RESEARCH FINDINGS

BASIC NEUROSCIENCE RESEARCH

Promoter Methylation and Tissue-Specific Transcription of the a7 Nicotinic Receptor Gene, CHRNA7 The α7 nicotinic acetylcholine receptor is known to regulate a wide variety of developmental and secretory functions in neural and non-neural tissues. The mechanisms that regulate its transcription in these varied tissues are not well understood. Epigenetic processes may play a role in the tissue-specific regulation of mRNA expression from the α7 nicotinic receptor subunit gene, CHRNA7. Promoter methylation was correlated with CHRNA7 mRNA expression in various tissue types and the role of DNA methylation in regulating transcription from the gene was tested by using DNA methyltransferase (DNMT1) inhibitors and methyl donors. CHRNA7 mRNA expression was silenced in SH-EP1 cells and bisulfite sequencing PCR revealed the CHRNA7 proximal promoter was hypermethylated. The proximal promoter was hypomethylated in the cell lines HeLa, SH-SY5Y, and SK-N-BE which express varying levels of CHRNA7 mRNA. Expression of CHRNA7 mRNA was present in SH-EP1 cells after treatment with the methylation inhibitor, 5-aza-2-deoxycytidine (5-Aza-CdR), and increased in SH-EP1 and HeLa cells using another methylation inhibitor, zebularine (ZEB). Transcription from the CHRNA7 promoter in HeLa cells was increased when the methyl donor methionine (MET) was absent from the media. Using methylation-sensitive restriction enzyme analysis (MSRE), there was a strong inverse correlation between CHRNA7 mRNA levels and promoter DNA methylation across several human tissue types. The results support a role for DNA methylation of the proximal promoter in regulation of CHRNA7 transcription. Canastar A, Logel J, Graw S, Finlay-Schultz J, Osborne C, Palionyte M, Drebing C, Plehaty M, Wilson L, Eyeson R, Leonard S. Promoter methylation and tissue-specific transcription of the a7 nicotinic receptor gene, CHRNA7. J Mol Neurosci. 2011 Nov 4. [Epub ahead of print]

Rapid Dopamine Signaling Differentially Modulates Distinct Microcircuits Within the Nucleus Accumbens During Sucrose-Directed Behavior The mesolimbic dopamine projection from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) is critical in mediating reward-related behaviors, but the precise role of dopamine in this process remains unknown. The authors completed a series of studies to examine whether coincident changes occur in NAc cell firing and rapid dopamine release during goal-directed behaviors for sucrose and if so, to determine whether the two are causally linked. They show that distinct populations of NAc neurons differentially encode sucrose-directed behaviors, and using a combined electrophysiology/electrochemistry technique, further show that it is at those locations that rapid dopamine signaling is observed. To determine causality, NAc cell firing was recorded during selective pharmacological inactivation of dopamine burst firing using the NMDA receptor antagonist, AP-5. The authors show that phasic dopamine selectively modulates excitatory but not inhibitory responses of NAc neurons during sucrose-seeking behavior. Thus, rapid dopamine signaling does not exert global actions in the NAc but selectively modulates discrete NAc microcircuits that ultimately influence goal-directed actions. Cacciapaglia, F, Wightman, RM, Carelli, RM. Rapid dopamine signaling differentially modulates distinct microcircuits within the nucleus accumbens during sucrose-directed behavior. J Neurosci. 2011, 31: 13860-13869.

Aversive Stimulus Differentially Triggers Subsecond Dopamine Release In Reward Regions Aversive stimuli have a powerful impact on behavior and are considered to be the opposite valence of pleasure. Recent studies have determined some populations of ventral tegmental area (VTA) dopaminergic neurons are activated by several types of aversive stimuli, whereas other distinct populations are either inhibited or unresponsive. However, it is not clear where these aversion-responsive neurons project, and whether alterations in their activity translate into dopamine release in the terminal field. Here the authors show unequivocally that the neurochemical and anatomical substrates responsible for the perception and processing of pleasurable stimuli within the striatum are also activated by tail pinch, a classical painful and aversive stimulus. Dopamine release is triggered in the dorsal striatum and nucleus accumbens (NAc) core by tail pinch and is time locked to the duration of the stimulus, indicating that the dorsal striatum and NAc core are neural substrates, which are involved in the perception of aversive stimuli. However, dopamine is released in the NAc shell only when tail pinch is removed, indicating that the alleviation of aversive condition could be perceived as a rewarding event. Budygin, EA, Park, J, Bass, CE, Grinevich, VP, Bonin, KD, Wightman, RM. Aversive stimulus differentially triggers subsecond dopamine release in reward regions. Neuroscience, 2011 Nov 7 [Epub ahead of print].

Δ9-THC Increases Endogenous AHA1 Expression In Rat Cerebellum and May Modulate CB1 Receptor Function During Chronic Use To characterize the long-term effects of adolescent marijuana abuse, the authors performed a proteomic analysis of cerebellar extracts from adult female rats with and without ovariectomy that were treated with Δ9-THC for 40 days during adolescence. Six proteins were found to significantly differ among the four treatment groups, with Δ9-THC and ovariectomy (OVX) decreasing the mitochondrial proteins, pyruvate carboxylase and NADH dehydrogenase, whereas the levels of putative cytosolic molecular chaperones NM23B, translationally controlled tumor protein, DJ-1 and activator of heat-shock 90kDa protein ATPase homolog 1 (AHA1) were increased. The authors further analyzed the effects of AHA1, a HSP90 co-chaperone, on CB1R and CB2R trafficking and signaling in transfected HEK293T and Neuro-2A cells. In HEK293T cells, AHA1 over-expression enhanced plasma membrane levels of CB1R and increased CB1R-mediated effects on cAMP levels and on MAPK phosphorylation. AHA1 over-expression also enhanced cell surface levels of endogenous CB1R and the effects of Δ9-THC on the cAMP levels in Neuro-2A cells. In contrast, over-expression of AHA1 did not affect the subcellular localization and signaling of CB2R. These data indicate that chronic Δ9-THC administration in adolescence altered the endogenous levels of specialized proteins in the cerebellum, such as AHA1, and that this protein can change CB1R cell surface levels and signaling. Filipeanu CM, Guidry JJ, Leonard ST, Winsauer PH. Δ9-THC Increases endogenous AHA1 expression in rat cerebellum and may modulate CB1 receptor function during chronic use. J Neurochem. 2011 Sep; 118(6): 1101-1112.

Early-Life Experience Decreases Drug-Induced Reinstatement of Morphine CPP in Adulthood via Microglial-Specific Epigenetic Programming of Anti-Inflammatory IL-10 Expression A critical component of drug addiction research involves identifying novel biological mechanisms and environmental predictors of risk or resilience to drug addiction and associated relapse. Increasing evidence suggests microglia and astrocytes can profoundly affect the physiological and addictive properties of drugs of abuse, including morphine. The authors report that glia within the rat nucleus accumbens (NAcc) respond to morphine with an increase in cytokine/chemokine expression, which predicts future reinstatement of morphine conditioned place preference (CPP) following a priming dose of morphine. This glial response to morphine is

influenced by early-life experience. A neonatal handling paradigm that increases the quantity and quality of maternal care significantly increases baseline expression of the anti-inflammatory cytokine IL-10 within the NAcc, attenuates morphine-induced glial activation, and prevents the subsequent reinstatement of morphine CPP in adulthood. IL-10 expression within the NAcc and reinstatement of CPP are negatively correlated, suggesting a protective role for this specific cytokine against morphine-induced glial reactivity and drug-induced reinstatement of morphine CPP. Neonatal handling programs the expression of IL-10 within the NAcc early in development, and this is maintained into adulthood via decreased methylation of the IL-10 gene specifically within microglia. The effect of neonatal handling is mimicked by pharmacological modulation of glia in adulthood with ibudilast, which increases IL-10 expression, inhibits morphine-induced glial activation within the NAcc, and prevents reinstatement of morphine CPP. Taken together, the authors have identified a novel gene × early-life environment interaction on morphine-induced glial activation and a specific role for glial activation in drug-induced reinstatement of drug-seeking behavior. Schwarz JM, Hutchinson MR, Bilbo SD. Early-life experience decreases drug-induced reinstatement of morphine CPP in adulthood via microglial-specific epigenetic programming of anti-inflammatory IL-10 expression. J Neurosci. 2011 Dec 7; 31(49): 17835-17847.

Enzymatic Formation of N-Acylethanolamines From N-Acylethanolamine Plasmalogen Through N-Acylphosphatidylethanolamine-Hydrolyzing Phospholipase D-Dependent and -Independent Pathways Bioactive N-acylethanolamines include anandamide (an endocannabinoid), N-palmitoylethanolamine (an anti-inflammatory), and N-oleoylethanolamine (an anorexic). In the brain, these molecules are formed from N-acylphosphatidylethanolamines (NAPEs) by a specific phospholipase D, called NAPE-PLD, or through NAPE-PLD-independent multi-step pathways, as illustrated in the current study employing NAPE-PLD-deficient mice. Although N-acylethanolamine plasmalogen (1-alkenyl-2-acyl-glycero-3-phospho(N-acyl)ethanolamine, pNAPE) is presumably a major class of N-acylethanolamine phospholipids in the brain, its enzymatic conversion to N-acylethanolamines is poorly understood. In the present study, the authors focused on the formation of N-acylethanolamines from pNAPEs. While recombinant NAPE-PLD catalyzed direct release of N-palmitoylethanolamine from N-palmitoylethanolamine plasmalogen, the same reaction occurred in the brain homogenate of NAPE-PLD-deficient mice, suggesting that this reaction occurs through both the NAPE-PLD-dependent and -independent pathways. Liquid chromatography-mass spectrometry revealed a remarkable accumulation of 1-alkenyl-2-hydroxy-glycero-3-phospho(N-acyl)ethanolamines (lyso pNAPEs) in the brain of NAPE-PLD-deficient mice. The authors also found that brain homogenate formed N-palmitoylethano-lamine, N-oleoylethanolamine, and anandamide from their corresponding lyso pNAPEs by a Mg(2+)-dependent "lysophospholipase D". Moreover, the brain levels of alkenyl-type lysophosphatidic acids, the other products from lyso pNAPEs by lysophospholipase D, also increased in NAPE-PLD-deficient mice. Glycerophosphodiesterase GDE1 can hydrolyze glycerophospho-N-acylethanolamines to N-acylethanolamines in the brain. In addition, they discovered that recombinant GDE1 has a weak activity to generate N-palmitoylethanolamine from its corresponding lyso pNAPE, suggesting that this enzyme is at least in part responsible for the lysophospholipase D activity. These results strongly suggest that brain tissue N-acylethanolamines, including anandamide, can be formed from N-acylated plasmalogen through an NAPE-PLD-independent pathway as well as by their direct release via NAPE-PLD. Tsuboi K, Okamoto Y, Ikematsu N, Inoue M, Shimizu Y, Uyama T, Wang J, Deutsch DG, Burns MP, Ulloa NM, Tokumura A, Ueda N. Enzymatic formation of N-acylethanolamines from N-acylethanolamine plasmalogen through N-acylphosphatidylethanolamine-hydrolyzing

phospholipase D-dependent and –independent pathways. Biochim Biophys Acta. 2011 Oct; 1811(10): 565-577.

Cocaine-Induced Cortical Microischemia In the Rodent Brain: Clinical Implications
Cocaine-induced stroke is among the most serious medical complications associated with its abuse. However, the extent to which acute cocaine may induce silent microischemia predisposing the cerebral tissue to neurotoxicity has not been investigated; in part, because of limitations of current neuroimaging tools, that is, lack of high spatiotemporal resolution and sensitivity to simultaneously measure cerebral blood flow (CBF) in vessels of different calibers (including capillaries) quantitatively and over a large field of view. Here the authors combine ultrahigh-resolution optical coherence tomography to enable tracker-free three-dimensional (3D) microvascular angiography and a new phase-intensity-mapping algorithm to enhance the sensitivity of 3D optical Doppler tomography for simultaneous capillary CBF quantization. They apply the technique to study the responses of cerebral microvascular networks to single and repeated cocaine administration in the mouse somatosensory cortex. They show that within 2–3 min after cocaine administration CBF markedly decreased (for example, ~70%), but the magnitude and recovery differed for the various types of vessels; arterioles had the fastest recovery (~5 min), capillaries varied drastically (from 4–20 min) and venules showed relatively slower recovery (~12 min). More importantly, the authors showed that cocaine interrupted CBF in some arteriolar branches for over 45 min and this effect was exacerbated with repeated cocaine administration. These results provide evidence that cocaine doses within the range administered by drug abusers induces cerebral microischemia and that these effects are exacerbated with repeated use. Thus, cocaine-induced microischemia is likely to be a contributor to its neurotoxic effects. Ren H, Du C, Yuan Z, Park K, Volkow ND, Pan Y. Cocaine-induced cortical microischemia in the rodent brain: clinical implications. Mol Psychiat. 2011 Nov 29; [Epub ahead of print].

The Effect of Gp120 On Morphine's Antinociceptive and Neurophysiological Actions Recently, the authors have shown that morphine's analgesic activity can be attenuated by chemokines, specifically CCL5 and CXCL12. Because the HIV-1 coat protein, glycoprotein 120 (gp120), binds to the same receptors as do CCL5 and CXCL12, experiments were designed to investigate the effect of gp120 in the brain on antinociception induced by morphine in the cold-water (-3°C) tail-flick (CWT) and hot-plate (+54°C) tests. In addition, mu-opioid-receptor-mediated effects in brain periaqueductal grey (PAG) slices were examined with whole-cell patch-clamp recordings. The results showed that (1) pretreatment with gp120 itself (10, 25, 50, 100 or 133 ng, PAG) had no nociceptive effect in the CWT; (2) pretreatment with gp120 (25 or 100 ng) dose-dependently reduced antinociception induced by subcutaneous (sc) injection of morphine (3 or 6 mg/kg) or PAG injection of morphine (100 ng) in the CWT; (3) a PAG injection of gp120 (133 ng), given 30 min before sc injection of morphine (6 mg/kg), similarly reduced morphine antinociception in the hot-plate test; (4) the inhibitory effect of gp120 on morphine-induced antinociception in the CWT was reversed by AMD3100, an antagonist of CXCR4; (5) pretreatment of slices with gp120 (200 pM) prevented morphine (10 μM)-induced hyperpolarization and reduction of input resistance in PAG neurons. Electrophysiology studies paralleled gp120-induced desensitization of a mu-opioid-receptor-mediated response in PAG neurons at the single-cell level. These studies are the first to demonstrate that the analgesic activity of morphine can be reduced by the presence of gp120 in the PAG and that pretreatment with AMD3100 is able to restore the analgesic effects of morphine. Chen X, Kirby LG, Palma J, Benamar K, Geller EB, Eisenstein TK, Adler MW. The effect of gp120 on morphine's

antinociceptive and neurophysiological actions. Brain Behav Immun. 2011 Oct; 25(7): 1434-1443.

A Catalytically Silent FAAH-1 Variant Drives Anandamide Transport In Neurons The endocannabinoid anandamide is removed from the synaptic space by a selective transport system, expressed in neurons and astrocytes, that remains molecularly uncharacterized. Here the authors describe a partly cytosolic variant of the intracellular anandamide-degrading enzyme fatty acid amide hydrolase-1 (FAAH-1), termed FAAH-like anandamide transporter (FLAT), that lacked amidase activity but bound anandamide with low micromolar affinity and facilitated its translocation into cells. Known anandamide transport inhibitors, such as AM404 and OMDM-1, blocked these effects. The authors also identified a competitive antagonist of the interaction of anandamide with FLAT, the phthalazine derivative ARN272, that prevented anandamide internalization in vitro, interrupted anandamide deactivation in vivo and exerted profound analgesic effects in rodent models of nociceptive and inflammatory pain, which were mediated by CB(1) cannabinoid receptors. The results identify FLAT as a critical molecular component of anandamide transport in neural cells and a potential target for therapeutic drugs. Fu J, Bottegoni G, Sasso O, Bertorelli R, Rocchia W, Masetti M, Guijarro A, Lodola A, Armirotti A, Garau G, Bandiera T, Reggiani A, Mor M, Cavalli A, Piomelli D. A catalytically silent FAAH-1 variant drives anandamide transport in neurons. Nat Neurosci. 2011 Nov 20; 15(1): 64-69.

Endocannabinoid Hydrolysis Generates Brain Prostaglandins That Promote Neuroinflammation NaPhospholipase A2(PLA2) enzymes are considered the primary source of arachidonic acid for cyclooxygenase (COX)–mediated biosynthesis of prostaglandins. Here, the authors show that a distinct pathway exists in brain, where monoacylglycerol lipase (MAGL) hydrolyzes the endocannabinoid 2-arachidonoylglycerol to generate a major arachidonate precursor pool for neuroinflammatory prostaglandins. MAGL-disrupted animals show neuroprotection in a parkinsonian mouse model. These animals are spared the hemorrhaging caused by COX inhibitors in the gut, where prostaglandins are instead regulated by cytosolic PLA2. These findings identify MAGL as a distinct metabolic node that couples endocannabinoid to prostaglandin signaling networks in the nervous system and suggest that inhibition of this enzyme may be a new and potentially safer way to suppress the proinflammatory cascades that underlie neurodegenerative disorders. Nomura DK, Morrison BE, Blankman JL, Long JZ, Kinsey SG, Marcondes MC, Ward AM, Hahn YK, Lichtman AH, Conti B, Cravatt BF. Endocannabinoid hydrolysis generates brain prostaglandins that promote neuroinflammation. Science. 2011 Nov 11; 334(6057): 809-813.

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.

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. 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, Hallfors J, Broms U, Pergadia ML, Saccone SF, Loukola A, Madden PA, Kaprio J. Nicotine Tob Res. 2011 Oct 29. [Epub ahead of print]

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. Neuron. 2011 Dec 22; 72(6): 977-990.

