at the Crossroads in Bethesda, Maryland on March 20, 2012. The panelists were Dr. Elizabeth Stormshak, University of Oregon, Dr. Guillermo Prado, University of Miami, and Dr. Nancy Gonzales, Arizona State University, and the Discussant was Dr. Felipe Castro, University of Texas, El Paso.

Dr. Jag Khalsa, DPMCDA, participated in the Board Meeting of the Treatment Communities of America (TCA) and presented NIDA's research efforts in the area of medical consequences and their management in drug abusing populations infected with multiple infections, February 10, 2012, Washington, DC.

Dr. Jag Khalsa represented NIDA and NIH participating in the HHS-sponsored meeting on Viral Hepatitis. The meeting was organized and chaired by the Special Assistant to the Deputy Secretary of HHS where many aspects of viral hepatitis C, and co-infections with HIV, TB and other infections were discussed. An executive summary with some sort of guidelines is expected in the coming months.

Dr. Jag Khalsa, DPMCDA, presented/co-chaired three symposia at the Annual Conference of the American Society of Addiction Medicine (ASAM), April 19-22, 2012, Atlanta. Dr. Khalsa will also participate in the ASAM Medical Science Program Committee that plans for symposia for the next annual conference.

Dr. Jag Khalsa participated in the Annual meeting of the Society of NeuroImmune Pharmacology (SNIP), co-chairing the NIH workshop on Mentoring and Funding Opportunities, Honolulu, Hawaii, April 24-28, 2012.

Dr. Kristopher Bough, DPMCDA, organized a pre-conference workshop entitled "Biomarkers for Tobacco Dependence". This full-day meeting was co-chaired by Drs. Jed Rose and Caryn Lerman, and held at the Society for Research on Nicotine and Tobacco in Houston, TX on March 12, 2012.

Dr. Ivan Montoya, DPMCDA, and Dr. Will Aklin, DBNBR, organized and co-chaired a symposium at the annual meeting of the American Psychiatric Association focusing on cognitive remediation as a tool for the treatment of drug abuse.

The American Society of Addiction Medicine (ASAM) held its 43rd Annual Medical-Scientific Conference April 19-22, 2012 in Atlanta, Georgia. Dr. Geetha Subramaniam, CCTN, was invited to present an expert review of "Pharmacotherapies for the Treatment of Substance Use Disorders in Youth."

The American Association for the Treatment of Opioid Dependence (AATOD) held its National Conference April 21-25, 2012 in Las Vegas, Nevada. Dr. Udi Ghitza organized, moderated, and chaired a session “Integrating Medication Assisted Treatment of Opioid Dependence with Primary Care Services”.

Dr. Meena Hiremath, OEA, served as a reviewer for applications seeking support from the 2012 Summer Research with NIDA Internship Program, February 2012.

Dr. Gerald McLaughlin, OEA, organized and chaired a workshop for the NIH Scientific Program and Review Interest Group (SPRIG) with the topic of Public Private Partnerships, January 20, 2012, in Rockville, Maryland.

Dr. Scott Chen, OEA, was appointed to the NIH-wide Staff Training in Extramural Programs Committee (STEP), which annually designs, develops, and offers a variety of training activities for all NIH extramural staff.

Dr. Scott Chen was a co-Chair and co-organizer, with Dr. Samia Noursi (NIDA) for a Scientific Program and Review Interest Group (SPRIG) seminar:  Promoting “IT” Tools for Effective Communication held on March 9, 2012 in Rockville  MD. NIH speakers included: George Santangelo, Richard Ikeda, Oliver "Pete" Morton, and Luci Roberts.

# MEDIA AND EDUCATION ACTIVITIES

## MEDIA SUPPORT OF EVENTS AND MEETINGS:

**National Inhalant Prevention Coalition Press Conference**
NIDA Acting Deputy Director Dr. David Shurtleff participated in the National Inhalant Prevention Coalition Press Conference on March 15th in Washington, DC. The press team coordinated the logistics, prepared a media advisory, gathered materials for inclusion in the press kits, attended the event and provided live tweets from the press conference.