Chronic Morphine Alters the Presynaptic Protein Profile: Identification of Novel Molecular Targets Using Proteomics and Network Analysis Opiates produce significant and persistent changes in synaptic transmission; knowledge of the proteins involved in these changes may help to understand the molecular mechanisms underlying opiate dependence. Using an integrated quantitative proteomics and systems biology approach, the authors explored changes in the presynaptic protein profile following a paradigm of chronic morphine administration that leads to the development of dependence. For this, they isolated presynaptic fractions from the striata of rats treated with saline or escalating doses of morphine, and analyzed the proteins in these fractions using differential isotopic labeling. The authors identified 30 proteins that were significantly altered by morphine and integrated them into a protein-protein interaction (PPI) network representing potential morphine-regulated protein complexes. Graph theory-based analysis of this network revealed clusters of densely connected and functionally related morphine-regulated clusters of proteins. One of the clusters contained molecular chaperones thought to be involved in regulation of neurotransmission. Within this cluster, cysteine-string protein (CSP) and the heat shock protein Hsc70 were downregulated by morphine. Interestingly, Hsp90, a heat shock protein that normally interacts with CSP and Hsc70, was upregulated by morphine. Moreover, treatment with the selective Hsp90 inhibitor, geldanamycin, decreased the somatic signs of naloxone-precipitated morphine withdrawal, suggesting that Hsp90 upregulation at the presynapse plays a role in the expression of morphine dependence. Thus, integration of proteomics, network analysis, and behavioral studies has provided a greater understanding of morphine-induced alterations in synaptic composition, and identified a potential novel therapeutic target for opiate dependence. Abul-Husn NS, Annangudi SP, Ma'ayan A, Ramos-Ortolaza DL, Stockton SD Jr, Gomes I, Sweedler JV, Devi LA. Chronic morphine alters the presynaptic protein profile: identification of novel molecular targets using proteomics and network analysis. PLoS One. 2011; 6(10): e25535.

Molecular Mechanism For a Gateway Drug: Epigenetic Changes Initiated By Nicotine Prime Gene Expression By Cocaine In human populations, cigarettes and alcohol generally serve as gateway drugs, which people use first before progressing to marijuana, cocaine, or other illicit substances. To understand the biological basis of the gateway sequence of drug use, the authors developed an animal model in mice and used it to study the effects of nicotine on subsequent responses to cocaine. They found that pretreatment of mice with nicotine increased the response to cocaine, as assessed by addiction-related behaviors and synaptic plasticity in the striatum, a brain region critical for addiction-related reward. Locomotor sensitization was increased by 98%, conditioned place preference was increased by 78%, and cocaine-induced reduction in long-term potentiation (LTP) was enhanced by 24%. The responses to cocaine were altered only when nicotine was administered first, and nicotine and cocaine were then administered concurrently. Reversing the order of drug administration was ineffective; cocaine had no effect on nicotine-induced behaviors and synaptic plasticity. Nicotine primed the response to cocaine by enhancing its ability to induce transcriptional activation of the FosB gene through inhibition of histone deacetylase, which caused global histone acetylation in the striatum. The authors tested this conclusion further and found that a histone deacetylase inhibitor simulated the actions of nicotine by priming the response to cocaine and enhancing FosB gene expression and LTP depression in the nucleus accumbens. Conversely, in a genetic mouse model characterized by reduced histone acetylation, the effects of cocaine on LTP were diminished.

The authors achieved a similar effect by infusing a low dose of theophylline, an activator of histone deacetylase, into the nucleus accumbens. These results from mice prompted an analysis of epidemiological data, which indicated that most cocaine users initiate cocaine use after the onset of smoking and while actively still smoking, and that initiating cocaine use after smoking increases the risk of becoming dependent on cocaine, consistent with our data from mice. If these findings in mice apply to humans, a decrease in smoking rates in young people would be expected to lead to a decrease in cocaine addiction. Levine A, Huang Y, Drisaldi B, Griffin EA Jr, Pollak DD, Xu S, Yin D, Schaffran C, Kandel DB, Kandel ER. Molecular mechanism for a gateway drug: epigenetic changes initiated by nicotine prime gene expression by cocaine. Sci Transl Med. 2011 Nov 2; 3(107): 107ra109.

A Role For Repressive Histone Methylation In Cocaine-Induced Vulnerability To Stress
Substance abuse increases an individual's vulnerability to stress-related illnesses, which is presumably mediated by drug-induced neural adaptations that alter subsequent responses to stress. Here, the authors identify repressive histone methylation in nucleus accumbens (NAc), an important brain reward region, as a key mechanism linking cocaine exposure to increased stress vulnerability. Repeated cocaine administration prior to subchronic social defeat stress potentiated depressive-like behaviors in mice through decreased levels of histone H3 lysine 9 dimethylation in NAc. Cre-mediated reduction of the histone methyltransferase, G9a, in NAc promoted increased susceptibility to social stress, similar to that observed with repeated cocaine. Conversely, G9a overexpression in NAc after repeated cocaine protected mice from the consequences of subsequent stress. This resilience was mediated, in part, through repression of BDNF-TrkB-CREB signaling, which was induced after repeated cocaine or stress. Identifying such common regulatory mechanisms may aid in the development of new therapies for addiction and depression. Covington HE 3rd, Maze I, Sun H, Bomze HM, DeMaio KD, Wu EY, Dietz DM, Lobo MK, Ghose S, Mouzon E, Neve RL, Tamminga CA, Nestler EJ. A role for repressive histone methylation in cocaine-induced vulnerability to stress. Neuron. 2011 Aug 25; 71(4): 656-670.

A Genomewide Linkage Scan of Cocaine Dependence and Major Depressive Episode In Two Populations Cocaine dependence (CD) and major depressive episode (MDE) frequently co-occur with poorer treatment outcome and higher relapse risk. Shared genetic risk was affirmed; to date, there have been no reports of genomewide linkage scans (GWLSs) surveying the susceptibility regions for comorbid CD and MDE (CD-MDE). The authors aimed to identify chromosomal regions and candidate genes susceptible to CD, MDE, and CD-MDE in African Americans (AAs) and European Americans (EAs). A total of 1896 individuals were recruited from 384 AA and 355 EA families, each with at least a sibling-pair with CD and/or opioid dependence. Array-based genotyping of about 6000 single-nucleotide polymorphisms was completed for all individuals. Parametric and non-parametric genomewide linkage analyses were performed. The authors found a genomewide-significant linkage peak on chromosome 7 at 183.4 cM for non-parametric analysis of CD-MDE in AAs (lod=3.8, genomewide empirical p=0.016; point-wise p=0.00001). A nearly genomewide significant linkage was identified for CD-MDE in EAs on chromosome 5 at 14.3 cM (logarithm of odds (lod)=2.95, genomewide empirical p=0.055; point-wise p=0.00012). Parametric analysis corroborated the findings in these two regions and improved the support for the peak on chromosome 5 so that it reached genomewide significance (heterogeneity lod=3.28, genomewide empirical p=0.046; point-wise p=0.00053). This is the first GWLS for CD-MDE. The genomewide significant linkage regions on chromosomes 5 and 7 harbor four particularly promising candidate genes: SRD5A1, UBE3C,

PTPRN2, and VIPR2. Replication of the linkage findings in other populations is warranted, as is a focused analysis of the genes located in the linkage regions implicated here. Yang BZ, Han S, Kranzler HR, Farrer LA, Gelernter J. A genomewide linkage scan of cocaine dependence and major depressive episode in two populations. Neuropsychopharmacology. 2011 Nov; 36(12): 2422-2430.

CSNK1E Is a Genetic Regulator of Sensitivity To Psychostimulants and Opioids Csnk1e, the gene encoding casein kinase 1-epsilon, has been implicated in sensitivity to amphetamines. Additionally, a polymorphism in Csnk1e was associated with heroin addiction, suggesting that this gene may also affect opioid sensitivity. In this study, the authors first conducted genome-wide quantitative trait locus (QTL) mapping of methamphetamine (MA)-induced locomotor activity in C57BL/6J (B6) × DBA/2J (D2)-F(2) mice and a more highly recombinant F(8) advanced intercross line. The authors identified a QTL on chromosome 15 that contained Csnk1e (63-86 Mb; Csnk1e=79.25 Mb). They replicated this result and further narrowed the locus using B6.D2 (Csnk1e) and D2.B6(Csnk1e) reciprocal congenic lines (78-86.8 and 78.7-81.6 Mb, respectively). This locus also affected sensitivity to the μ-opioid receptor agonist fentanyl. Next, the authors directly tested the hypothesis that Csnk1e is a genetic regulator of sensitivity to psychostimulants and opioids. Mice harboring a null allele of Csnk1e showed an increase in locomotor activity following MA administration. Consistent with this result, co-administration of a selective pharmacological inhibitor of Csnk1e (PF-4800567) increased the locomotor stimulant response to both MA and fentanyl. These results show that a narrow genetic locus that contains Csnk1e is associated with differences in sensitivity to MA and fentanyl. Furthermore, gene knockout and selective pharmacological inhibition of Csnk1e define its role as a negative regulator of sensitivity to psychostimulants and opioids. Bryant CD, Parker CC, Zhou L, Olker C, Chandrasekaran RY, Wager TT, Bolivar VJ, Loudon AS, Vitaterna MH, Turek FW, Palmer AA. Csnk1e is a genetic regulator of sensitivity to psychostimulants and opioids. Neuropsychopharmacology. 2011 Nov 16. [Epub ahead of print]

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. 2011 Oct 27 [Epub ahead of print]

Clonal Production and Organization of Inhibitory Interneurons In the Neocortex The neocortex contains excitatory neurons and inhibitory interneurons. Clones of neocortical excitatory neurons originating from the same progenitor cell are spatially organized and contribute to the formation of functional microcircuits. In contrast, relatively little is known about the production and organization of neocortical inhibitory interneurons. The authors found that neocortical inhibitory interneurons were produced as spatially organized clonal units in the developing ventral telencephalon. Furthermore, clonally related interneurons did not randomly disperse but formed spatially isolated clusters in the neocortex. Individual clonal clusters consisting of interneurons expressing the same or distinct neurochemical markers exhibited clear vertical or horizontal organization. These results suggest that the lineage relationship plays a pivotal role in the organization of inhibitory interneurons in the neocortex. Brown KN, Chen S, Han Z, Lu CH, Tan X, Zhang XJ, Ding L, Lopez-Cruz A, Saur D, Anderson SA, Huang K, Shi SH. Clonal production and organization of inhibitory interneurons in the neocortex. Science. 2011 Oct 28; 334(6055): 480-486.

Control of Excitatory CNS Synaptogenesis By Astrocyte-Secreted Proteins Hevin and SPARC Astrocytes regulate synaptic connectivity in the CNS through secreted signals. Here the authors identified two astrocyte-secreted proteins, hevin and SPARC, as regulators of excitatory synaptogenesis in vitro and in vivo. Hevin induces the formation of synapses between cultured rat retinal ganglion cells. SPARC is not synaptogenic, but specifically antagonizes synaptogenic function of hevin. Hevin and SPARC are expressed by astrocytes in the superior colliculus, the synaptic target of retinal ganglion cells, concurrent with the excitatory synaptogenesis. Hevin-null mice had fewer excitatory synapses; conversely, SPARC-null mice had increased synaptic connections in the superior colliculus. Furthermore, the authors found that hevin is required for the structural maturation of the retinocollicular synapses. These results identify hevin as a positive and SPARC as a negative regulator of synapse formation and signify that, through regulation of relative levels of hevin and SPARC, astrocytes might control the formation, maturation, and plasticity of synapses in vivo. Kucukdereli H, Allen NJ, Lee AT, Feng A, Ozlu MI, Conatser LM, Chakraborty C, Workman G, Weaver G, Weaver M, Sage EH, Barres BA, Eroglu C. Control of excitatory CNS synaptogenesis by astrocyte-secreted proteins Hevin and SPARC. Proc Natl Acad Sci U S A. 2011 Aug 9; 108(32): E440-449.

The Brain-Specific MicroRNA Mir-128b Regulates the Formation of Fear-Extinction Memory MicroRNAs are small non-coding RNAs that mediate post-transcriptional gene silencing. Fear-extinction learning in C57/Bl6J mice led to increased expression of the brain-specific microRNA miR-128b, which disrupted stability of several plasticity-related target genes and regulated formation of fear-extinction memory. Increased miR-128b activity may therefore facilitate the transition from retrieval of the original fear memory toward the formation of a new fear-extinction memory. Lin Q, Wei W, Coelho CM, Li X, Baker-Andresen D, Dudley K, Ratnu VS, Boskovic Z, Kobor MS, Sun YE, Bredy TW. The brain-specific microRNA miR-128b regulates the formation of fear-extinction memory. Nat Neurosci. 2011 Aug 14; 14(9): 1115-1117.

BASIC BEHAVIORAL RESEARCH

Bingeing on Fat Enhances Cocaine Seeking and Taking Binge eating and substance dependence are disorders characterized by a loss of control over consummatory behaviors. Given the common characteristics of these two types of disorders, it is not surprising that the comorbidity between eating disorders and substance abuse disorders is high (20-40%; Conason et al., 2006). It is unknown, however, whether loss of control in one disorder predisposes an individual to loss of control in the other. The present study, therefore, used a rodent model to test whether a history of binge eating would augment subsequent responding for cocaine. Using the limited access protocol described by Corwin et al. (1998), 45 adult male Sprague-Dawley rats were maintained on one of four dietary protocols for a period of six weeks: chow only (Chow; n = 9), continuous access to an optional source of dietary fat (Ad Lib; n = 12), 1-h access to an optional source of dietary fat daily (Daily; n = 12), or 1-h access to an optional source of dietary fat on Monday, Wednesday, and Friday (MWF; n = 12). All four groups also had unrestricted access to a nutritionally complete diet of chow and water. Fat-bingeing behaviors developed in the MWF rats, the group with the most restricted access to the optional fat. Thereafter, cocaine-seeking and -taking behaviors were assessed in all rats using a self-administration protocol modified from that described by Deroche-Gamonet et al. (2004), which focused on the motivation for and preoccupation with obtaining and consuming drug (assessed using a progressive ratio [PR] schedule of reinforcement) and persistence in responding for drug during periods of signaled drug non-availability (SNA). Rats with the MWF history tended to take more cocaine late in fixed ratio (FR) training, they persisted in their efforts to obtain cocaine in the face of signaled non-availability, worked harder for cocaine on a PR schedule of reinforcement, and exhibited more goal-directed behavior toward the cocaine-associated operandum. These results demonstrate a link between binge-type intake of fat and the development of drug-seeking and -taking behaviors, suggesting that a history of fat bingeing may predispose individuals to exhibit more robust "addiction-like" behaviors toward a substance of abuse. Thus, it appears that conditions promoting excessive behavior toward one substance (e.g., a palatable fatty food) beget excessive behavior toward another (e.g., cocaine). Puhl MD, Cason AM, Wojnicki FH, Corwin RL, Grigson PS. A history of bingeing on fat enhances cocaine seeking and taking. Behav Neurosci. 2011 Dec; 125(6): 930-942.

Social Influences Promote Nicotine Self-Administration in Adolescent Rats Cigarette smoking is a social behavior. Smoking is also accompanied by distinctive gustatory and olfactory stimulation. However, none of these factors affecting nicotine intake are modeled in existing preclinical studies. The authors report a novel model of adolescent nicotine self-administration (SA) in rats where licking on drinking spouts was used as the operant behavior to activate the concurrent delivery of nicotine (i.v.) and an appetitive olfactogustatory (OG) cue, and social interaction was required for stable SA. The operant chamber was divided by a panel that separated the SA rat and another rat serving as the demonstrator, who had free access to the OG cue but did not receive nicotine. Orofacial contacts were permitted by the divider. Conditioned taste aversion prevented solo rats from self-administering nicotine. However, stable nicotine (15–30 μg/kg, free base) SA was established in the presence of demonstrator rats with free access to the OG cue. Omitting the olfactory component of the cue prevented the acquisition of nicotine SA. Mecamylamine, a nicotinic antagonist, reduced licking behavior. Familiar peers were more effective demonstrators in facilitating the acquisition of nicotine SA than were unfamiliar rats. No sex difference in nicotine intake was found. These data indicate that the contingent OG cue is associated with the aversive property of nicotine that prevents subsequent

drug intake. Social information encoded in olfaction not only permits the establishment of stable nicotine SA but also enhances nicotine intake. These findings implicate adolescent social interactions in promoting smoking behavior by surmounting the aversive property of nicotine. Chen H, Sharp BM, Matta SG, Wu Q. Social interaction promotes nicotine self-administration with olfactogustatory cues in adolescent rats. Neuropsychopharmacol. 2011 Dec; 36(13): 2629-2638.

Nicotine-induced Stress is Attenuated by Social Interaction in Adolescent Rats Most smokers begin smoking during adolescence, a period during which social reward is highly influential. Initial exposure to nicotine can produce anxiogenic effects that may be influenced by social context. This study examined play behavior and plasma corticosterone following nicotine administration (0.6 mg/kg, s.c.) in both male and female adolescent (PND39) Sprague–Dawley rats in either isolate or social contexts. In blood samples collected immediately following the 15-min test session, nicotine increased plasma corticosterone relative to saline in both male and female isolate rats, but failed to do so in both males and females placed together in same-sex pairs. Nicotine also attenuated several indices of play behavior including nape attacks, pins and social contact. In isolate rats, nicotine selectively increased locomotor activity in females; however, when administered to social pairs, nicotine decreased locomotion in both sexes. These findings suggest that the presence of a social partner may decrease the initial negative, stress-activating effects of nicotine, perhaps leading to increased nicotine reward. Pentkowski NS, Painter MR, Thiel KJ, Peartree NA, Cheung THC, Deviche P, Adams M, Alba J, Neisewander JL. Nicotine-induced plasma corticosterone is attenuated by social interactions in male and female adolescent rats. Pharmacol Biochem Behav. 2011 Nov; 100(1): 1-7.

Preclinical Validation of Interoceptive Cue Extinction as Relapse Prevention Cocaine not only induces intense rewarding sensations but also craving for more cocaine, particularly during abstinence, an effect that contributes, together with other factors, to relapse. Here the authors sought to prevent this effect by extinguishing the conditioned interoceptive cues of cocaine that are thought to be acquired during repeated cocaine use. Cocaine-induced craving was studied in rats using the well-validated model of drug-primed reinstatement of cocaine seeking. To extinguish the conditioned interoceptive effects of cocaine, rats received daily repeated cocaine priming in the absence of drug reinforcement. Cocaine-primed reinstatement of cocaine seeking dramatically decreased with repeated cocaine priming regardless of the testing dose and even following a history of extended access to cocaine self-administration. The extinction of cocaine-primed reinstatement of cocaine seeking was enduring, generalized to stress—another major trigger of drug craving and relapse—and was context-dependent. These findings clearly show that it is feasible to prevent the ability of cocaine and stress to induce cocaine seeking using an approach designed to extinguish the drug's conditioned interoceptive cues. Although this preclinical extinction approach has limitations that need to be overcome in future research (i.e., its context-dependency), it may nevertheless represent a promising basis for the development of a novel exposure therapy against cocaine relapse. Mihindou C, Vouillac C, Koob GF, Ahmed SH. Preclinical validation of a novel cocaine exposure therapy for relapse prevention. Biol Psychiat. 2011 Sept; 70(6): 593-598.

Inhibition of the Glycine Transporter-1 Facilitates Cocaine-cue Extinction and Attenuates Reacquisition of Cocaine-seeking Behavior Combining extinction training with cognitive-enhancing pharmacotherapy represents a novel strategy for improving the efficacy of exposure therapy for drug relapse prevention. The authors investigated if the selective glycine transporter-

1 (GlyT-1) inhibitor RO4543338 could facilitate extinction of cocaine-conditioned responses and attenuate reacquisition of cocaine-seeking behavior. Rats were trained to self-administer cocaine (0.3mg/kg), which was associated with a 2-s light cue under a second-order schedule of i.v. drug injection. Rats received vehicle, 30 or 45mg/kg of RO4543338 prior to three 1-h extinction-training sessions spaced at weekly intervals. Responses were extinguished by substituting saline for cocaine while maintaining response-contingent cue presentations. Reacquisition of cocaine-seeking behavior during self-administration sessions began 1 week after the last extinction session. Control experiments were conducted under conditions that precluded explicit extinction of cocaine-conditioned responses. Compared to vehicle, 30 and 45mg/kg RO4543338 significantly decreased responding early in extinction training and during subsequent reacquisition sessions. The latter effect persisted for at least five sessions. In control studies, reacquisition of cocaine-seeking behavior was not altered when RO4543338 was administered either prior to weekly self-administration control sessions or prior to weekly control sessions in which cocaine and cues were omitted and the levers retracted. As the GlyT-1 inhibitor facilitated cocaine-cue extinction learning and attenuated subsequent reacquisition of cocaine-seeking behavior, this class of compounds may have utility as a pharmacological adjunct to cocaine-cue exposure therapy in addicts. Nic Dhonnchadha BA, Pinard E, Alberati D, Wettstein JG, Spealman RD, Kantak KM. Inhibiting glycine transporter-1 facilitates cocaine-cue extinction and attenuates reacquisition of cocaine-seeking behavior. Drug Alcohol Depend. 2011 Oct 10. [Epub ahead of print]

Mesolimibic Neuroadaptations During Cocaine Abstinence Enhance Drug-Seeking Through an Epigenetic Mechanism Recent evidence suggests that the persistence of cocaine seeking during periods of protracted drug abstinence following chronic cocaine exposure is mediated, in part, by neuroadaptations in the mesolimbic dopamine system. Specifically, incubation of cocaine-seeking behavior coincides with increased brain-derived neurotrophic factor (BDNF) protein expression in the ventral tegmental area (VTA). However, the molecular mechanisms that regulate time-dependent changes in VTA BDNF protein expression during cocaine abstinence are unclear. The goal of these experiments was to determine whether VTA BDNF transcript levels are altered following cocaine abstinence and identify the molecular mechanisms regulating cocaine-induced changes in VTA BDNF transcription. Rats were allowed to self-administer cocaine (0.25 mg/infusion, i.v.) for 14 days on a fixed-ratio schedule of reinforcement followed by 7 days of forced drug abstinence. BDNF protein and exon I-containing transcripts were significantly increased in the VTA of cocaine-experienced rats following 7 days of forced drug abstinence compared to yoked saline controls. Cocaine-induced changes in BDNF mRNA were associated with increased acetylation of histone 3 and binding of CREB-binding protein to exon I-containing promoters in the VTA. Taken together, these results suggest that drug abstinence following cocaine self-administration remodels chromatin in the VTA resulting in increased expression of BDNF, which may contribute to neuroadaptations underlying cocaine craving and relapse. Schmidt HD, Sangrey GR, Darnell SB, Schassburger RL, Cha JH, Pierce RC, Sadri-Vakili G. Increased brain-derived neurotrophic factor (BDNF) expression in the ventral tegmental area during cocaine abstinence is associated with increased histone acetylation at BDNF exon I-containing promoters. J Neurochem. 2011 Nov 2. [Epub ahead of print]

BEHAVIORAL AND BRAIN DEVELOPMENT RESEARCH

The Combined Effects of Prenatal Drug Exposure and Early Adversity on Neurobehavioral Disinhibition in Childhood and Adolescence The negative effects of prenatal substance exposure on neurobiological and psychological development and of early adversity are clear, but little is known about their combined effects. In this study, multilevel analyses of the effects of prenatal substance exposure and early adversity on the emergence of neurobehavioral disinhibition in adolescence were conducted. Neurobehavioral disinhibition has previously been observed to occur frequently in multiproblem youth from high-risk backgrounds. In the present study, neurobehavioral disinhibition was assessed via behavioral dysregulation and poor executive function composite measures. Data were drawn from a prospective longitudinal investigation of prenatal substance exposure that included 1,073 participants followed from birth through adolescence. The results from latent growth modeling analyses showed mean stability but significant individual differences in behavioral dysregulation and mean decline with individual differences in executive function difficulties. Prior behavioral dysregulation predicted increased executive function difficulties. Prenatal drug use predicted the emergence and growth in neurobehavioral disinhibition across adolescence (directly for behavioral dysregulation and indirectly for executive function difficulties via early adversity and behavioral dysregulation). Prenatal drug use and early adversity exhibited unique effects on growth in behavioral dysregulation; early adversity uniquely predicted executive function difficulties. These results are discussed in terms of implications for theory development, social policy, and prevention science. Fisher PA, Lester BM, DeGarmo DS, Lagasse LL, Lin H, Shankaran S, Bada HS, Bauer CR, Hammond J, Whitaker T, Higgins R. The combined effects of prenatal drug exposure and early adversity on neurobehavioral disinhibition in childhood and adolescence. Dev Psychopathol. 2011 Aug; 23(3): 777-788.

Long-term Impact of Maternal Substance Use During Pregnancy and Extrauterine Environmental Adversity: Stress Hormone Levels of Preadolescent Children Prenatal cocaine exposure (PCE) is associated with blunted stress responsivity within the extrauterine environment. This study investigated the association between PCE and diurnal salivary cortisol levels in preadolescent children characterized by high biological and/or social risk (n = 725). Saliva samples were collected at their home. Analyses revealed no group differences in basal evening or morning cortisol levels; however, children with higher degrees of PCE exhibited blunted overnight increases in cortisol, controlling for additional risk factors. Race and caregiver depression were also associated with diurnal cortisol patterns. Although repeated PCE may contribute to alterations in the normal or expected stress response later in life, sociodemographic and environmental factors are likewise important in understanding hormone physiology, especially as more time elapses from the PCE. Anticipating the potential long-term medical, developmental, or behavioral effects of an altered ability to mount a normal protective cortisol stress response is essential in optimizing the outcomes of children with PCE. Bauer CR, Lambert BL, Bann CM, Lester BM, Shankaran S, Bada HS, Whitaker TM, Lagasse LL, Hammond J, Higgins RD. Long-term impact of maternal substance use during pregnancy and extrauterine environmental adversity: stress hormone levels of preadolescent children. Pediatr Res. 2011 Aug; 70(2): 213-219.

Prenatal Cocaine Exposure and Small-for-Gestational-Age Status: Effects on Growth at 6 Years of Age The objective of this study was to evaluate the impact of prenatal cocaine exposure and small-for-gestational-age (SGA) status on childhood growth. Cocaine exposure was defined by history or meconium metabolites. Hierarchical linear modeling was used to examine cocaine exposure and SGA status on growth, while controlling for exposure to other drugs and alcohol use. At birth cocaine-exposed infants (n=364) had significantly lower growth parameters compared to non-exposed children (n=771). At 6 years, weight was similar between exposed and unexposed children. SGA infants continued to be growth impaired. There was a significant interaction between prenatal cocaine exposure and SGA status at 6 years. The negative effects of cocaine on weight and height were greater among non-SGA than SGA children (432 vs. 280 gm, and 0.7 and 0.5 cm, respectively) while negative effects of SGA status on weight and height were larger in non-cocaine exposed compared to the exposed children (2.3 kg vs.1.6 kg and 2.2 and 1.0 cm). Children exposed to prenatal cocaine were similar in weight to non-exposed children at 6 years of age. Cocaine had an unexplained greater detrimental effect on non-SGA than SGA children. SGA status at birth has an independent detrimental effect on childhood growth. Shankaran S, Das A, Bauer CR, Bada HS, Lester BM, Wright LL, Higgins RD, Poole WK. Prenatal cocaine exposure and small-for-gestational-age status: effects on growth at 6 years of age. Neurotoxicol Teratol. 2011 Sep-Oct; 33(5): 575-581.

An Expanded Model of the Temporal Stability of Condom Use Intentions: Gender-Specific Predictors among High-Risk Adolescents Adolescents involved with the criminal justice system are at particularly high-risk for the Human Immunodeficiency Virus and sexually transmitted infections. The purpose of this study was to longitudinally examine gender-specific models of condom use, incorporating temporal stability of intentions. Adolescents on probation (N=728) were recruited to complete longitudinal surveys including measures of Theory of Planned Behavior and gender-specific constructs, relationship length, and condom use. Gender-specific models of condom use behavior suggested by previous research were mostly replicated. For young women, the effect of baseline intentions on subsequent condom use behavior was stronger when intentions were either stable or increasing. For young men, more stable, increasing intentions were directly associated with more condom use. There was preliminary evidence to suggest an association between temporal stability of intentions and decreasing condom use in stable relationships. Intervention efforts should be tailored by gender and aim to forestall decreasing intentions and condom use over time by addressing difficulties in maintaining condom use. Broaddus MR, Schmiege SJ, Bryan AD. An expanded model of the temporal stability of condom use intentions: gender-specific predictors among high-risk adolescents. Ann Behav Med. 2011 Aug;42(1): 99-110.

Sources and Frequency of Secondhand Smoke Exposure During Pregnancy This study examined sources of exposure to secondhand smoke (SHS) during pregnancy and misclassification of women as having no SHS exposure if partner smoking was used as the only measure of SHS exposure. The authors also examined changes in SHS exposure across the three trimesters of pregnancy. The sample consisted of 245 pregnant women who were in a serious relationship with a partner and 106 for examination of change over time. Women's smoking status was determined by a combination of self-reports and oral fluid assays. Women's reports of partner smoking, smoking by other social network members, and frequency of exposure to SHS were obtained. The most common source of SHS exposure during pregnancy was the partner (n = 245). However, reliance on the partner smoking measure alone would have misclassified a substantial number of women as having no SHS exposure during pregnancy. The importance of

exposure from the general social network was also evident in the finding that among nonsmoking women with nonsmoking partners, 50% reported some level of SHS exposure in the preceding week. Contrary to expectations, there were no changes in SHS exposure across the three trimesters of pregnancy (n = 106). Results highlight the need for treatment plans to target sources of exposure from other members of women's social networks in addition to partners. It may be unrealistic to expect women's cessation efforts to be successful in the face of consistent and continued SHS exposure through pregnancy. Eiden RD, Molnar DS, Leonard KE, Colder CR, Homish GG, Maiorana N, Schuetze P, Connors GJ. Sources and frequency of secondhand smoke exposure during pregnancy. Nicotine Tob Res. 2011 Aug;13(8): 653-660.

Physiological Regulation in Cigarette Exposed Infants: An Examination of Potential Moderators The primary purpose of this study was to examine pathways from prenatal cigarette exposure to physiological regulation at 2 months of age. Specifically, the authors explored the possibility that any association between prenatal cigarette exposure and infant physiological regulation was moderated by fetal growth, prenatal or postnatal environmental tobacco smoke (ETS) exposure or maternal depressive symptomatology during pregnancy. They evaluated whether exposed infants who were also exposed to ETS after birth, were small for gestational age (SGA) or had mothers with higher depressive symptoms during pregnancy had the highest levels of physiological dysregulation. Respiratory sinus arrhythmia (RSA) was obtained from 234 (166 exposed and 68 nonexposed) infants during sleep. As expected, cigarette-exposed infants had significantly lower RSA than nonexposed infants. This association was not moderated by prenatal or postnatal ETS exposure or maternal depressive symptomatology during pregnancy. However, small for gestational age status did moderate this association such that nonexposed infants who were not small for gestational age had a significantly higher RSA than nonexposed small for gestational age infants and exposed infants. These findings provide additional evidence that prenatal cigarette exposure is directly associated with dysregulation during infancy. Schuetze P, Eiden RD, Colder CR, Gray TR, Huestis MA. Physiological regulation in cigarette exposed infants: an examination of potential moderators. Neurotoxicol Teratol. 2011 Sep-Oct;33(5): 567-774.

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 care 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.

Early Adolescent Cocaine Use as Determined by Hair Analysis in a Prenatal Cocaine Exposure Cohort Preclinical and other research suggest that youth with prenatal cocaine exposure (PCE) may be at high risk for cocaine use due to both altered brain development and exposure to unhealthy environments. Participants are early adolescents who were prospectively enrolled in a longitudinal study of PCE prior to or at birth. Hair samples were collected from the youth at ages 10½ and 12½ (N=263). Samples were analyzed for cocaine and its metabolites using ELISA screening with gas chromatography/mass spectroscopy (GC/MS) confirmation of positive samples. Statistical analyses included comparisons between the hair-positive and hair-negative groups on risk and protective factors chosen a priori as well as hierarchical logistical regression analyses to predict membership in the hair-positive group. Hair samples were positive for cocaine use for 14% (n=36) of the tested cohort. Exactly half of the hair-positive preteens had a history of PCE. Group comparisons revealed that hair-negative youth had significantly higher IQ scores at age 10½; the hair-positive youth had greater availability of cigarettes, alcohol, and other drugs in the home; caregivers with more alcohol problems and depressive symptoms; less nurturing home environments; and less positive attachment to their primary caregivers and peers. The caregivers of the hair-positive preteens reported that the youth displayed more externalizing and social problems, and the hair-positive youth endorsed more experimentation with cigarettes, alcohol, and/or other drugs. Mental health problems, peer drug use, exposure to violence, and neighborhood characteristics did not differ between the groups. Regression analyses showed that the availability of drugs in the home had the greatest predictive value for hair-positive group membership while higher IQ, more nurturing home environments, and positive attachment to caregivers or peers exerted some protective effect. The results do not support a direct relationship between PCE and early adolescent experimentation with cocaine. Proximal risk and protective factors-those associated with the home environment and preteens' caregivers-were more closely related to early cocaine use than more distal factors such as neighborhood characteristics. Consistent with theories of adolescent problem behavior, the data demonstrate the complexity of predicting pre-adolescent drug use and identify a number of individual and contextual factors that could serve as important foci for intervention. Warner TD, Behnke M, Eyler FD, Szabo NJ. Early adolescent cocaine use as determined by hair analysis in a prenatal cocaine exposure cohort. Neurotoxicol Teratol. 2011 Jan-Feb; 33(1): 88-99.

Temperament and Sleep-Wake Behaviors from Infancy to Toddlerhood Sleep-wake behaviors and temperament were examined longitudinally for trait stability and relationship to behavioral state regulation from infancy to early childhood. Subjects were 120 low-risk, full-term infants from a middle class sample. At 6 weeks, parents completed 3 consecutive days of the Baby's Day Diary which measures sleep, wake, fuss, feed and cry states and the Infant Characteristics Questionnaire. At 16 months, parents assessed sleep behaviors with the Sleep Habits Inventory and temperament with the Toddler Symptom Checklist. At 24 months, parents repeated 3 days of the Baby's Day Diary. Structural Equation Modeling was used to examine cross-age hypotheses for sleep-wake and temperament associations. From early infancy to toddlerhood, sleep-wake behaviors and irritable temperament were notably stable but independent in this cohort. Hayes MJ, McCoy SK, Fukumizu M, Wellman JD, Dipietro JA. Temperament and sleep-wake behaviors from infancy to toddlerhood. Infant Child Dev. 2011 Sep; 20(5): 495-508.