**Addiction Performance Project**
The NIDA press team promoted, via traditional and social media outreach, the performances of the Addiction Performance Project (APP) in Chicago, IL (April 16, 2012) and Philadelphia, PA (May 8 & 9, 2012). APP is a CME & CE program to help break down the stigma associated with addiction and promote a healthy dialogue that fosters compassion, cooperation, and understanding for patients living with this disease. This project is part of NIDA's outreach to practicing health professionals and those in training.

**Blending Initiative: Accelerating Knowledge Exchange in Substance Abuse Treatment**
The NIDA press team prepared media outreach surrounding the NIDA Blending Initiative: Accelerating Knowledge Exchange in Substance Abuse Treatment meeting held in Atlanta, GA on April 19, 2012, at the American Society of Addiction Medicine Conference. The Blending Initiative meeting provided a forum to discuss emerging research findings and their implications in clinical practice. Workshops were offered on a variety of topics including: making Motivational Interviewing accessible to primary care: new approaches to pharmacotherapy for SUD; Screening, Brief Intervention, Referral to Treatment (SBIRT); and HIV testing and intervention in integrated treatment settings.

**American Health Care Journalists Conference**
NIDA Director Dr. Nora Volkow participated in a panel titled "New understandings in the science of addiction and treatment" that was held at the American Health Care Journalists Conference in Atlanta, GA on April 21, 2012. The conference featured world-class speakers, important news briefings and helpful sessions all aimed at aiding reporters, editors and news producers in better covering the latest health issues. NIDA Press Officer Stephanie Older accompanied Dr. Volkow to Atlanta.

**60 Minutes Profile Piece on NIDA Director Dr. Nora Volkow**
Press Officer Stephanie Older accompanied Dr. Volkow and the 60 Minutes crew to Mexico City January 17-20, 2012, for filming at the Trotsky Museum, Mexico's National Pulmonary Institute, and the National University, all part of a larger profile piece on Dr. Volkow that is expected to air this spring. Stephanie continues to work with the 60 Minutes producers to wrap up filming. She assisted the producers and the press team at Brookhaven National Laboratory on February 10th and at NIDA's IRP on February 22nd.

**Screening of the Motion Picture Documentary "Addiction, Inc."**
June 1, 2012 in the Lipsett Auditorium on the NIH campus in Bethesda, MD, from 2-5 pm. Dr. Nora Volkow will host a free screening of the motion picture documentary "Addiction, Inc." The 100 minute film will start at 2 pm and the film's producer (Charles Evans) will be in the auditorium to answer questions. The film chronicles the experience of research scientist Victor DeNoble, who became a whistleblower for tobacco company activities in the 1980s. Dr. DeNoble will be available for questions via videocast from his home in California.

**NOTE: New Date for National Drug Facts Week**
The next National Drug Facts Week (NDFW) will be held the week of January 28-February 3, 2013. Drug Facts Chat Day will be on Tuesday, January 29th. NDFW is a health observance week for teens that aims to shatter the myths about drugs and drug abuse. Chat Day provides students the opportunity to ask leading researchers questions about drug use, abuse, and addiction, as well as the associated health effects and risks.

As part of the **CCTN Seminar Series**, the following seminars were presented:
January 24, 2012, Michelle Feige, MSW, Public Health Advisor in the Division of Education and Development at the Office for Human Research Protections (OHRP), Office of the Secretary, DHHS, presented "The Advanced Notice of Proposed Rulemaking (ANPRM) – aka Lots of Unanswered Questions."

February 28, 2012, Marilyn A. Huestis**,** Ph.D., from the Intramural Research Program at NIDA, presented "Chronic Daily Cannabis Smoking: A Mechanism for Long-Term Cognitive Impairment and Differentiating New Cannabis Use from Residual Cannabinoid Excretion."

March 1, 2012, Helen Pettinati, Ph.D., from the University of Pennsylvania's Perelman School of Medicine, presented "Patient Adherence in Pharmacotherapy Trials: Can We Produce Better Outcomes."

March 22, 2012, Mary E Johnson-Rochee and Scott Doubet (DEA Washington Diversion Group) gave an informal presentation titled "What to Expect when DEA Visits."