Impact of Prenatal Exposure to Cocaine and Tobacco on Diffusion Tensor Imaging and Sensation Seeking in Adolescents The objective of this study was to study white matter integrity with diffusion tensor imaging in adolescents with prenatal cocaine exposure, tobacco exposure, or both. Subjects included 20 adolescents with prenatal cocaine exposure (15 with tobacco exposure) and 20 non-cocaine-exposed subjects (8 with tobacco exposure). Diffusion tensor imaging measures were assessed in 5 subregions of the corpus callosum. The Sensation Seeking Scale for Children was administered to evaluate behavioral inhibition. No significant differences were found between the cocaine-exposed and non-cocaine-exposed groups in each subregion of the corpus callosum on measures of fractional anisotropy (FA) and mean diffusivity, although the cocaine-exposed group showed a trend (P = .06) toward higher FA in projections to the supplementary motor area and premotor cortex. Prenatal tobacco exposure was associated with decreased FA in the supplementary motor area and premotor cortex projections after adjustment for relevant co-variates (P = .03). Decreased FA was related to more sensation seeking in the adolescents who were prenatally exposed to tobacco. Prenatal tobacco exposure could affect white matter integrity, which is related to sensation seeking in adolescents. Developmental neurotoxins might have differential influences on white matter maturation in adolescence. Liu J, Cohen RA, Gongvatana A, Sheinkopf SJ, Lester BM. Impact of prenatal exposure to cocaine and tobacco on diffusion tensor imaging and sensation seeking in adolescents. J Pediatr. 2011 Nov; 159(5): 771-775.

Development of Neural Systems for Processing Social Exclusion from Childhood to Adolescence Adolescence is a period of development in which peer relationships become especially important. A computer-based game (Cyberball) has been used to explore the effects of social exclusion in adolescents and adults. The current functional magnetic resonance imaging (fMRI) study used Cyberball to extend prior work to the cross-sectional study of younger children and adolescents (7 to 17 years), identifying age-related changes in the neural correlates of social exclusion across the important transition from middle childhood into adolescence. Additionally, a control task illustrated the specificity of these age-related changes for social exclusion as distinct from expectancy violation more generally. During exclusion, activation in and functional connectivity between ventrolateral prefrontal cortex and ventral anterior cingulate cortex increased with age. These effects were specific to social exclusion and did not exist for expectancy violation. Our results illustrate developmental changes from middle childhood through adolescence in both affective and regulatory brain regions during social exclusion. Bolling DZ, Pitskel NB, Deen B, Crowley MJ, Mayes LC, Pelphrey KA. Development of neural systems for processing social exclusion from childhood to adolescence. Dev Sci. 2011 Nov;14(6): 1431-1444.

Breastfeeding, Brain Activation to Own Infant Cry, and Maternal Sensitivity Research points to the importance of breastfeeding for promoting close mother-infant contact and social-emotional development. Recent functional magnetic resonance imaging (fMRI) studies have identified brain regions related to maternal behaviors. However, little research has addressed the neurobiological mechanisms underlying the relationship between breastfeeding and maternal behavior in human mothers. The authors investigated the associations between breastfeeding, maternal brain response to own infant stimuli, and maternal sensitivity in the early postpartum. Methods: Seventeen biological mothers of healthy infants participated in two matched groups according to feeding method - exclusive breastfeeding and exclusive formula-feeding at 2-4 weeks postpartum. fMRI scanning was conducted in the first postpartum month to examine maternal brain activation in response to her own baby's cry versus control baby-cry. Dyadic

interactions between mothers and infants at 3-4 months postpartum were videotaped in the home and blindly coded for maternal sensitivity. In the first postpartum month, breastfeeding mothers showed greater activations in the superior frontal gyrus, insula, precuneus, striatum, and amygdala while listening to their own baby-cry as compared to formula-feeding mothers. For both breastfeeding and formula-feeding mothers, greater activations in the right superior frontal gyrus and amygdala were associated with higher maternal sensitivity at 3-4 months postpartum. Results suggest links between breastfeeding and greater response to infant cues in brain regions implicated in maternal-infant bonding and empathy during the early postpartum. Such brain activations may facilitate greater maternal sensitivity as infants enter their social world. Kim P, Feldman R, Mayes LC, Eicher V, Thompson N, Leckman JF, Swain JE. Breastfeeding, brain activation to own infant cry, and maternal sensitivity. J Child Psychol Psychiatry. 2011 Aug; 52(8): 907-915.

Caregiver and Self-Report of Mental Health Symptoms in 9-Year Old Children with Prenatal Cocaine Exposure The objective of this study was to assess the effect of prenatal cocaine exposure on mental health symptoms in 9-year old children controlling for potential confounders. Three hundred and thirty two children (170 prenatally cocaine-exposed (PCE), 162 non cocaine-exposed (NCE) were assessed using self (Dominic Interactive; DI) and caregiver report (Child Behavior Checklist; CBCL). Higher levels of PCE were associated with caregiver report of clinically elevated aggressive and delinquent behavior. With each increased unit of PCE, children were 1.3 times more likely to be rated as aggressive (OR=1.30, 95% CI: 1.02-1.67, $p<0.04$). For each increased unit of PCE, girls were 2 times more likely to be rated as having delinquent behavior (OR=2.08, 95% CI: 1.46-2.96, $p<0.0001$). PCE status was also associated with increased odds of delinquent behavior (OR=2.41; 95% CI: 1.16-4.97, $p=0.02$), primarily due to the increased risk among girls with PCE. While girls with PCE status were 7 times more likely than NCE girls to have delinquent behaviors (OR=7.42; 95% CI: 2.03-27.11, $p<0.002$) boys with PCE did not demonstrate increased risk (OR=0.98; 95% CI: 0.36-2.65, $p>0.97$). Foster or adoptive parents were more likely to rate their PCE children as having more thought problems, inattention, delinquent behavior, aggression, externalizing and overall problems ($p<0.05$) than biologic mothers or relative caregivers. Higher 2nd trimester tobacco exposure was associated with increased odds of caregiver reported anxiety (OR=1.73; 95% CI 1.06-2.81, $p<0.03$) and marijuana exposure increased the odds of thought problems (OR=1.68; 95% CI 1.01-2.79, $p<0.05$). Children with PCE self-reported fewer symptoms of oppositional defiant disorder (ODD) compared to NCE children (OR=0.44, 95% CI: 0.21-0.92, $p<0.03$). Greater tobacco exposure was associated with increased odds of child reported ODD (OR=1.24; 95% CI 1.03-1.78, $p<0.03$). Higher PCE was associated with disruptive behaviors including aggression and delinquent behavior among girls by caregiver report, but not child report. These findings highlight the need for early behavioral assessment using multiple informants in multi-risk children. McLaughlin AA, Minnes S, Singer LT, Min M, Short EJ, Scott TL, Satayathum S. Caregiver and self-report of mental health symptoms in 9-year old children with prenatal cocaine exposure. Neurotoxicol Teratol. 2011 Sep-Oct; 33(5): 582-591.

Neurochemical Alterations in Adolescent Chronic Marijuana Smokers: A Proton MRS Study Converging evidence from neuroimaging and neuropsychological studies indicates that heavy marijuana use is associated with cingulate dysfunction. However, there has been limited human data documenting in vivo biochemical brain changes after chronic marijuana exposure. Previous proton magnetic resonance spectroscopy studies have demonstrated reduced basal ganglia glutamate and dorsolateral prefrontal cortex N-acetyl aspartate levels in adult chronic

marijuana users. Similar studies have not been reported in adolescent populations. The present study used proton magnetic resonance spectroscopy to determine whether reductions in glutamate, N-acetyl aspartate and/or other proton metabolite concentrations would be found in the anterior cingulate cortex (ACC) of adolescent marijuana users compared with non-using controls. Adolescent marijuana users ($N = 17$; average age 17.8 years) and similarly aged healthy control subjects ($N = 17$; average age 16.2 years) were scanned using a Siemens 3T Trio MRI system. Proton magnetic resonance spectroscopy data were acquired from a 22.5 mL voxel positioned bilaterally within the ACC. Spectra were fitted using commercial software and all metabolite integrals were normalized to the scaled unsuppressed water integral. Analysis of variance and analysis of covariance were performed to compare between-group metabolite levels. The marijuana-using cohort showed statistically significant reductions in anterior cingulate glutamate (− 15%, $p < 0.01$), N-acetyl aspartate (− 13%, $p = 0.02$), total creatine (− 10%, $p < 0.01$) and *myo*-inositol (− 10%, $p = 0.03$). Within-voxel tissue-type segmentation did not reveal any significant differences in gray/white matter or cerebrospinal fluid content between the two groups. The reduced glutamate and N-acetyl aspartate levels in the adolescent marijuana-using cohort are consistent with precedent human ^{1}H MRS data, and likely reflect an alteration of anterior cingulate glutamatergic neurotransmission and neuronal integrity within these individuals. The reduced total creatine and *myo*-inositol levels observed in these subjects might infer altered ACC energetic status and glial metabolism, respectively. These results expand on previous functional MRI data reporting altered cingulate function in individuals with marijuana-abuse. Prescot AP. Locatelli AE, Renshaw PF, Yurgelun-Todd DA. Neurochemical alterations in adolescent chronic marijuana smokers: A proton MRS study. Neuroimage. 2011 Jul 1; 57(1): 69-75.

A Longitudinal Study of Substance Use and Violent Victimization in Adulthood Among a Cohort of Urban African Americans This article examines the effects of experiencing violent victimization in young adulthood on pathways of substance use from adolescence to mid-adulthood. Data come from four assessments of an African American community cohort followed longitudinally from age 6 to 42. The cohort lived in the urban, disadvantaged Woodlawn neighborhood of Chicago in 1966. All first graders from the public and parochial schools were asked to participate (N = 1,242). Dependent variables - alcohol, marijuana, and cocaine use - came from self-reports at age 42. Young adult violent victimization was reported at age 32, as were acts of violence, substance use, social integration, and socioeconomic resources. First grade risk factors came from mothers' and teachers' reports. Adolescent substance use was self-reported. Structural equation models indicate a pathway from adolescent substance use to young adult violent victimization for females and those who did not grow up in extreme poverty (betas ranging from .15 to .20, $p < .05$). In turn, experiencing violent victimization in young adulthood increased alcohol, marijuana, and cocaine use, yet results varied by gender and early poverty status (betas ranging from .12 to .15, $p < .05$). Violent victimization appears to play an important role in perpetuating substance use among the African American population. However, within-group variations are evident, identifying those who are not raised in extreme poverty as the most negatively affected by violence. Doherty EE, Robertson JA, Green KM, Fothergill KE, Ensminger ME. A longitudinal study of substance use and violent victimization in adulthood among a cohort of urban African Americans. Addiction. 2011 Sep 21. [Epub ahead of print].

Gender Effects on Amygdala Morphometry in Adolescent Marijuana Users Adolescent developments in limbic structures and the endogenous cannabinoid system suggest that teenagers may be more vulnerable to the negative consequences of marijuana use. This study examined the relationships between amygdala volume and internalizing symptoms in teenaged chronic marijuana users. Participants were 35 marijuana users and 47 controls ages 16-19 years. Exclusions included psychiatric (e.g., mood and anxiety) or neurologic disorders. Substance use, internalizing (anxiety/depression) symptoms and brain scans were collected after 28 days of monitored abstinence. Reliable raters manually traced amygdala and intracranial volumes on high-resolution magnetic resonance images. Female marijuana users had larger right amygdala volumes and more internalizing symptoms than female controls, after covarying head size, alcohol, nicotine and other substance use ($p<0.05$), while male users had similar volumes as male controls. For female controls and males, worse mood/anxiety was linked to smaller right amygdala volume ($p<0.05$), whereas more internalizing problems was associated with bigger right amygdala in female marijuana users. Gender interactions may reflect marijuana-related interruptions to sex-specific neuromaturational processes and staging. Subtle amygdala development abnormalities may underlie particular vulnerabilities to sub-diagnostic depression and anxiety in teenage female marijuana users. McQueeny T, Padula CB, Price J, Medina KL, Logan P, Tapert SF. Gender effects on amygdala morphometry in adolescent marijuana users. Behav Brain Res. 2011 Oct 10; 224(1): 128-134.

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 24 h 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. 2011 Sep 28. [Epub ahead of print].

Diffusion-Tensor Imaging Assessment of White Matter Maturation in Childhood and Adolescence The purpose of this study was to test a first hypothesis that fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values continue to change in late childhood and adolescence and a second hypothesis that less mature white matter (WM) regions have a higher rate of change than WM regions that are relatively more mature. Eighty-seven healthy children (50 girls, 37 boys; mean age, 11.2 ± 3.6 years; range, 4.2-17.7 years) underwent six-direction diffusion-tensor imaging with a 3-T MRI system. Three neuroradiologists independently drew

regions of interest in 10 WM regions and measured FA and ADC values. To test the first hypothesis, the authors correlated these values with subject age by linear regression analysis ($p < 0.05$). To test the second hypothesis, they determined whether regions with lower FA and higher ADC in the 4- to 7-year old group had a higher slope of FA increase and ADC decrease over the entire age range. For this assessment, they used linear regression analysis ($p < 0.05$) and curve fitting. In the test of the first hypothesis, increases in FA with age were noted in all WM regions and were statistically significant in six regions. Decreases in ADC values with age were noted in all brain regions except the genu of the corpus callosum. In all other regions except the splenium of the corpus callosum, the decreases were statistically significant. In the test of the second hypothesis, the relation between FA in the 4- to 7-year-old subjects and the FA increase in the entire sample was best described with a linear equation. The rate of age-related FA increase tended to be greater with lower initial FA ($r = -0.384$, $p = 0.271$). The relation between ADC in the 4- to 7-year-old subjects and ADC decrease in the entire population was best described with a second-order equation. The rate of age-related ADC decrease tended to be greater with higher initial ADC ($r = 0.846$, $p = 0.001$). For ADC values of 100 or less at age 4-7 years, the rate of ADC change with age tended to be decrease as initial ADC increased. In general, both hypotheses were verified. Overall, FA values continue to increase and ADC values continue to decrease during childhood and adolescence. The most rapid changes were found in WM regions that were least mature in the first few years of the study period. Moon WJ, Provenzale JM, Sarikaya B, Ihn YK, Morlese J, Chen S, DeBellis MD. Diffusion-tensor imaging assessment of white matter maturation in childhood and adolescence. AJR Am J Roentgenol. 2011 Sep; 197(3): 704-712.

Annotating Individual Human Genomes Advances in DNA sequencing technologies have made it possible to rapidly, accurately and affordably sequence entire individual human genomes. As impressive as this ability seems, however, it will not likely amount to much if one cannot extract meaningful information from individual sequence data. Annotating variations within individual genomes and providing information about their biological or phenotypic impact will thus be crucially important in moving individual sequencing projects forward, especially in the context of the clinical use of sequence information. In this paper the authors consider the various ways in which one might annotate individual sequence variations and point out limitations in the available methods for doing so. It is arguable that, in the foreseeable future, DNA sequencing of individual genomes will become routine for clinical, research, forensic, and personal purposes. The authors therefore also consider directions and areas for further research in annotating genomic variants. Torkamani A, Scott-Van Zeeland AA, Topol EJ, Schork NJ. Annotating individual human genomes. Genomics. 2011 Oct; 98(4): 233-241.

Reduced Cortical Gray Matter Volume in Male Adolescents with Substance and Conduct Problems Boys with serious conduct and substance problems (Antisocial Substance Dependence (ASD)) repeatedly make impulsive and risky decisions in spite of possible negative consequences. Because prefrontal cortex (PFC) is involved in planning behavior in accord with prior rewards and punishments, structural abnormalities in PFC could contribute to a person's propensity to make risky decisions. The authors acquired high-resolution structural images of 25 male ASD patients (ages 14-18 years) and 19 controls of similar ages using a 3T MR system. They conducted whole-brain voxel-based morphometric analysis ($p<0.05$, corrected for multiple comparisons at whole-brain cluster-level) using Statistical Parametric Mapping version-5 and tested group differences in regional gray matter (GM) volume with analyses of covariance, adjusting for total GM volume, age, and IQ; they further adjusted between-group analyses for

ADHD and depression. As secondary analyses, they tested for negative associations between GM volume and impulsivity within groups and separately, GM volume and symptom severity within patients using whole-brain regression analyses. The data showed that ASD boys had significantly lower GM volume than controls in left dorsolateral PFC (DLPFC), right lingual gyrus and bilateral cerebellum, and significantly higher GM volume in right precuneus. Left DLPFC GM volume showed negative association with impulsivity within controls and negative association with substance dependence severity within patients. ASD boys show reduced GM volumes in several regions including DLPFC, a region highly relevant to impulsivity, disinhibition, and decision-making, and cerebellum, a region important for behavioral regulation, while they showed increased GM in precuneus, a region associated with self-referential and self-centered thinking. Dalwani M, Sakai JT, Mikulich-Gilbertson SK, Tanabe J, Raymond K, McWilliams SK, Thompson LL, Banich MT, Crowley TJ. Reduced cortical gray matter volume in male adolescents with substance and conduct problems. Drug Alcohol Depend. 2011 Nov 1; 118(2-3): 295-305.

Risky Decisions and Their Consequences: Neural Processing by Boys with Antisocial Substance Disorder Adolescents with conduct and substance problems ("Antisocial Substance Disorder" (ASD)) repeatedly engage in risky antisocial and drug-using behaviors. The authors hypothesized that, during processing of risky decisions and resulting rewards and punishments, brain activation would differ between abstinent ASD boys and comparison boys. They compared 20 abstinent adolescent male patients in treatment for ASD with 20 community controls, examining rapid event-related blood-oxygen-level-dependent (BOLD) responses during functional magnetic resonance imaging. In 90 decision trials participants chose to make either a cautious response that earned one cent, or a risky response that would either gain 5 cents or lose 10 cents; odds of losing increased as the game progressed. They also examined those times when subjects experienced wins, or separately losses, from their risky choices. They contrasted decision trials against very similar comparison trials requiring no decisions, using whole-brain BOLD-response analyses of group differences, corrected for multiple comparisons. During decision-making ASD boys showed hypoactivation in numerous brain regions robustly activated by controls, including orbitofrontal and dorsolateral prefrontal cortices, anterior cingulate, basal ganglia, insula, amygdala, hippocampus, and cerebellum. While experiencing wins, ASD boys had significantly less activity than controls in anterior cingulate, temporal regions, and cerebellum, with more activity nowhere. During losses ASD boys had significantly more activity than controls in orbitofrontal cortex, dorsolateral prefrontal cortex, brain stem, and cerebellum, with less activity nowhere. The study concludes that adolescent boys with ASD had extensive neural hypoactivity during risky decision-making, coupled with decreased activity e authoduring reward and increased activity during loss. These neural patterns may underlie the dangerous, excessive, sustained risk-taking of such boys. The findings suggest that the dysphoria, reward insensitivity, and suppressed neural activity observed among older addicted persons also characterize youths early in the development of substance use disorders. Crowley TJ, Dalwani MS, Mikulich-Gilbertson SK, Du YP, Lejuez CW, Raymond KM, Banich MT. Risky decisions and their consequences: neural processing by boys with Antisocial Substance Disorder. PLoS One. 2010 Sep 22; 5(9): e12835.

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 peri-adolescent (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 study concludes that 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 peri-adolescents 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.

EPIDEMIOLOGY AND ETIOLOGY RESEARCH

Characteristics Associated with the Diversion of Controlled Medications among Adolescents The objective of this study was to estimate the lifetime prevalence of diversion (i.e., trading, selling, giving away or loaning) of four classes of controlled medications (pain, stimulant, anti-anxiety, and sleeping) among adolescents, and to identify demographic and behavioral characteristics of adolescents who divert their own controlled medications. A web-based survey was self-administered by 2744 secondary school students from two southeastern Michigan school districts in 2009-2010. The sample consisted of 51% females, 65% Whites, 29% African-Americans, 4% Asians, 1% Hispanics and 1% from other racial categories. Thirty-three percent of the students had ever been prescribed at least one controlled pain, stimulant, anti-anxiety, or sleeping medication. Approximately 13.8% (n=117) of lifetime prescribed users of controlled medications (n=848) had ever traded, sold, given away or loaned their medications. Multiple logistic regression analyses indicated that being approached to divert medications, nonmedical use of prescription medications, externalizing behaviors, and being non-White were significantly associated with the diversion of controlled medications. Multiple logistic regression analysis indicated that the odds of substance use and abuse for lifetime prescribed users who diverted their controlled medications were significantly greater than prescribed users who never diverted. The findings indicate that approximately one in seven prescribed users had diverted their controlled medications in their lifetimes. Being approached to divert medications and substance use are more prevalent among adolescents who diverted their controlled medications. Careful assessments, diligent prescribing and monitoring of controlled medications, and continual patient education could be useful in reducing medication diversion. McCabe S, West B, Teter C, Ross-Durow P, Young A, Boyd C. Characteristics associated with the diversion of controlled medications among adolescents. Drug Alcohol Depend. 2011; 118 (2-3): 452-458.

Medical Misuse of Controlled Medications among Adolescents The objectives of this study were to determine the past-year medical misuse prevalence for 4 controlled medication classes (pain, stimulant, sleeping, and antianxiety) among adolescents, and to assess substance use outcomes among adolescents who report medical misuse. A Web-based survey was self-administered by 2744 secondary school students in 2009-2010. The study setting comprised two southeastern Michigan school districts. The participant sample had a mean age of 14.8 years and was 51.1% female. The racial/ethnic distribution was 65.0% white, 29.5% African American, 3.7% Asian, 1.3% Hispanic, and 0.5% other. Past-year medical use and misuse of 4 controlled medication classes were the main outcome measures. Eighteen percent of the sample reported past-year medical use of at least 1 prescribed controlled medication. Among past-year medical users, 22.0% reported misuse of their controlled medications, including taking too much, intentionally getting high or using to increase alcohol or other drug effects. Medical misusers were more likely than nonmisusers to divert their controlled medications and to abuse other substances. The odds of a positive screening result for drug abuse were substantially higher among medical misusers (adjusted odds ratio, 7.8; 95% confidence interval, 4.3-14.2) compared with medical users who used their controlled medications appropriately. The odds of drug abuse did not differ between medical users who used their controlled medications appropriately and nonusers. The authors conclude that most adolescents who used controlled medications took their medications appropriately. Substance use and diversion of controlled medications were more prevalent among adolescents who misused their controlled medications. Careful therapeutic monitoring could reduce medical misuse and diversion of controlled medications among adolescents. McCabe S, West B, Cranford J, Ross-Durow P, Young A, Teter C, Boyd C.

Medical misuse of controlled medications among adolescents. Arch Pediatr Adolesc Med. 2011; 165 (8): 729-735.

Alternate Routes of Administration and Risk for HIV Among Prescription Opioid Abusers Route of administration is an important contributor to the adverse health consequences of prescription medication abuse. The current study examines characteristics associated with non-oral routes of administration among a large sample of prescription opioid abusers and explores needle-related human immunodeficiency virus (HIV) risk behaviors as well. In the study, 791 opioid abusers completed a one-time structured interview, including complete histories of illicit and prescription drug abuse and route of drug administration. The most common method of pill use was oral (91%), followed by intranasal (53.1%), injection (23.8%), and smoking (14.5%). The youngest prescription opioid abusers, ages 18-24, displayed significantly higher odds of using alternate routes of administration and of reusing nonsterile needles for injection. HIV prevention programming should be developed for young prescription opioid injectors. Surratt H, Kurtz S, Cicero T. Alternate routes of administration and risk for HIV among prescription opioid abusers. J Addict Dis. 2011; 30(4): 334-341.

Initiation into Prescription Opioid Misuse Amongst Young Injection Drug Users Prescription opioids are the most frequently misused class of prescription drugs amongst young adults. Initiation into prescription opioid misuse is an important public health concern since opioids are increasingly associated with drug dependence and fatal overdose. Descriptive data about initiation into prescription opioid misuse amongst young injection drug users (IDUs) are scarce. An exploratory qualitative study was undertaken to describe patterns of initiation into prescription opioid misuse amongst IDUs aged 16-25 years. Those young IDUs who had misused a prescription drug at least three times in the past three months were recruited during 2008 and 2009 in Los Angeles (n=25) and New York (n=25). Informed by an ethno-epidemio-logical approach, descriptive data from a semi-structured interview guide were analysed both quantitatively and qualitatively. Initiation into prescription opioid misuse was facilitated by easy access to opioids via participant's own prescription, family, or friends, and occurred earlier than misuse of other illicit drugs, such as heroin. Nearly all transitioned into sniffing opioids, most injected opioids, and many initiated injection drug use with an opioid. Motives for transitions to sniffing and injecting opioids included obtaining a more potent high and/or substituting for heroin; access to multiple sources of opioids was common amongst those who progressed to sniffing and injecting opioids. Prescription opioid misuse was a key feature of trajectories into injection drug use and/or heroin use amongst this sample of young IDUs. A new pattern of drug use may be emerging whereby IDUs initiate prescription opioid misuse before using heroin. Lankenau S, Teti M, Silva K, Bloom J, Harocopos A, Treese M. Initiation into prescription opioid misuse amongst young injection drug users. Int J Drug Policy. 2011.

Reporting Bias in the Association Between Age at First Alcohol use and Heavy Episodic Drinking Given the weight placed on retrospective reports of age at first drink in studies of later drinking-related outcomes, it is critical that its reliability be established and possible sources of systematic bias be identified. The overall aim of the current study was to explore the possibility that the estimated magnitude of association between early age at first drink and problem alcohol use may be inflated in studies using retrospectively reported age at alcohol use onset. The sample was comprised of 1,716 participants in the Missouri Adolescent Female Twin Study who reported an age at first drink in at least 2 waves of data collection (an average of 4 years apart). Difference in reported age at first drink at Time 2 versus Time 1 was categorized as 2 or more

years younger, within 1 year (consistent), or 2 or more years older. The strength of the association between age at first drink and peak frequency of heavy episodic drinking (HED) at Time 1 was compared with that at Time 2. The association between reporting pattern and peak frequency of HED was also examined. A strong association between age at first drink and HED was found for both reports, but it was significantly greater at Time 2. Just over one-third of participants had a 2 year or greater difference in reported age at first drink. The majority of inconsistent reporters gave an older age at Time 2 and individuals with this pattern of reporting engaged in HED less frequently than consistent reporters. The low rate of HED in individuals reporting an older age at first drink at Time 2 suggests that the upward shift in reported age at first drink among early initiates is most pronounced for light drinkers. Heavy drinkers may therefore be overrepresented among early onset users in retrospective studies, leading to inflated estimates of the association between early age at initiation and alcohol misuse. Sartor C, Bucholz K, Nelson E, Madden P, Lynskey M, Heath A. Reporting bias in the association between age at first alcohol use and heavy episodic drinking. Alcohol Clin Exp Res. 2011; 35(8): 1418-1425.

Estimated Effect Of Prenatal Cocaine Exposure On Examiner-Rated Behavior At Age 7 Years Prenatal cocaine exposure has been linked to increased child behavior difficulties in some studies but not others. The primary aim of this study was to estimate the relationship between in utero cocaine exposure and child behavioral functioning at age 7 years with ratings made by blinded examiners during a structured testing session. A second aim was to examine whether caregiver drug use and psychological problems might mediate suspected relationships between prenatal cocaine exposure and aspects of examiner-rated behavior. Four hundred and seven children (212 cocaine-exposed, 195 non-exposed) participating in the longitudinal Miami Prenatal Cocaine Study (MPCS) were rated with regard to their behavior during a neuropsychological assessment conducted at age 7 years. Raters were trained research psychometricians blinded to drug exposure status. Individual behavioral items were summarized and the cocaine-behavior relationship was estimated within the context of latent variable modeling, using Mplus software. Two latent variables, Behavioral Regulation and Sociability, were derived via exploratory latent structure analysis with promax rotation. Prenatal cocaine exposure, statistically controlling for child sex, test age, and prenatal exposure to alcohol, tobacco, and marijuana, was associated with Behavioral Regulation (estimated slope ß=-0.25; 95% CI=-0.48, -0.02; p=0.04) but not Sociability (estimated slope ß=-0.03; 95% CI=-0.26, 0.20; p=0.79). Neither postnatal drug use by caregivers nor the severity of their psychological problems at age 5 follow-up predicted levels of child Behavioral Regulation or Sociability at age 7 years (p>0.10). Examiner ratings of child behavior at age 7 revealed less optimal behavioral regulation for prenatally cocaine-exposed compared to non-exposed children, in contrast with what had been previously found from parent-report data. This evidence highlights the potential value of trained observers in assessing behavioral outcomes of children exposed in utero to drugs and other toxicants. Accornero V, Anthony J, Morrow C, Xue L, Mansoor E, Johnson A, McCoy C, Bandstra E. Estimated effect of prenatal cocaine exposure on examiner-rated behavior at age 7 years. Neurotoxicol Teratol. 2011; 33 (3): 370-378.

Substance-Related Traffic-Risk Behaviors Among College Students Drunk driving is a major public health concern, but drugged driving has received little attention. This study examines drugged driving and riding with a drugged driver in a college student sample, in terms of prevalence, age-related trends, race/sex differences, overlap with drunk driving, and risk for alcohol and marijuana dependence. Students (N=1194) ages 19-22 were interviewed annually for 3years about past-year frequency of drugged driving, riding with a drugged/drunk driver,

drunk driving, access to a car, and alcohol/drug dependence. Annual follow-up rates were excellent (88-91%). Repeated measures analyses were conducted using generalized estimating equations (GEE). One in six (17% (wt)) 19-year-olds with access to a car drove drugged in the past year; prevalence remained stable through age 22. Drugged driving was more prevalent among males ($p<.001$) and whites ($p<.01$). Riding with a drugged driver varied by race and sex (overall prevalence 28% (wt) at age 19), was stable from age 19 to 21, and decreased by age 22 ($p<.05$). Annually, half of drugged drivers also drove drunk (ranges between 47% and 60%). Both drugged and drunk driving were independently associated with increased risk for alcohol dependence, holding constant age, sex, and race. Drunk driving did not add to the risk for marijuana dependence in the context of drugged driving. The prevalence of drugged driving is similar to drunk driving among college students. Both are strongly associated with underlying alcohol and drug dependence. Prevention and treatment implications are discussed. Arria A, Caldeira K, Vincent K, Garnier-Dykstra L, O 'Grady K. Substance-related traffic-risk behaviors among college students. Drug Alcohol Depend. 2011.

A Genome-Wide Association Study of DSM-IV Cannabis Dependence Despite twin studies showing that 50-70% of variation in DSM-IV cannabis dependence is attributable to heritable influences, little is known of specific genotypes that influence vulnerability to cannabis dependence. The authors conducted a genome-wide association study of DSM-IV cannabis dependence. Association analyses of 708 DSM-IV cannabis-dependent cases with 2346 cannabis-exposed non-dependent controls was conducted using logistic regression in PLINK. None of the 948,142 single nucleotide polymorphisms met genome-wide significance (P at E-8). The lowest P values were obtained for polymorphisms on chromosome 17 (rs1019238 and rs1431318, P values at E-7) in the ANKFN1 gene. While replication is required, this study represents an important first step toward clarifying the biological underpinnings of cannabis dependence. Agrawal A, Lynskey M, Hinrichs A, Grucza R, Saccone S, Krueger R, Neuman R, Howells W, Fisher S, Fox L, Cloninger R, Dick D, Doheny K, Edenberg H, Goate A, Hesselbrock V, Johnson E, Kramer J, Kuperman S, Nurnberger J, Pugh E, Schuckit M, Tischfield J, Tischfield J, Rice J, Bucholz K, Bierut L. A genome-wide association study of dsm-iv cannabis dependence. Addict Biol. 2011; 16(3): 1369-1600.

Probability and Predictors of Transition From First Use To Dependence On Nicotine, Alcohol, Cannabis, and Cocaine: Results of the National Epidemiologic Survey On Alcohol and Related Conditions NESARC This study aims to estimate general and racial-ethnic specific cumulative probability of developing dependence among nicotine, alcohol, cannabis or cocaine users, and to identify predictors of transition to substance dependence. Analyses were done for the subsample of lifetime nicotine (n=15,918), alcohol (n=28,907), cannabis (n=7389) or cocaine (n=2259) users who participated in the first and second wave of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). Discrete-time survival analyses were implemented to estimate the cumulative probability of transitioning from use to dependence and to identify predictors of transition to dependence. The cumulative probability estimate of transition to dependence was 67.5% for nicotine users, 22.7% for alcohol users, 20.9% for cocaine users, and 8.9% for cannabis users. Half of the cases of dependence on nicotine, alcohol, cannabis and cocaine were observed approximately 27, 13, 5 and 4 years after use onset, respectively. Significant racial-ethnic differences were observed in the probability of transition to dependence across the four substances. Several predictors of dependence were common across the four substances assessed. Transition from use to dependence was highest for nicotine users, followed by cocaine, alcohol and cannabis users. Transition to cannabis or

cocaine dependence occurred faster than transition to nicotine or alcohol dependence. The existence of common predictors of transition dependence across substances suggests that shared mechanisms are involved. The increased risk of transition to dependence among individuals from minorities or those with psychiatric or dependence comorbidity highlights the importance of promoting outreach and treatment of these populations. Lopez-Quintero C, Perez de los Cobos J, Hasin DS, Okuda M, Wang S, Grant BF, Blanco C. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: Results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Drug Alcohol Depend. 2011; 115(2 - Jan): 120-130.

Nicotine Withdrawal-Induced Negative Affect is a Function of Nicotine Dependence and Not Liability to Depression or Anxiety Individuals who quit smoking frequently experience symptoms of anxiety and/or depression. It is not clear whether these symptoms index liability to negative affect generally or whether such symptoms are a function of nicotine withdrawal and are thus indexed by nicotine dependence (ND). A population-based sample of twins (N = 4,777 individuals) reported their lifetime history of psychopathology, ND, and symptoms of anxiety and depression experienced after attempts to quit smoking. Co-twin phenotype was used to predict withdrawal-induced symptoms of negative affect and to test whether genetic factors influence liability to these symptoms. Co-twin & apos's ND was significantly associated with nicotine withdrawal-induced symptoms of anxiety and depression. Furthermore, monozygotic co-twins more strongly predicted outcome than did dizygotic co-twins, indicating that genetic factors contribute to risk. Co-twins & apos; history of psychopathology did not predict outcome, suggesting that liability to withdrawal-induced negative affect is independent of a liability to negative affect outside the context of nicotine withdrawal. These findings indicate that symptoms of anxiety or depression experienced in the context of nicotine withdrawal are best conceptualized as a component of the withdrawal syndrome, with the severity of symptoms indexed by level of ND. Genetic influences underlying ND contribute to the liability to these symptoms. Though psychopathology might be indirectly related to withdrawal-induced symptoms through its correlation with ND, it is not directly predictive of withdrawal symptoms. Edwards AC, Kendler KS. Nicotine withdrawal-induced negative affect is a function of nicotine dependence and not liability to depression or anxiety. Nicotine Tob Res. 2011; 13(8): 677-685.

Associations Between Herpes Simplex Virus Type 2 and HCV With HIV among Injecting Drug users in New York City: The Current Importance of Sexual Transmission of HIV The authors examined relationships between herpes simplex virus type 2 (HSV-2), a biomarker for sexual risk, and HCV, a biomarker for injecting risk, with HIV among injecting drug users (IDUs) who began injecting after large-scale expansion of syringe exchange programs in New York City. They recruited 337 heroin and cocaine users who began injecting in 1995 or later from persons entering drug detoxification. They administered a structured interview covering drug use and HIV risk behavior and collected serum samples for HIV, HCV, and HSV-2 testing. HIV prevalence was 8%, HSV-2 39%, and HCV 55%. They found a significant association between HSV-2 and HIV (odds ratio [OR] = 7.9; 95% confidence interval [CI] = 2.9, 21.4) and no association between HCV and HIV (OR = 1.14; 95% CI = 0.5, 2.6). Black IDUs had the highest prevalence of HSV-2 (76%) and HIV (24%) but the lowest prevalence of HCV (34%). The authors conclude that most HIV infections among these IDUs occurred through sexual transmission. The relative importance of injecting versus sexual transmission of HIV may be critical for understanding racial/ethnic disparities in HIV infection. Des Jarlais D, Arasteh K, McKnight C, Hagan H, Perlman D, Semaan S. Associations between herpes simplex virus type 2

and HCV with HIV among injecting drug users in New York City: The Current Importance Of Sexual Transmission Of HIV. Am J Public Health. 2011; 101(7): 1277-1283.