March 27, 2012, Joni Rutter, Acting Director, DBNBR at NIDA/NIH gave a presentation on "Database of Genotypes and Phenotypes (dbGaP): A Model for Data Harmonization."

## PRESS RELEASES

**January 17, 2012**
**Consumer-friendly publication will guide those struggling with addiction**

A new resource, Seeking Drug Abuse Treatment: Know What to Ask, will help individuals and families struggling with addiction ask the right questions before choosing a drug treatment program. It was developed by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health, and is available to the public free online or in hard copy through NIDA's DrugPubs service (see information below). "Treatment options can vary considerably, and

families often don't know where to begin," said NIDA Director Dr. Nora D. Volkow. "This booklet highlights the treatment components that research has shown are critical for success, to help people make an informed choice during a very stressful time."

The new publication is based on a NIDA resource describing the principles of drug addiction treatment from a research-based perspective. It recommends five helpful questions people should ask and explains what the research has found to be most effective. Specifically, the booklet explores these themes:

- Is the program's treatment plan backed by scientific evidence?
- Is it tailored to the individual needs of each patient?
- Does the program assess and adapt treatment as the patient's needs change?
- How long should the treatment take?
- How do 12 step programs fit into drug addiction treatment?

According to the National Survey on Drug Use and Health, in 2010 an estimated 22.1 million persons aged 12 years or older were classified with substance dependence or abuse in the past year (8.7 percent of the population aged 12 or older). The goal of drug abuse treatment is to stop drug use and help people return to productive functioning in the family, workplace, and community. However, keeping patients in treatment long enough to achieve that goal can be difficult. Finding the right treatment for an individual's specific needs is critical. This booklet describes available medications and evidence-based behavioral therapies; the need for comprehensive, tailored, and sustained treatment; as well as the reality of relapse and the role of community-level support.

Seeking Drug Abuse Treatment: Know What to Ask can be found online at www.drugabuse.gov/publications/seeking-drug-abuse-treatment. Hard copies can be ordered by calling 1-877-NIDA-NIH (1-877-643-2644) or by going online at http://drugpubs.drugabuse.gov/.

Principles of Drug Addiction Treatment: A Research Based Guide, which is the basis of this new publication, can be found at www.drugabuse.gov/PODAT/PODATIndex.html.

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**February 21, 2012**
**New site for adults with limited literacy skills, with audio versions of each page**

A new, easy-to-read website on drug abuse designed for adults with a low reading literacy level (eighth grade or below) was launched today by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health. The site, which provides plain language information on neuroscience, drug abuse prevention and treatment, is also a resource for adult literacy educators. It has a simple design with a large default text size, motion graphic videos and other features that make it easy to read and use.

"Drug abuse and addiction affects people of all reading levels, yet there are no websites with drug abuse information created specifically for adults with limited literacy," said NIDA Director Dr. Nora D. Volkow. "We hope this new site will inform a large segment of our population who may not have otherwise received potentially life-saving information."

The website's emphasis on plain language supports the U.S. Department of Health and Human Service's commitment to clear government communication that the public can understand and use. The site goes beyond plain language by using a website design and features that are easy to use, including animated videos that explain the science of addiction and how drugs affect the brain.

The website will use the ReadSpeaker text-to-speech tool that provides audio versions of each page without the need to download any software. The embedded highlighting tool enables website visitors to see synchronized highlighting of the text that is currently being read.

Before creating the site, NIDA interviewed adults who were seeking to improve their literacy skills to learn their challenges and preferences in using websites. NIDA also worked with groups that provide services to adult learners through nonprofit organizations, libraries, and in healthcare clinics. In addition, NIDA conducted website usability testing at nonprofit organizations that serve adults seeking to improve their reading and/or earn a GED.

NIDA's new easy-to-read site can be found at: www.easyread.drugabuse.gov. See NIH's Health Literacy Initiative for more information and additional resources on health literacy.

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**RESEARCH BRIEFS/ANNOUNCEMENTS**

*January 3, 2012* — The NIH Pain Consortium encouraged medical, dental, nursing and pharmacy schools to respond to a new funding opportunity to develop Centers of Excellence in Pain Education. On December 30, 2011, a Request for Proposals (RFP) was released by Altarum Institute and Palladian Partners, an Altarum company, on behalf of the NIH Pain Consortium, to develop and disseminate pain management curriculum resources for health care professionals and provide leadership for change in pain management education. The RFP can be found at: www.altarum.org/project-highlights-pain-education.

*February 2, 2012* – A NIDA-study, published in *Cell*, showed that internal states, such as hunger, have a powerful influence on behavior, but little is known about how they affect the underlying brain circuits in the living organism. In an innovative study, scientists introduced a modified dopamine receptor gene into the brain of a living vinegar fly, such that when dopamine bound to this receptor, a messenger molecule was released, traveled to the nucleus, and activated a fluorescent reporter gene that could be easily visualized. Investigators successfully used this technique to monitor circuit-specific dopamine activity in response to hunger. This powerful new technique may have general applicability in the genetic dissection of a broad range of internal states, including stress and drug craving. View study here: www.cell.com/abstract/S0092-8674(12)00009-8.

*February 6, 2012* – A new website about clinical research trials – what it is, why it matters, and how to get involved – was announced today by NIH. The press release can be found at: www.nih.gov/news/health/feb2012/od-06.htm. The new website can be found at: http://clinicalresearchtrials.nih.gov. To learn more about NIDA's Clinical Trials Network, click

on ww2.drugabuse.gov/ctn/. For information on clinical trials at NIDA's Intramural Research Program, click here: www.researchstudies.drugabuse.gov/.

*March 14, 2012* – NIDA is seeking new ways of detecting "designer drug" use (e.g., "K2/Spice" or "Bath Salts") by promoting the development of biofluid drug screens based on pharmacological activity (how the drug works in the body) rather than chemical structure. Because these "designer drugs" are constantly evolving, they frequently evade currently available structure-based drug screens. NIDA is also seeking solutions to a variety of other drug abuse issues. Grant application deadlines are April 5, August 5, or December 5, 2012. For more information, see the Omnibus Solicitation, issued by the U.S. Department of Health and Human Services: http://grants.nih.gov/grants/funding/sbirsttr1/2012-2_SBIR-STTR-topics.pdf.
For more information on NIDA's SBIR/STTR Program, including tips to improve a grant application, go to: www.drugabuse.gov/funding/funding-opportunities/science-education-grants-contracts/sbirsttr/about-national-institute-drug-abuse-sbirsttr-program.

*March 15, 2012* -- Were you unable to attend today's National Inhalant Prevention Coalition press conference? Feel free to check out their press release, now posted at www.inhalants.org. For more information on inhalant abuse, or to schedule an interview with an expert at NIDA, please contact the NIDA press team at media@nida.nih.gov or 301-443-6245.

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## MEDIA ADVISORIES

**March 12, 2012**
**NIDA's David Shurtleff will speak on inhalant abuse**

The National Inhalant Prevention Coalition, with support from SAMHSA and NIDA to hold a press conference to focus on the dangers of inhalant abuse, including helium inhalation.

## INTERVIEW HIGHLIGHTS: January 2012 – March 2012

*NBC Washington* — Dr. Wilson Compton was interviewed about prescription drug abuse.

*CNN* – Dr. Compton was interviewed about addiction and genetics.

*National Public Radio* – Dr. Nora Volkow was interviewed about brain addiction.

*Scientific American* – Dr. Volkow was interviewed about prescription drug abuse.

*The Associated Press* – Dr. Joseph Frascella was interviewed about methamphetamine.

*The Associated Press* – Dr. Marilyn Huestis was interviewed about marijuana use testing.

*The New York Times* – Dr. Markus Heilig was interviewed about his alcohol research.

*International Business Times* – Dr. Steven Grant was quoted in an article on "Madonna's 'Molly' Remarks at Ultra: What Is Molly and What Does It Do?" published on-line March 28, 2012

## OTHER EDUCATIONAL ACTIVITIES

### NIDA Launched an Easy-to-Read Website

On February 21, 2012, NIDA launched a new website designed for adults with reading literacy at eighth grade or below. The site provides plain language information on neuroscience and drug abuse prevention and treatment. It is anticipated that the site will be used by a wide audience, including adult literacy educators. The site was designed with a large default text size, motion graphic videos and other features that make it easy to read and use. It can be accessed at http://www.drugabuse.gov/news-events/news-releases/2012/02/nida-creates-easy-to-read-website-drug-abuse.