Individual, Social, And Environmental Factors Associated With Initiating Methamphetamine Injection: Implications For Drug Use And HIV Prevention Strategies The purpose of this study was to determine the incidence and predictors of initiating methamphetamine injection among a cohort of injection drug users (IDU). The authors conducted a longitudinal analysis of IDUs participating in a prospective study between June 2001 and May 2008 in Vancouver, Canada. IDUs who had never reported injecting methamphetamine at the study's commencement were eligible. They used Cox proportional hazards models to identify the predictors of initiating methamphetamine injection. The outcome was time to first report of methamphetamine injection. Time-updated independent variables of interest included sociodemographic characteristics, drug use patterns, and social, economic and environmental factors. Of 1317 eligible individuals, the median age was 39.9 and 522 (39.6%) were female. At the study's conclusion, 200 (15.2%) participants had initiated injecting methamphetamine (incidence density: 4.3 per 100 person-years). In multivariate analysis, age (adjusted hazard ratio [aHR]: 0.96 per year older, 95%CI: 0.95-0.98), female sex (aHR: 0.58, 95%CI: 0.41-0.82), sexual abuse (aHR: 1.63, 95%CI: 1.18-2.23), using drugs in Vancouver 's drug scene epicentre (aHR: 2.15 95%CI: 1.49-3.10), homelessness (aHR: 1.43, 95%CI: 1.01-2.04), non-injection crack cocaine use (aHR: 2.06, 95%CI: 1.36-3.14), and non-injection methamphetamine use (aHR: 3.69, 95%CI: 2.03-6.70) were associated with initiating methamphetamine injection. The authors observed a high incidence of methamphetamine initiation, particularly among young IDU, stimulant users, homeless individuals, and those involved in the city's open drug scene. These data should be useful for the development of a broad set of interventions aimed at reducing initiation into methamphetamine injection among IDU. Marshall B, Wood E, Shoveller J, Buxton J, Montaner J, Kerr T. Individual, social, and environmental factors associated with initiating methamphetamine injection: Implications for drug use and HIV prevention strategies. Prev Sci. 2011; 12(2): 173-180.

Dramatic Decline In The HIV-1 RNA Level Over Calendar Time In A Large Urban HIV Practice The authors have previously shown that as antiretroviral therapy has improved over time since 1995-1996, the likelihood of achieving virologic suppression has also improved. Antiretroviral therapy and antiretroviral therapy guidelines have continued to evolve, and they wished to determine the trend in human immunodeficiency virus (HIV-1) RNA levels over time in HIV-infected persons receiving care in our large urban HIV clinical practice in Baltimore, Maryland. The HIV-1 RNA level was assessed each year from 1996 through 2010 at the date closest to 1 July for all patients in care and followed up in the Johns Hopkins HIV Clinical Cohort. The clinic population's median HIV-1 RNA level and stratified threshold levels were plotted. The demographic characteristics of the population were also assessed over time. From 1996 (shortly after highly active antiretroviral therapy [HAART] was introduced) to 2010, the median HIV-1 RNA level decreased from 10,400 to <200 copies/mL. The proportion of patients with an HIV-1 RNA level >500 copies/mL decreased from 75% to only 16% during this same period. The population itself became older, had a higher proportion of women, and a lower proportion of patients with injection drug use as a transmission risk, but it was geographically stable. There was an increase in HAART use over time. These results demonstrate the remarkable impact of increased use of and improved management with HAART in this urban HIV-infected population. Moore R, Bartlett J. Dramatic decline in the HIV-1 RNA level over calendar time in a large urban HIV practice. Clin Infect Dis. 2011; 53(6): 600-604.

Incarceration Predicts Virologic Failure For HIV-Infected Injection Drug Users Receiving Antiretroviral Therapy Incarceration may lead to interruptions in antiretroviral therapy (ART) for persons receiving treatment for human immunodeficiency virus (HIV) infection. The authors assessed whether incarceration and subsequent release were associated with virologic failure for injection drug users (IDUs) who were previously successfully treated with ART. ALIVE is a prospective, community-based cohort study of IDUs in Baltimore, Maryland. IDUs receiving ART during 1998-2009 who successfully achieved an HIV RNA level below the limit of detection (<400 copies/mL) were followed up for development of virologic failure at the subsequent semiannual study visit. Logistic regression with generalized estimating equations was used to assess whether incarceration was independently associated with virologic failure. Of 437 HIV-infected IDUs who achieved undetectable HIV RNA for at least one study visit, 69% were male, 95% were African-American, and 40% reported at least one incarceration during follow-up. Virologic failure occurred at 26.3% of visits after a median of 6 months since achieving undetectable HIV RNA. In multivariate analysis accounting for demographic characteristics, drug use, and HIV disease stage, brief incarceration was strongly associated with virologic failure (adjusted odds ratio, 7.7; 95% confidence interval, 3.0-19.7), although incarceration lasting >30 days was not (odds ratio, 1.4; 95% confidence interval, .8-2.6). Among IDUs achieving viral suppression while receiving ART, virologic failure occurred with high frequency and was strongly associated with brief incarceration. Efforts should be made to ensure continuity of care both during and after incarceration to improve treatment outcomes and prevent viral resistance in this vulnerable population. Westergaard R, Kirk G, Richesson D, Galai N, Mehta S. Incarceration predicts virologic failure for hiv-infected injection drug users receiving antiretroviral therapy. Clin Infect Dis. 2011; 53(7): 725-731.

High Prevalence Of Childhood Emotional, Physical And Sexual Trauma Among A Canadian Cohort Of HIV-Seropositive Illicit Drug Users The psychosocial impacts of various types of childhood maltreatment on vulnerable illicit drug-using populations remain unclear. The authors examined the prevalence and correlates of antecedent emotional, physical and sexual abuse among a community-recruited cohort of adult HIV-seropositive illicit drug users. They estimated the prevalence of childhood abuse at baseline using data from the Childhood Trauma Questionnaire, a 28-item validated instrument used to retrospectively assess childhood maltreatment. Logistic regression was used to estimate relationships between sub-types of childhood maltreatment with various social-demographic, drug-using and clinical characteristics. Overall, 233 HIV-positive injection drug users (IDU) were included in the analysis, including 83 (35.6%) women. Of these, moderate or severe emotional childhood abuse was reported by 51.9% of participants, emotional neglect by 36.9%, physical abuse by 51.1%, physical neglect by 46.8% and sexual abuse by 41.6%. In multivariate analyses, emotional, physical and sexual abuses were independently associated with greater odds of recent incarceration. Emotional abuse and neglect were independently associated with a score of e16 on the Centre for Epidemiologic Studies Depression Scale. There was no association between any form of childhood maltreatment and clinical HIV variables, including viral load, CD4+ count and history of antiretroviral therapy use. These findings underscore the negative impact of childhood maltreatment on social functioning and mental health in later life. Given the substantial prevalence of childhood maltreatment among this population, there is a need for evidence-based resources to address the deleterious effect it has on the health and social functioning of HIV-positive IDU. Walton G, Co S, Milloy M, Qi J, Kerr T, Wood E. High Prevalence of childhood emotional, physical and sexual trauma among a canadian cohort of HIV-seropositive illicit drug users. AIDS Care. 2011; 23(6): 714-721.

Missing Data On The Estimation Of The Prevalence Of Accumulated Human Immunodeficiency Virus Drug Resistance In Patients Treated With Antiretroviral Drugs In North America Determination of the prevalence of accumulated antiretroviral drug resistance among persons infected with human immunodeficiency virus (HIV) is complicated by the lack of routine measurement in clinical care. By using data from 8 clinic-based cohorts from the North American AIDS Cohort Collaboration on Research and Design, drug-resistance mutations from those with genotype tests were determined and scored using the Genotypic Resistance Interpretation Algorithm developed at Stanford University. For each year from 2000 through 2005, the prevalence was calculated using data from the tested subset, assumptions that incorporated clinical knowledge, and multiple imputation methods to yield a complete data set. A total of 9,289 patients contributed data to the analysis; 3,959 had at least 1 viral load above 1,000 copies/mL, of whom 2,962 (75%) had undergone at least 1 genotype test. Using these methods, the authors estimated that the prevalence of accumulated resistance to 2 or more antiretroviral drug classes had increased from 14% in 2000 to 17% in 2005 ($P < 0.001$). In contrast, the prevalence of resistance in the tested subset declined from 57% to 36% for 2 or more classes. The authors' use of clinical knowledge and multiple imputation methods revealed trends in HIV drug resistance among patients in care that were markedly different from those observed using only data from patients who had undergone genotype tests. Abraham A, Lau B, Deeks S, Moore R, Zhang J, Eron J, Harrigan R, Gill M, Kitahata M, Klein M, Napravnik S, Rachlis A, Rodriguez B, Rourke S, Benson C, Bosch R, Collier A, Gebo K, Goedert J, Hogg R, Horberg M, Jacobson L, Justice A, Kirk G, Martin J, McKaig R, Silverberg M, Sterling T, Thorne J, Willig J, Gange S, Gange S. Missing data on the estimation of the prevalence of accumulated human immunodeficiency virus drug resistance in patients treated with antiretroviral drugs in north america. Am J Epidemiol. 2011; 174(6): 727-735.

Depressive Symptoms and Patterns Of Drug Use Among Street Youth Rates of depression among street youth are poorly characterized, particularly as they pertain to concurrent drug use. The authors sought to assess associations between drug type and degree of depression in this population. Between October 2005 and November 2007, data were collected from a cohort of street-recruited youth aged 14-26 residing in Vancouver, Canada, for the At-Risk Youth Study. Active drug users were classified by predominant substance of use: daily marijuana use, weekly cocaine/crack use, weekly crystal methamphetamine use, or weekly heroin use. Adjusted mean number of depressive symptoms (measured by the Center for Epidemiological Studies Depression [CES-D] scale) was compared among the four groups using multiple linear regression. Logistic regression was also used to assess adjusted odds of CES-D score e 22. Among 447 youth, mean CES-D score was the highest among heroin users (adjusted mean: 22.7; standard deviation [SD]:1.2), followed by crystal methamphetamine users (adjusted mean: 21.8; SD: 1.1), then cocaine and/or crack users (adjusted mean: 19.1; SD: 1.0), and finally, marijuana users (adjusted mean: 18.3; SD: 1.1), resulting in a difference that was significant among groups ($p < .001$). When compared with daily marijuana users, odds of CES-D score e 22 were higher among heroin users (adjusted odds ratio [AOR]: 2.64; 95% confidence interval [CI]: 1.39-4.99) and crystal methamphetamine users (AOR: 1.88; 95% CI: 1.04-3.42), but not among cocaine/crack users (AOR: 1.41; 95% CI: .79-2.52). To the authors' knowledge, this is the first report of drug use typologies and depression among street youth. Policymakers might heed the apparent vulnerability of heroin and crystal methamphetamine users to even greater degrees of depression than their peers. Hadland S, Marshall B, Kerr T, Qi J, Montaner J, Wood E. Depressive symptoms and patterns of drug use among street youth. J Adolesc Health. 2011; 48 (6): 585-590.

HIV-Related Risk Behaviors Among A Sample Of Men Who Have Sex With Men In Puerto Rico: An Overview Of Substance Use And Sexual Practices Despite the growing impact of the human immunodeficiency virus (HIV) epidemic in Puerto Rico (PR), limited epidemiological research on men who have sex with men (MSM) has been conducted. The aim of this study was to describe HIV-related risk behaviors in a sample of MSM in PR. A secondary data analysis of a household survey of the adult population of PR was performed in order to describe substance use and sexual practices related to HIV transmission and seropositivity for hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), HIV, and type 2 herpes simplex virus (HSV-2) in MSM. Data regarding substance use and sexual practices were collected using audio computer-assisted self-interviewing (A-CASI). Descriptive statistics were used to examine lifetime and recent (12 months) prevalence of substance use and sexual practices. Of the 640 men interviewed, 41 (6.4%) reported having ever had sex with another man on at least one occasion. Approximately one-fourth of MSM reported having used marijuana (24.4%) and cocaine (24.4%) in the past 12 months. Nearly 42% of the MSM reported an early age of sexual initiation (< 15 years), and 61% reported having had at least 10 sexual partners in their lifetime. Seropositivity rates for HAV, HSV-2, HIV, HCV, and HBV were 43.3%, 32.4%, 7.3%, 4.9%, and 4.9%, respectively. This is the first study to attempt to examine high-risk behaviors related to HIV in a population-based sample of MSM in PR. Concurrent efforts that will help to intensify research and prevention initiatives among MSM are necessary, especially those that will enhance awareness of screening for HIV, HCV, and other sexually transmitted infections, access to HAV and HBV vaccinations, substance use, and identification of social barriers. Colón-López V, Rodríguez-Díaz C, Ortiz A, Soto-Salgado M, Suárez E, Pérez C. HIV-related risk behaviors among a sample of men who have sex with men in Puerto Rico: An overview of substance use and sexual practices. P R Health Sci J. 2011; 30(2): 65-68.

Ecstasy Use and Associated Risk Factors Among Asian-American Youth: Findings From A National Survey This study examined ecstasy use and associated risk and protective factors among Asian American youth. Data from 996 Asian American adolescents and 1,108 Asian American young adults were used. Ecstasy use was relatively common among Asian American youth. Among adolescents, it was associated with older age, poor parent-child communication, having been approached by drug sellers, living in a metropolitan area, and positive attitudes toward substance use. Among Asian American young adults, it was associated with having been born in the United States, having been approached by drug sellers, criminal justice system involvement, and positive attitudes toward substance use. Implications for designing substance use prevention/intervention programs for this minority group are discussed. Wu P, Liu X, Kim J, Fan B. Ecstasy use and associated risk factors among asian-american youth: Findings from a national survey. J Ethn Subst Abuse. 2011; 10 (2): 112-125.

Ecstasy Use and Suicidal Behavior Among Adolescents: Findings From A National Survey The relationship between ecstasy use and suicidal behavior among adolescents in the United States was examined. Data from the adolescent subsample (ages 12-17, N = 19,301) of the 2000 National Household Survey on Drug Abuse were used in the analyses. Information on adolescent substance use, suicidal behaviors, and related sociodemographic, family, and individual factors was obtained in the survey. The rate of past year suicide attempt among adolescents with lifetime ecstasy use was almost double that of adolescents who had used other drugs only, and nine times that of adolescents with no history of illicit drug use. In multinomial logistic regression analyses controlling for related factors, the effect of ecstasy use remained significant. Adolescent ecstasy users may require enhanced suicide prevention and intervention efforts. Kim J, Fan B, Liu X,

Kerner N, Wu P. Ecstasy use and suicidal behavior among adolescents: findings from a national survey. Suicide Life Threat Behav. 2011; 41(4): 435-444.

Marijuana Exposure Opportunity and Initiation During College: Parent and Peer Influences Marijuana is the most prevalent illicit drug used by adolescents and young adults, yet marijuana initiation is rarely studied past adolescence. The present study sought to advance our understanding of parent and peer influences on marijuana exposure opportunity and incident use during college. A sample of 1,253 students was assessed annually for 4 years starting with the summer prior to college entry. More than one-third (38% (wt)) of students had already used marijuana at least once prior to college entry; another 25% (wt) initiated use after starting college. Of the 360 students who did not use marijuana prior to college, 74% were offered marijuana during college; of these individuals, 54% initiated marijuana use. Both low levels of parental monitoring during the last year of high school and a high percentage of marijuana-using peers independently predicted marijuana exposure opportunity during college, holding constant demographics and other factors (AOR = 0.92, 95% CI = 0.88-0.96, $p < .001$ and AOR = 1.11, 95% CI = 1.08-1.14, $p < .001$, respectively). Among individuals with exposure opportunity, peer marijuana use (AOR = 1.04, 95% CI = 1.03-1.05, $p < .001$), but not parental monitoring, was associated with marijuana initiation. Results underscore that peer influences operate well into late adolescence and young adulthood and thus suggest the need for innovative peer-focused prevention strategies. Parental monitoring during high school appears to influence exposure opportunity in college; thus, parents should be encouraged to sustain rule-setting and communication about adolescent activities and friend selection throughout high school. Pinchevsky G, Arria A, Caldeira K, Garnier-Dykstra L, Vincent K, O 'Grady K. Marijuana exposure opportunity and initiation during college: parent and peer influences. Prev Sci. 2011.

Treatment Use and Barriers Among Adolescents With Prescription Opioid Use Disorders This study examined national trends, patterns, correlates, and barriers to substance abuse treatment use by adolescents aged 12-17 years who met at least one of the past-year criteria for prescription opioid abuse or dependence (N=1788). Data were from the 2005-2008 National Surveys of Drug Use and Health (NSDUH). Past-year substance use disorders, major depression, and treatment use were assessed by audio computer-assisted self-interviewing. About 17% of adolescents with opioid dependence (n=434) and 16% of those with opioid abuse (n=355) used any substance abuse treatment in the past year compared with 9% of subthreshold users, i.e., adolescents who reported 1-2 prescription opioid dependence criteria but no abuse criteria (n=999). Only 4.2% of adolescents with opioid dependence, 0.5% of those with abuse, and 0.6% of subthreshold users reported a perceived need for treatment of nonmedical opioid use. Self-help groups and outpatient rehabilitation were the most commonly used sources of treatment. Few black adolescents used treatment (medical settings, 3.3%; self-help groups, 1.7%) or reported a need for treatment (1.8%). Talking to parents/guardians about dangers of substance use increased the odds of treatment use. Barriers to treatment use included "wasn't ready to stop substance use," "didn't want others to find out," and "could handle the problem without treatment." Adolescents with prescription opioid use disorders markedly underutilize treatment. Non-financial barriers are pervasive, including stigma and a lack of perceived treatment need. Wu L, Blazer D, Li T, Woody G. Treatment use and barriers among adolescents with prescription opioid use disorders. Addict Behav. 2011; 36(12): 1233-1239.

Drug Use Trajectory Patterns Among Older Drug Users To better understand patterns of drug use trajectories over time, it is essential to have standard measures of change. The goal of this study was to introduce measures the authors developed to quantify change in drug use behaviors. A secondary goal is to provide effective visualizations of these trajectories for applied use. They analyzed data from a sample of 92 older drug users (ages 45 to 65) to identify transition patterns in drug use trajectories across the life course. Data were collected for every year since birth using a mixed methods design. The community-drawn sample of active and former users were 40% female, 50% African American, and 60% reporting some college or greater. Their life histories provided retrospective longitudinal data on the diversity of paths taken throughout the life course and changes in drug use patterns that occurred over time. Bayesian analysis was used to model drug trajectories displayed by innovative computer graphics. The mathematical techniques and visualizations presented here provide the foundation for future models using Bayesian analysis. In this paper the authors introduce the concepts of transition counts, transition rates and relapse/remission rates, and describe how these measures can help us better understand drug use trajectories. Depicted through these visual tools, measurements of discontinuous patterns provide a succinct view of individual drug use trajectories. The measures the authors use on drug use data will be further developed to incorporate contextual influences on the drug trajectory and build predictive models that inform rehabilitation efforts for drug users. Although the measures developed here were conceived to better examine drug use trajectories, the applications of these measures can be used with other longitudinal datasets. Boeri M, Whalen T, Tyndall B, Ballard E. Drug use trajectory patterns among older drug users. Subst Abuse Rehabil. 2011; 2011(2): 89-102.

Discordance Between Adolescent Real and Ideal Sex Partners and Association With Sexually Transmitted Infection Risk Behaviors Epidemic levels of sexually transmitted infections (STIs) among urban youth have drawn attention to the potential role of sex partner selection in creating risk for STIs. The objectives of this study were to describe the ideal preferences and real selection of sex partners, to evaluate sex partner ideal versus real discordance using quantitative methods, and to determine the association between discordance and STI risk behaviors. Data are obtained from an urban, household sample of 429 individuals aged 15-24 years. Trait clusters were developed for participants' ratings of their real and ideal sex partners and tested for reliability. Discordance between the ratings of real and ideal partners was measured. Logistic regression was used to assess associations between sex partner discordance and STI risk behaviors. Ratings of the real sex partners were often lower than participants' ideal sex partner ratings. A total of 33% of male adolescents and young men and 66% of female adolescents and young women were discordant on at least one trait cluster. Male adolescents and young men who were discordant on the emotional support they expected of their partner were more likely to report more than two sex partners in the past 90 days (odds ratio = 2.13, 95% confidence interval: 1.06-4.26) and perceived partner concurrency (odds ratio = 3.85, 95% confidence interval: 1.53-9.72). For female adolescents and young women, discordance on fidelity or emotional support significantly increased the odds of all risk behaviors. Male and female adolescents with discordant real and ideal sex partner ratings were more likely to report STI-related risk behaviors. Further steps should involve identification of factors associated with ideal versus real sex partner discordance, such as features of the social context. Polk S, Ellen J, Chung S, Huettner S, Jennings J. Discordance between adolescent real and ideal sex partners and association with sexually transmitted infection risk behaviors. J Adolesc. Health. 2011; 48(6): 604-609.

Substance Use and The Quality Of Patient-Provider Communication In HIV Clinics The objective of this study was to estimate the influence of substance use on the quality of patient-provider communication during HIV clinic encounters. Patients were surveyed about unhealthy alcohol and illicit drug use and rated provider communication quality. Audio-recorded encounters were coded for specific communication behaviors. Patients with vs. without unhealthy alcohol use rated the quality of their provider & apos' communication lower; illicit drug user ratings were comparable to non-users. Visit length was shorter, with fewer activating/engaging and psychosocial counseling statements for those with vs. without unhealthy alcohol use. Providers and patients exhibited favorable communication behaviors in encounters with illicit drug users vs. non-users, demonstrating greater evidence of patient-provider engagement. The quality of patient-provider communication was worse for HIV-infected patients with unhealthy alcohol use but similar or better for illicit drug users compared with non-users. Interventions should be developed that encourage providers to actively engage patients with unhealthy alcohol use. Korthius TP, Saha S, Chander G, McCarthy D, Moore RD, Cohn JA, Sharp VL, Beach MC. Substance use and the quality of patient-provider communication in HIV clinics. AIDS Behav. 2011; 15(4): 832-841.

Risk Factors For Tuberculosis After Highly Active Antiretroviral Therapy Initiation In The United States And Canada: Implications For Tuberculosis Screening Screening for tuberculosis prior to highly active antiretroviral therapy (HAART) initiation is not routinely performed in low-incidence settings. Identifying factors associated with developing tuberculosis after HAART initiation could focus screening efforts. Sixteen cohorts in the United States and Canada contributed data on persons infected with human immunodeficiency virus (HIV) who initiated HAART December 1995-August 2009. Parametric survival models identified factors associated with tuberculosis occurrence. Of 37,845 persons in the study, 145 were diagnosed with tuberculosis after HAART initiation. Tuberculosis risk was highest in the first 3 months of HAART (20 cases; 215 cases per 100000 person-years; 95% confidence interval [CI]: 131-333 per 100000 person-years). In a multivariate Weibull proportional hazards model, baseline CD4+ lymphocyte count <200, black race, other nonwhite race, Hispanic ethnicity, and history of injection drug use were independently associated with tuberculosis risk. In addition, in a piece-wise Weibull model, increased baseline HIV-1 RNA was associated with increased tuberculosis risk in the first 3 months; male sex tended to be associated with increased risk. Screening for active tuberculosis prior to HAART initiation should be targeted to persons with baseline CD4 <200 lymphocytes/mm³ or increased HIV-1 RNA, persons of nonwhite race or Hispanic ethnicity, history of injection drug use, and possibly male sex. Sterling T, Lau B, Zhang J, Freeman A, Bosch R, Brooks J, Deeks S, French A, Gange S, Gebo K, John Gill M, Horberg M, Jacobson L, Kirk G, Kitahata M, Klein M, Martin J, Rodriguez B, Silverberg M, Willig J, Eron J, Goedert J, Hogg R, Justice A, McKaig R, Napravnik S, Thorne J, Moore R, Moore R. Risk factors for tuberculosis after highly active antiretroviral therapy initiation in the United States and Canada: Implications for tuberculosis screening. J Infect Dis. 2011; 204(6): 893-901.

Trends In Human Immunodeficiency Virus Incidence and Risk Behavior Among Injection Drug Users In Montreal, Canada: A 16-Year Longitudinal Study The authors sought to investigate trends in the incidence of human immunodeficiency virus (HIV) infection, evaluate changes in risk behavior, and assess associations between syringe access programs and HIV seroconversion among injection drug users (IDUs) in Montreal, Canada, who were recruited and followed for a prospective cohort study between 1992 and 2008. Methods included Kaplan-Meier survival analysis and time-varying Cox regression models. Of 2,137 HIV-seronegative

IDUs at enrollment, 148 became HIV-positive within 4 years (incidence: 3.3 cases/100 person-years; 95% confidence interval: 2.8, 3.9). An annual HIV incidence decline of 0.06 cases/100 person-years prior to 2000 was followed by a more rapid annual decline of 0.24 cases/100 person-years during and after 2000. Behavioral trends included increasing cocaine and heroin use and decreasing proportions of IDUs reporting any syringe-sharing or sharing a syringe with an HIV-positive person. In multivariate analyses, HIV seroconversion was associated with male gender, unstable housing, intravenous cocaine use, and sharing syringes or having sex with an HIV-positive partner. Always acquiring syringes from safe sources conferred a reduced risk of HIV acquisition among participants recruited after 2004, but this association was not statistically significant for participants recruited earlier. In conclusion, HIV incidence has declined in this cohort, with an acceleration of the reduction in HIV transmission after 2000. Bruneau J, Daniel M, Abrahamowicz M, Zang G, Lamothe F, Vincelette J. Trends in Human Immunodeficiency Virus incidence and risk behavior among injection drug users in Montreal, Canada: A 16-year longitudinal study. Am J. Epidemiol. 2011; 173(9): 1049-1058.

Individual and Network Factors Associated With Non-Fatal Overdose Among Rural Appalachian Drug Users Fatal overdoses involving prescription opioids have increased significantly in recent years in the United States-especially in rural areas. However, there are scant data about non-fatal overdose among rural drug users. The purpose of this study is to examine the prevalence and correlates of non-fatal overdose and witnessed overdose among rural Appalachian drug users. Rural drug users were participants in a longitudinal study of social networks and HIV transmission. An interviewer-administered questionnaire elicited information in the following domains: sociodemographic characteristics, drug use (including lifetime overdose and witnessed overdose), psychiatric disorders, HIV risk behaviors and social networks (support, drug and sex networks). Negative binomial regression was used to model the number of lifetime overdoses and witnessed overdoses. Of the 400 participants, 28% had ever experienced a non-fatal overdose, while 58.2% had ever witnessed an overdose (fatal or non-fatal). Factors independently associated with a greater number of overdoses included having ever been in drug treatment, past 30-day injection of prescription opioids, meeting the criteria for post-traumatic stress disorder and/or antisocial personality disorder and having more members in one's support network. Rural drug users with history of overdose were more likely to have injected with prescription opioids--which is different from urban heroin users. However, the remaining correlates of non-fatal overdose among this cohort of rural drug users were similar to those of urban heroin users, which suggests current overdose prevention strategies employed in urban settings may be effective in preventing fatal overdose in this population. Havens J, Oser C, Knudsen H, Lofwall M, Stoops W, Walsh S, Leukefeld C, Kral A. Individual and network factors associated with non-fatal overdose among rural appalachian drug users. Drug Alcohol Depend. 2011; 115(1-2): 107-112.

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, we 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 B, Shoveller J, 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.

Changes In the Prevalence Of Injection Drug Use Among Adolescents and Young Adults In Large U.S. Metropolitan Areas Young injection drug users (IDUs) are at risk for acquiring blood-borne diseases like HIV and Hepatitis C. Little is known about the population prevalence of young IDUs. The authors (1) estimate annual population prevalence rates of young IDUs (aged 15-29) per 10,000 in 95 large U.S. metropolitan statistical areas (MSAs) from 1992 to 2002; (2) assess the validity of these estimates; and (3) explore whether injection drug use among youth in these MSAs began to rise after HAART was discovered. A linear mixed model (LMM) estimated the annual population prevalence of young IDUs in each MSA and described trends therein. The population prevalence of IDUs among youths across 95 MSAs increased from 1996 (mean = 95.64) to 2002 (mean = 115.59). Additional analyses of the proportion of young IDUs using health services suggest this increase may have continued after 2002. Harm reduction and prevention research and programs for young IDUs are needed. Chatterjee S, Tempalski B, Pouget E, Cooper H, Cleland C, Friedman S. Changes in the prevalence of injection drug use among adolescents and young adults in large u.s. metropolitan areas. AIDS Behav. 2011; 15(7): 1570-1578.

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 S, Kral A. 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.

The Influence of the Perceived Consequences Of Refusing To Share Injection Equipment Among Injection Drug Users: Balancing Competing Risks Injection drug users (IDUs) are at risk for HIV and other bloodborne pathogens through receptive syringe sharing (RSS) and receptive paraphernalia sharing (RPS). Research into the influence of the perceived risk of HIV infection on injection risk behavior has yielded mixed findings. One explanation may be that consequences other than HIV infection are considered when IDUs are faced with decisions about whether or not to share equipment. The authors investigated the perceived consequences of refusing to share injection equipment among 187 IDUs recruited from a large syringe exchange

program in Los Angeles, California, assessed their influence on RSS and RPS, and evaluated gender differences. Two sub-scales of perceived consequences were identified: structural/external consequences and social/internal consequences. In multiple linear regressions, the perceived social/internal consequences of refusing to share were associated with both RSS and RPS, after controlling for other psychosocial constructs and demographic variables. Few statistically significant gender differences emerged. Assessing the consequences of refusing to share injection equipment may help explain persistent injection risk behavior, and may provide promising targets for comprehensive intervention efforts designed to address both individual and structural risk factors. Wagner K, Lankenau S, Palinkas L, Richardson J, Chou C, Unger J. The influence of the perceived consequences of refusing to share injection equipment among injection drug users: Balancing competing risks. Addict Behav. 2011; 36(8): 835-842.

A Dose-Dependent Relationship Between Exposure To A Street-Based Drug Scene And Health-Related Harms Among People Who Use Injection Drugs While the community impacts of drug-related street disorder have been well described, lesser attention has been given to the potential health and social implications of drug scene exposure on street-involved people who use illicit drugs. Therefore, the authors sought to assess the impacts of exposure to a street-based drug scene among injection drug users (IDU) in a Canadian setting. Data were derived from a prospective cohort study known as the Vancouver Injection Drug Users Study. Four categories of drug scene exposure were defined based on the numbers of hours spent on the street each day. Three generalized estimating equation (GEE) logistic regression models were constructed to identify factors associated with varying levels of drug scene exposure (2-6, 6-15, over 15 hours) during the period of December 2005 to March 2009. Among the sample of 1,486 IDU, at baseline, a total of 314 (21%) fit the criteria for high drug scene exposure (>15 hours per day). In multivariate GEE analysis, factors significantly and independently associated with high exposure included: unstable housing (adjusted odds ratio [AOR] = 9.50; 95% confidence interval [CI], 6.36-14.20); daily crack use (AOR = 2.70; 95% CI, 2.07-3.52); encounters with police (AOR = 2.11; 95% CI, 1.62-2.75); and being a victim of violence (AOR = 1.49; 95 % CI, 1.14-1.95). Regular employment (AOR = 0.50; 95% CI, 0.38-0.65), and engagement with addiction treatment (AOR = 0.58; 95% CI, 0.45-0.75) were negatively associated with high exposure. These findings indicate that drug scene exposure is associated with markers of vulnerability and higher intensity addiction. Intensity of drug scene exposure was associated with indicators of vulnerability to harm in a dose-dependent fashion. These findings highlight opportunities for policy interventions to address exposure to street disorder in the areas of employment, housing, and addiction treatment. Debeck K, Wood E, Zhang R, Buxton J, Montaner J, Kerr T. A Dose-Dependent relationship between exposure to a street-based drug scene and health-related harms among people who use injection drugs. J Urban Health. 2011; 88(4): 724-735.

Does Initiation Of HIV Antiretroviral Therapy Influence Patterns Of Syringe Lending Among Injection Drug Users? The delivery of antiretroviral therapy (ART) to injection drug users (IDU) may be influenced by provider concerns regarding the potential for increased HIV-related risk behavior following the initiation of HIV treatment. The authors evaluated whether ART initiation was associated with changes in syringe lending patterns among a long-term prospective cohort of HIV-positive IDU in Vancouver, Canada. Among 380 ART-naïve individuals eligible for this analysis, the median age was 34.2 (interquartile range [IQR] 27.7-40.8), 171 (45.0%) were female, and the median follow-up duration was 60 months (IQR=18-113). Between May 1996 and April 2008, 260 (68.4%) participants initiated ART. In a generalized linear mixed-effects model which compared each individual's likelihood of sharing

syringes prior to and following the initiation of ART, syringe lending was not significantly associated with ART initiation in unadjusted (odds ratio=0.72, 95% CI: 0.38-1.36) or adjusted (odds ratio=0.78, 95% CI: 0.42-1.45) analyses. Concerns regarding increased injection risk behaviors following the initiation of ART were not observed in this setting. Kuyper L, Milloy M, Marshall B, Zhang R, Kerr T, Montaner J, Wood E. Does initiation of HIV antiretroviral therapy influence patterns of syringe lending among injection drug users? Addict Behav. 2011; 36 (5): 560-563.

Homelessness and Adherence To Antiretroviral Therapy Among A Cohort Of HIV-Infected Injection Drug Users Homelessness is prevalent among HIV-infected injection drug users (IDU) and may adversely affect access and adherence to antiretroviral therapy (ART). There are limited descriptions of the effect of homelessness on adherence to ART in long-term cohorts of HIV-infected IDU. The authors used data from a community-recruited prospective cohort of HIV-infected IDU, including comprehensive ART dispensation records, in a setting where HIV care is free. They examined the relationship between the homelessness measured longitudinally, and the odds of e95% adherence to ART using generalized estimating equations logistic regression modeling adjusting for sociodemographics, drug use, and clinical variables. Between May 1996 and September 2008, 545 HIV-infected IDU were recruited and eligible for the present study. The median follow-up duration was 23.8 months (IQR 8.5-91.6 months) contributing 2,197 person-years of follow-up. At baseline, homeless participants were slightly younger (35.8 vs. 37.9 years, p = 0.01) and more likely to inject heroin at least daily (37.1% vs. 24.6%. p = 0.004) than participants who had housing. The multivariate model revealed that homelessness (adjusted odds ratio [AOR] 0.66; 95% CI: 0.53-0.84) and frequent heroin use (AOR 0.40; 95% CI: 0.30-0.53) were significantly and negatively associated with ART adherence, whereas methadone maintenance was positively associated (AOR 2.33; 95% CI: 1.86-2.92). Sub-optimal ART adherence was associated with homelessness and daily injection heroin use among HIV-infected IDU. Given the survival benefit of ART, it is critical to develop and evaluate innovative strategies such as supportive housing and methadone maintenance to address these risk factors to improve adherence. Palepu A, Milloy M, Kerr T, Zhang R, Wood E. Homelessness and adherence to antiretroviral therapy among a cohort of hiv-infected injection drug users. J Urban Health. 2011; 88(3): 545-555.