## RECENT AND UPCOMING CONFERENCES/EXHIBITS

Blending Conference on SBIRT of ASAS Annual Meeting
Atlanta, GA -- 4/19-22/12

American Psychiatric Association Annual Meeting
Philadelphia, PA -- 5/5-9/12

XIX International AIDS Conference
Washington, DC -- 7/22-27/12

American Psychological Association Annual Convention
Orlando, FL -- 8/2-5/12

## PLANNED MEETINGS

The National Institute on Drug Abuse (NIDA) is organizing a program at the **2012 American Psychological Association (APA) Annual Meeting** in Orlando, Florida, August 2-5, 2012. Staff throughout the Institute are involved in planning sessions on a wide range of topics related to addiction research. NIDA will also co-sponsor an Early Career Investigator Poster Session with APA's Divisions 28 and 50 and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as part of the two Divisions' Social Hour.

Dr. David McCann, DPMCDA, has organized and will chair a panel session entitled **"Common Targets for the Treatment of Substance Use Disorders and Co-occurring Psychiatric Disorders"** at the NCDEU meeting on May 29, 2012 in Phoenix, Arizona.

Dr. David McCann has organized and will chair a symposium entitled **"Recent Advances in Medications Development for the Treatment of Substance Use Disorders"** at the College on Problems of Drug Dependence (CPDD) meeting on June 12, 2012 in Palm Springs, California.

Dr. Jag Khalsa, as a member of the Program Committee of the **American Conference for the Treatment of HIV (ACTHIV)**, will co-chair a symposium on HIV Co-morbidities at its Biennial Conference, May 10-12, 2012, Denver, CO.

Dr. Kris Bough, DPMCDA, organized a workshop on "**Biomarker Development for Substance-Use Disorders**" to be held at the College on Problems of Drug Dependence annual meeting -- Palm Springs, CA – June 9, 2012.

With Deb Olster (OBSSR) as co-lead, Minda Lynch (DBNBR) is organizing an OppNet sponsored meeting of scientific experts to advise NIH on **Optimizing the Translation of Animal Behavioral Models**, in June 2012 at NIH.

# PUBLICATIONS

## NIDA PUBLICATIONS

**NIDA Notes**
The final print issue of *NIDA Notes* was mailed in early April. The first all-Web *NIDA Notes* articles have been posted, and new articles are slated to appear biweekly. View newsletter: http://www.drugabuse.gov/news-events/nida-notes

**Addiction Science & Clinical Practice**
*Addiction Science & Clinical Practice*, the journal founded by NIDA to promote research-practice dialogue, posted its first articles under its new owner, *Biomed Central*, and new Editors, Richard Saitz, M.D., Ph.D. and Jeffrey Samet, M.D., M.A., M.P.H. NIDA continues to support the journal during this start-up period. View journal: http://www.ascpjournal.org/

**Drugs: Shatter the Myths**
**NIH Pub. No.: 12-7589**
Q&A booklet answers teens' most frequently asked questions about drugs, alcohol, and drug abuse. Written and designed specifically for teens, with teen input.

**Brain Power! The NIDA Junior Scientist Program: Grade 2-3 (Revised) (In Press)**
**NIH Pub. No.: 12-4575**
This package is designed to interest and educate students in an age-appropriate manner about their brains, why they should protect them, and how drugs such as nicotine and inhalants can hurt their brains. The parent' guide describes activities that can be done with the whole family and includes a listing of resources. This package also includes a DVD.

**Brain Power! The NIDA Junior Scientist Program: Grade 4-5 (Revised) (In Press)**
**NIH Pub. No.: 12-5730**
This package introduces students in grades 4-5 to the human brain and to the effects of abused drugs on the brain. It explores how different regions of the brain work, and how various drugs affect the brain. The last module introduces students to addiction and the drug abuse problem in the United States and allows students to explore the impact of drug use on society and the differences between legal and illegal drugs. This package also includes a DVD.

**Commonly Abused Drug Chart (Reprinted) (In Press)**
This chart lists drugs most widely abused, their trade names and slang names, effects of intoxication, and long-term consequences.

**Scholastic Posters**
**NIH Pub No.: AVD222 (Prescription Drugs)**
**NIH Pub No.: AVD224(S) (Marijuana)**
NIDA partnered with Scholastic as part of the *"Heads Up: Real News About Drugs and Your Body"* series, and created a poster featuring Prescription Drugs and two versions (bilingual and English) of a poster featuring Marijuana.

**Marijuana: Facts for Teens (Spanish) (Revised) (In Press)**
**NIH Pub. No.: 12-4037(S)**
Explains current knowledge about marijuana and the latest scientific information on its effects. Provides teens with answers to frequently asked questions about marijuana, including what it is, who uses it, and how it affects a person physically and mentally after short- and long-term use.

**Marijuana: Facts Parents Need to Know (Spanish) (Revised) (In Press)**
**NIH Pub. No.: 12-4036(S)**
Provides valuable information from research on the dangers of marijuana. Gives parents explanations of the latest scientific information about the drug and suggestions on how to talk to teenagers about this drug.

**Mind Over Matter: The Brain's Response to Methamphetamine (In Press)**
**NIH Pub. No.: 12-4394**
Explains how methamphetamine acts in the body and the brain, with an emphasis on harmful effects. Uses drug information to teach scientific principles and encourage interest in science, while increasing awareness of significant drug dangers.

## International Program-Related Publications

***NIDA International Program E-News***

- *February 2012* – This issue reported on the orientation for NIDA IP fellows, including presentations by fellows from Burma (Myanmar), Ghana, Iran, and Mexico. Other articles announced the first U.S.–Mexico Drug Abuse Prevention Research Fellow, Argentina Elisa N. Servin Aguirre, M.D.; and a new INVEST Fellow, Sujung Yoon, M.D., Ph.D., of South Korea. The issue also recruited applicants for the NIDA Hubert H. Humphrey Drug Abuse Research Fellowship, announced the 2011 International Society of Addiction Journal Editors (ISAJE)/World Health Organization (WHO) Young Scholar, and announced the agenda for the 2012 InWomen Conference, which is partially supported by NIDA IP.

***INVEST Fellow Translates NIDA Publications Into Farsi***
Upon reading NIDA's popular publication, *Drugs, Brains, and Behavior: The Science of Addiction*, NIDA INVEST Drug Abuse Research Fellow Saeed Momtazi, M.D., Iran, knew it would be useful to other Iranians involved in the field of substance abuse and addiction. Dr. Momtazi and his colleagues are translating the publication, as well as several other NIDA materials, into their most common Persian language, Farsi.

## CTN- Related Publications

Six 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 26 CTN studies are now available on the NIDA Data Sharing Web Site http://www.nida.nih.gov/CTN/Data.html. Over 1,300 data sets have been downloaded by researchers from 19 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 CTN 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


Adamczyk A, Mejias R, Takamiya K, Yocum J, Krasnova IN, et al., GluA3-deficiency in mice is associated with increased social and aggressive behavior and elevated dopamine in striatum. Behav Brain Res. 2012 Apr 1; 229(1): 265-272. Epub 2012 Jan 21.

Beauvais G, Atwell K, Jayanthi S, Ladenheim B, Cadet JL. Involvement of dopamine receptors in binge methamphetamine-induced activation of endoplasmic reticulum and mitochondrial stress pathways. PLoS One. 2011; 6(12): e28946. Epub 2011 Dec 13.

Ghitza, UE. Human brain imaging of opioid receptors: Application to CNS biomarker and drug development. In: Seeman P, Madras B, editors. Imaging of the human brain in health and disease. Neuroscience-Net; 2012. Chapter 3.

Hu LL, Sparenborg S, Tai B. Privacy protection for patients with substance use problems. Subst Abuse Rehabil. 2011; 2: 227-233.

Lu, H, Zou, Q, Raichle, ME, Stein, EA and Yang, Y. Rats possess a default mode brain network. Proc. Nat'l Acad Sci (USA) 2012; 109: 3979-3984.

Rose, EJ, Ross, TJ, Salmeron, BJ, Lee, M, Shakleya, DM. Huestis, M and Stein, EA. Chronic exposure to nicotine reduces reward-related activity in the striatum but not the midbrain of smokers. Biological Psychiatry 2012; 71: 206-213.

Tai B, Boyle M, Ghitza U, Kaplan RM, Clark HW, Gersing K. Meaningful use of electronic behavioral health data in primary health care. Sci Transl Med. 2012 Feb 1; 4(119):119mr3.

Tai B, McLellan AT. Integrating information on substance use disorders into electronic health record systems. J Subst Abuse Treat. 2011 Dec 7. [Epub ahead of print]

Tai B, Wu LT, Clark HW. Electronic health records: essential tools in integrating substance abuse treatment with primary care. Subst Abuse Rehabil. 2012 Feb: 3(1): 1–8.

Wu, CW, Gu, H, Zou, Q, Lu, H, Stein, EA and Yang, Y. TE-Dependent spatial and spectral specificity of functional connectivity. NeuroImage 2012; 59: 3075-3084.

Xiao J, Kannan G, Jones-Brando L, Brannock C, Krasnova IN, Cadet JL, Pletnikov M, Yolken RH. Sex-specific changes in gene expression and behavior induced by chronic Toxoplasma infection in mice. Neuroscience. 2012 Mar 29; 206: 39-48. Epub 2012 Jan 3.

Several staff and grantees from NIH and DHHS contributed to the May supplement of the American Journal of Public Health:
Boyce CA, Willis TD, Beatty L. A Call to Action for health disparities in boys and men: Innovative research on addiction, trauma, and related comorbidities. American Journal of Public Health 2012; 102(S2): S168-S170. doi: 10.2105/ajph.2012.300793

Hill CV, Lynne-Landsman SD, Boyce CA. Maternal and Child Health Disparities: Considering the influence of fathers. American Journal of Public Health 2012; 102(S2): S164-S165. doi: 10.2105/ajph.2012.300792

Jones DJ, Crump AD, Lloyd JJ. Health disparities in boys and men of color. American Journal of Public Health 2012; 102(S2): S170-S172. doi: 10.2105/ajph.2011.300646

# STAFF HIGHLIGHTS

## *Staff Honors and Awards*

**Dr. Thomas Brady**, DESPR, was awarded the 2012 JMATE Government Facilitation of Evidence-Based Practice Award posthumously on April 11, 2010 for his work as a government official dedicated to moving the field towards evidence-based practice related to adolescent substance abuse treatment. Key review criteria include evidence of: (1) facilitating the development, adoption, and/or use of evidence-based practices in community-based settings; (2) a sustained commitment to work with community-based treatment providers to help them actually use the knowledge/skills/materials/technologies; and (3) a specific focus on adolescent treatment.

**Dr. Ivan Montoya**, DPMCDA, has been appointed Chair of the newly formed Addictions Institutional Review Board (IRB) for the research involving human subjects conducted at the Intramural Research Programs of NIDA and NIAAA.

**Dr. Samia Noursi**, DBNBR and Deputy Coordinator, Women and Sex/Gender Differences Research was invited to serve on the Planning Committee for the development of the third in the series of online courses, The Science of Sex and Gender in Human Health, developed in collaboration between NIH and the U.S. Food and Drug Administration.

**Dr. Harold Perl**, DESPR, was awarded a 2011 Meritorious Research Service Commendation by the American Psychological Association's Board of Scientific Affairs at the December 2011 APA Board of Directors meeting in Washington, DC. The award recognizes individuals who have made outstanding contributions to psychological science through their service as employees of the federal government or other organizations.

## *Staff Changes*

### New Employees

**Helio Chaves** joined NIDA as the Deputy Executive Officer in March 2012. Helio is a seasoned professional who possesses more than 15 years of diverse experience in both private and government sectors. Helio's immediate past assignment was with the PSC where he served as the Director of the Division of (Grants) Payment Management. Other prior roles include Director of the Division of User Fees at the FDA, Budget Officer at the PSC, Accounting Operations Supervisor at the Holocaust Memorial Museum and Staff Accountant at the CPA firm Watkins, Meegan, Drury & Co. Helio has a Bachelor of Science degree in accounting from the University of Massachusetts at Dartmouth.

## Retirements and Departures

**Thomas Hilton, Ph.D.** joined NIDA's Services Research Branch as a Program Official in 1999. His grant portfolio at NIDA originally emphasized organizational effectiveness in health service delivery and he recently started a portfolio focusing on addiction recovery and services reengineering. Tom also had a portfolio of grants advancing research methodology and psychological measurement. His role as PROMIS Science Officer also kept expanding as he convinced the Military and VA to adopt PROMIS. This is a position for which he is doubly well-suited because he is a retired Navy Medical Service Corps Captain. His military service began in 1968 when he joined the Navy Reserves. On April 30, 2012, Tom retired after 44 years of government service.

**Dr. Nicolette Borek**, DCNBR, has accepted a new position in the Office of Science in the Center for Tobacco Products at the Food and Drug Administration (FDA) working on the Population Assessment of Tobacco and Health Study (PATHS). She served over several years at NIDA as a highly valued colleague including positions as Acting Branch Chief, BBDB; Deputy Branch Chief, BBDB; and Chair of the NIDA Child and Adolescent Working Group. Her expertise in prenatal exposures and HIV/AIDS has been of great value to NIDA and interagency scientific research collaborations including the Adolescent Medicine Trials Network for HIV/*AIDS* Interventions (ATN) and the *Pediatric HIV/AIDS Cohort Study* (*PHACS).* In her new position, she will serve as an excellent resource for bridging successful collaborations on emerging initiatives between FDA and NIDA on tobacco research.

## New Roles within NIDA

**Jennifer Bidle** was selected as the as the new Chief of the Management Analysis Branch (MAB), Office of Management, NIDA in April 2012. Jennifer began her government career at the NIH in the Office of Management Assessment 10 years ago and has worked for NIDA in the Management Analysis Branch since August 2008. She earned an undergraduate degree in Health Administration and Policy from the University of Maryland Baltimore County and a Master of Business Administration from Mount St. Mary's University. During her time at NIDA, Jennifer has accomplished several tasks including developing standard OM communication methods, conducting workload analyses and risk management reviews, and participating in strategic planning efforts.

**Dr. Harold Perl** joined DESPR as Acting Branch Chief for the Prevention Research Branch, effective March 19th, 2012. Dr. Perl comes to the Prevention Branch from NIDA's CCTN where he had been Senior Lead for Behavioral Research, Dissemination and Training since 2005. Prior to joining NIDA, he served in various programmatic and management capacities at the National Institute on Alcohol Abuse and Alcoholism (NIAAA) between 1989 and 2005, culminating as Chief of the Health Services Research Branch, with responsibility for developing and overseeing programs that focused on alcohol health services research and the dissemination and implementation of science-based substance abuse treatment practices.

## GRANTEE HONORS

**Mary Jeanne Kreek, M.D.**, of Rockefeller University, was awarded the Alumni Achievement Award from Wellesley College which is "the highest honor given to alumnae for excellence and distinction in their fields of endeavor and has been presented annually since 1970."

**Dr. Guillermo Prado** was selected to receive the Young Investigator's Award by the Society for Research on Adolescence. This award is given to a young scholar whose research, publications, grants, conference presentations, and visibility in the field represent a significant contribution to understanding adolescent development and behavior.

**CTN Delaware Valley Node**

The Treatment Research Institute (TRI) announces that **A. Thomas McLellan, Ph.D.** has returned to continue his leadership role as CEO. Dr. McLellan appointed David Metzger as the Director of Research at TRI.

**CTN Florida Node Alliance**

Gateway Community Services welcomes **Dr. Candace Hodgkins** as the new CEO of Gateway Community Services effective January 1, 2012.

**CTN Western States Node**

**Grant Colfax, MD**, of the Western States Node, has been appointed by President Obama as Director of the Office of National AIDS Policy (ONAP). "Grant Colfax will lead my Administration's continued progress in providing care and treatment to people living with HIV/AIDS," said President Obama.