Patient, Resident Physician, and Visit Factors Associated With Documentation Of Sexual History In The Outpatient Setting Providers need an accurate sexual history for appropriate screening and counseling, but data on the patient, visit, and physician factors associated with sexual history-taking are limited. The objectives of this study were to assess patient, resident physician, and visit factors associated with documentation of a sexual history at health care maintenance (HCM) visits. The study design was a retrospective cross-sectional chart review. Review of all HCM clinic notes (n = 360) by 26 internal medicine residents from February to August of 2007 at two university-based outpatient clinics were employed. Documentation of sexual history and patient, resident, and visit factors were abstracted using structured tools. The authors employed a generalized estimating equations method to control for correlation between patients within residents. They performed multivariate analysis of the factors significantly associated with the outcome of documentation of at least one component of a sexual history. Among 360 charts reviewed, 25% documented at least one component of a sexual history with a mean percent by resident of 23% (SD = 18%). Factors positively associated with documentation were: concern about sexually transmitted infection (referent: no concern; OR = 4.2 [95% CI = 1.3-13.2]); genitourinary or abdominal complaint (referent: no complaint; OR = 4.3 [2.2-8.5]);

performance of other HCM (referent: no HCM performed; OR = 3.2 [1.5-7.0]), and birth control use (referent: no birth control; OR = 3.0 [1.1, 7.8]). Factors negatively associated with documentation were: age groups 46-55, 56-65, and >65 (referent: 18-25; ORs = 0.1, 0.1, and 0.2 [0.0-0.6, 0.0-0.4, and 0.1-0.6]), and no specified marital status (referent: married; OR = 0.5 [0.3-0.8]). These findings highlight the need for an emphasis on documentation of a sexual history by internal medicine residents during routine HCM visits, especially in older and asymptomatic patients, to ensure adequate screening and counseling. Loeb D, Lee R, Binswanger I, Ellison M, Aagaard E. Patient, resident physician, and visit factors associated with documentation of sexual history in the outpatient setting. J Gen Intern Med. 2011; 26(8): 887-893.

HIV Risk After Release From Prison: A Qualitative Study Of Former Inmates Former prison inmates are at risk for HIV and hepatitis C (HCV) infection. This study was designed to understand how former inmates perceived their risk for HIV and HCV infection after release from prison, the behaviors and environmental factors that put patients at risk for new infection, and the barriers to accessing health care. This was a qualitative study using individual, face-to-face, semistructured interviews exploring participants' perceptions and behaviors putting them at risk for HIV and HCV infection and barriers to engaging in regular medical care after release. Interview transcripts were coded and analyzed using a team-based general inductive approach. Participants were racially and ethnically diverse and consisted of 20 men and 9 women with an age range of 22-57 years who were interviewed within the first 2 months after their release from prison to the Denver, Colorado community. Four major themes emerged: (1) risk factors including unprotected sex, transactional sex, and drug use were prevalent in the postrelease period; (2) engagement in risky behavior occurred disproportionately in the first few days after release; (3) former inmates had educational needs about HIV and HCV infection; and (4) former inmates faced major challenges in accessing health care and medications. Risk factors for HIV and HCV infection were prevalent among former inmates immediately after release. Prevention efforts should focus on education, promotion of safe sex and needle practices, substance abuse treatment, and drug-free transitional housing. Improved coordination between correctional staff, parole officers, and community health care providers may improve continuity of care. Adams J, Nowels C, Corsi K, Long J, Steiner J, Binswanger I. HIV risk after release from prison: a qualitative study of former inmates. J Acquir Immune Defic Syndr. 2011; 57(5): 429-434.

Sexual Contexts and the Process Of Risk Reduction Understanding the dynamics of sexual risks for HIV among men who have sex with men has been one of the ongoing challenges of HIV prevention. While the majority of HIV-prevention interventions target individual behaviour and decision making, multiple studies point to the importance of social context in shaping risk behaviour. Analysis of qualitative data from a study of men who have sex with men, drug use and sex found that sexual encounters were made up multiple contextual and interpersonal elements, which interacted to shape sexual practices and risk reduction strategies. Semi-structured interviews were conducted with 60 racially diverse men who have sex with men in NYC, recruited from multiple venues. The majority of respondents were gay-identified and half were 40 or older. Respondents described risk assessment and risk-reduction processes that develop throughout a sexual encounter, embedded in ongoing negotiations of sexual practices. Strategies of risk assessment and reduction draw on probability-based approaches to HIV prevention, presenting a challenge to health education. Braine N, van Sluytman L, Acker C, Friedman S, Des Jarlais DC. Sexual contexts and the process of risk reduction. Cult Health Sex. 2011; 13(7): 797-814.

Immune Status At Presentation For HIV Clinical Care In Rio De Janeiro and Baltimore
Late presentation to HIV clinical care increases individual risk for (multiple) clinical events and death, and decreases successful response to highly active antiretroviral therapy (HAART). In Brazil, provision of HAART free of charge to all individuals infected with HIV could lead to increased testing and linkage to care. The authors assessed the immune status of 2555 patients who newly presented for HIV clinical care between 1997 and 2009 at the Johns Hopkins Clinical Cohort, in Baltimore, MD, and at the Instituto de Pesquisa Clinica Evandro Chagas Clinical Cohort, in Rio de Janeiro, Brazil. The mean change in the CD4 cell count per year was estimated using multivariate linear regression models. Overall, from 1997 to 2009, 56% and 54% of the patients presented for HIV clinical care with CD4 count d350 cells per cubic millimeter in Baltimore and Rio de Janeiro, respectively. On average, 75% of the patients presented with viral load >10,000 copies per millimeter. In Rio de Janeiro only, the overall adjusted per year increase in the mean CD4 cell count was statistically significant (5 cells/mm, 95% confidence interval: 1 to 10 cells/mm). The authors found that, over years, the majority of patients presented late, that is, with a CD4 count <350 cells per cubic millimeter. These findings indicate that, despite the availability of HAART for more than a decade, and mass media campaigns stimulating HIV testing in both countries, the proportion of patients who start therapy at an advanced stage of the disease is still high. Moreira R, Luz P, Struchiner C, Morgado M, Veloso V, Keruly J, Grinsztejn B, Moore R. Immune status at presentation for HIV clinical care in Rio De Janeiro and Baltimore. J Acquir Immune Defic Syndr. 2011; 57 (Suppl 3): 171-178.

Interest In Low-Threshold Employment Among People Who Inject Illicit Drugs: Implications For Street Disorder Income generation opportunities available to people who use illicit drugs have been associated with street disorder. Among a cohort of injection drug users (IDU) we sought to examine street-based income generation practices and willingness to forgo these sources of income if other low-threshold work opportunities were made available. Data were derived from a prospective community recruited cohort of IDU. The authors assessed the prevalence of engaging in disorderly street-based income generation activities, including sex work, drug dealing, panhandling, and recycling/salvaging/vending. Using multivariate logistic regressions based on Akaike information criterion and the best subset selection procedure, they identified factors associated with disorderly income generation activities, and assessed willingness to forgo these sources of income during the period of November 2008 to July 2009. Among our sample of 874 IDU, 418 (48%) reported engaging in a disorderly income generation activity in the previous six months. In multivariate analyses, engaging in disorderly income generation activities was independently associated with high intensity stimulant use, as well as binge drug use, having encounters with police, being a victim of violence, sharing used syringes, and injecting in public areas. Among those engaged in disorderly income generation, 198 (47%) reported a willingness to forgo these income sources if given opportunities for low-threshold employment, with sex workers being most willing to engage in alternative employment. The authors conclude that engagement in disorderly street-based income generation activities was associated with high intensity stimulant drug use and various markers of risk. They found that a high proportion of illicit drug users were willing to cease engagement in these activities if they had options for causal low-threshold employment. These findings indicate that there is a high demand for low-threshold employment that may offer important opportunities to reduce drug-related street disorder and associated harms. Debeck K, Wood E, Qi J, Fu E, McArthur D, Montaner J, Kerr T. Interest in low-threshold employment among people who inject illicit drugs: implications for street disorder. Int J Drug Policy. 2011; 22(5): 376-384.

"It's One Of The Better Drugs To Use": Perceptions Of Cocaine Use Among Gay and Bisexual Asian American Men Research on drug use among gay and bisexual men has primarily focused on examining the link between drug use- most notably, methamphetamine- sexual practices, and risk of HIV transmission. Drawing on in-depth qualitative data from 40 interviews with gay and bisexual Asian American men, he authors examine perceptions and meanings associated with cocaine use in the San Francisco Bay Area gay community. They found that the participants, in contrast to their negative perceptions of methamphetamine use, believed that cocaine enhanced sociability and was acceptable for use in most social situations. Furthermore, participants perceived little connection between cocaine use and risky sexual practices, emphasizing the drug&apos's safety relative to other illicit substances. Based on these findings, we suggest that an increase in the favorability of cocaine use might be an unintended consequence of methamphetamine prevention campaigns targeting the gay community, with their emphasis on the harmful effects of drug use, unsafe sex, and HIV risk. Fazio A, Hunt G, Moloney M. "It's one of the better drugs to use": Perceptions of cocaine use among gay and bisexual Asian American men. Qual Health Res. 2011; 21(5): 625-641.

The Association Between Early Conduct Problems and Early Marijuana Use In College Students Early conduct problems have been linked to early marijuana use in adolescence. The present study examines this association in a sample of 1,076 college students that was divided into three groups: 1) early marijuana users (began marijuana use prior to age 15; n=126), 2) late marijuana users (began marijuana use at or after age 15; n=607), and 3) non-users (never used marijuana; n=343). A conduct problem inventory used in previous studies was adapted for use in the present study. Early conduct problems were associated with early marijuana use but not with late marijuana use, holding constant other risk factors. Results suggest that early conduct problems are a risk factor for early marijuana use even among academically-achieving college-bound students. Falls B, Wish E, Garnier L, Caldeira K, O 'Grady K, Vincent K, Arria A. The association between early conduct problems and early marijuana use in college students. J Child Adolesc Subst Abuse. 2011; 20(3): 221-236.

Development and Validation Of the Appearance and Performance Enhancing Drug Use Schedule Appearance-and-performance enhancing drug (APED) use is a form of drug use that includes use of a wide range of substances such as anabolic-androgenic steroids (AASs) and associated behaviors including intense exercise and dietary control. To date, there are no reliable or valid measures of the core features of APED use. The present study describes the development and psychometric evaluation of the Appearance and Performance Enhancing Drug Use Schedule (APEDUS) which is a semi-structured interview designed to assess the spectrum of drug use and related features of APED use. Eighty-five current APED using men and women (having used an illicit APED in the past year and planning to use an illicit APED in the future) completed the APEDUS and measures of convergent and divergent validity. Inter-rater agreement, scale reliability, one-week test-retest reliability, convergent and divergent validity, and construct validity were evaluated for each of the APEDUS scales. The APEDUS is a modular interview with 10 sections designed to assess the core drug and non-drug phenomena associated with APED use. All scales and individual items demonstrated high inter-rater agreement and reliability. Individual scales significantly correlated with convergent measures (DSM-IV diagnoses, aggression, impulsivity, eating disorder pathology) and were uncorrelated with a measure of social desirability. APEDUS subscale scores were also accurate measures of AAS dependence. The APEDUS is a reliable and valid measure of APED phenomena and an accurate measure of the core pathology associated with APED use. Issues with assessing APED use are

considered and future research is considered. Hildebrandt T, Langenbucher J, Lai J, Loeb K, Hollander E. Development and validation of the appearance and performance enhancing drug use schedule. Addict Behav. 2011; 36(10): 949-958.

Sociodemographic Correlates Of Transitions From Alcohol Use To Disorders and Remission In the Sao Paulo Megacity Mental Health Survey, Brazil The objective of this study was to evaluate sociodemographic correlates associated with transitions from alcohol use to disorders and remission in a Brazilian population. Data are from a probabilistic, multi-stage clustered sample of adult household residents in the Sao Paulo Metropolitan Area. Alcohol use, regular use (at least 12 drinks/year), DSM-IV abuse and dependence and remission from alcohol use disorders (AUDs) were assessed with the World Mental Health version of the Composite International Diagnostic Interview. Age of onset (AOO) distributions of the cumulative lifetime probability of each alcohol use stage were prepared with data obtained from 5037 subjects. Correlates of transitions were obtained from a subsample of 2942 respondents, whose time-dependent sociodemographic data were available. Lifetime prevalences were 85.8% for alcohol use, 56.2% for regular use, 10.6% for abuse and 3.6% for dependence; 73.4 and 58.8% of respondents with lifetime abuse and dependence, respectively, had remitted. The number of sociodemographic correlates decreased from alcohol use to disorders. All transitions across alcohol use stages up to abuse were consistently associated with male gender, younger cohorts and lower education. Importantly, low education was a correlate for developing AUD and not remitting from dependence. Early AOO of first alcohol use was associated with the transition of regular use to abuse. The present study demonstrates that specific correlates differently contribute throughout alcohol use trajectory in a Brazilian population. It also reinforces the need for preventive programs focused on early initiation of alcohol use and high-risk individuals, in order to minimize the progression to dependence and improve remission from AUD. Silveira CM, Viana MC, Erica R, de Andrade AG, Anthony JC, Andrade LH. Sociodemographic correlates of transitions from alcohol use to disorders and remission in the Sao Paulo Megacity Mental Health Survey, Brazil. Alcohol Alcohol. 2011; 46(3): 324-332.

High Burden Of Homelessness Among Sexual-Minority Adolescents: Findings From A Representative Massachusetts High School Sample The authors compared the prevalence of current homelessness among adolescents reporting a minority sexual orientation (lesbian/gay, bisexual, unsure, or heterosexual with same-sex sexual partners) with that among exclusively heterosexual adolescents. They combined data from the 2005 and 2007 Massachusetts Youth Risk Behavior Survey, a representative sample of public school students in grades 9 though 12 (n = 6317). Approximately 25% of lesbian/gay, 15% of bisexual, and 3% of exclusively heterosexual Massachusetts public high school students were homeless. Sexual-minority males and females had an odds of reporting current homelessness that was between 4 and 13 times that of their exclusively heterosexual peers. Sexual-minority youths' greater likelihood of being homeless was driven by their increased risk of living separately from their parents or guardians. The authors conclude that youth homelessness is linked with numerous threats such as violence, substance use, and mental health problems. Although discrimination and victimization related to minority sexual orientation status are believed to be important causal factors, research is needed to improve our understanding of the risks and protective factors for homelessness and to determine effective strategies to prevent homelessness in this population. Corliss H, Goodenow C, Nichols L, Austin S. High burden of homelessness among sexual-minority adolescents: findings from a representative Massachusetts high school sample. Am J Public Health. 2011; 101(9): 1683-1689.

PREVENTION RESEARCH

HPV Vaccination among a Community Sample of Young Adult Women Despite the high efficacy of the human papillomavirus (HPV) vaccine, uptake has been slow and little data on psychosocial barriers to vaccination exist. A community sample of 428 women enrolled in a longitudinal study of social development in the Seattle WA metropolitan area were interviewed about HPV vaccine status, attitudes, and barriers to HPV vaccination in spring 2008 or 2009. Nineteen percent of women had initiated vaccination, 10% had completed the series, and <40% of unvaccinated women intended to get vaccinated. Peer approval was associated with vaccine initiation (adjusted prevalence ratio (APR) 2.1; 95% confidence interval 1.4-3.2) and intention to vaccinate (APR 1.4; 1.1-1.9). Belief the vaccine is <75% ineffective was associated with less initiation (APR 0.6; 0.4-0.9) or intention to vaccinate (APR 0.5; 0.4-0.7). Vaccine initiation was also less likely among cigarette smokers and illegal drug users, whereas intention to vaccinate was more common among women currently attending school or with >5 lifetime sex partners, but less common among women perceiving low susceptibility to HPV (APR 0.6; 0.5-0.9). HPV vaccination uptake was low in this community sample of young adult women. Increasing awareness of susceptibility to HPV and the high efficacy of the vaccine, along with peer interventions to increase acceptability, may be most effective. Manhart L, Burgess-Hull A, Fleming C, Bailey J, Haggerty K, Catalano R. HPV vaccination among a community sample of young adult women. Vaccine. 2011; 29(32): 5238-5244.

Long-term Effects of Prenatal and Infancy Nurse Home Visitation on the Life Course of Youths: 19-year Follow-up of a Randomized Trial The objective of this study was to examine the effect of prenatal and infancy nurse home visitation on the life course development of 19-year-old youths whose mothers participated in the program. The study design was a randomized trial conducted in a semirural community in New York. Three hundred ten youths from the 400 families enrolled in the Elmira Nurse-Family Partnership program participated. Intervention Families received a mean of 9 home visits (range, 0-16) during pregnancy and 23 (range, 0-59) from birth through the child's second birthday. Main outcome measures were youth self-reports of educational achievement, reproductive behaviors, welfare use, and criminal involvement. Relative to the comparison group, girls in the pregnancy and infancy nurse-visited group were less likely to have been arrested (10% vs 30%; relative risk [RR], 0.33; 95% confidence interval [CI], 0.13-0.82) and convicted (4% vs 20%; 0.20; 0.05-0.85) and had fewer lifetime arrests (mean: 0.10 vs 0.54; incidence RR [IRR], 0.18; 95% CI, 0.06-0.54) and convictions (0.04 vs 0.37; 0.11; 0.02-0.51). Nurse-visited girls born to unmarried and low-income mothers had fewer children (11% vs 30%; RR, 0.35; 95% CI, 0.12-1.02) and less Medicaid use (18% vs 45%; 0.40; 0.18-0.87) than their comparison group counterparts. Prenatal and infancy home visitation reduced the proportion of girls entering the criminal justice system. For girls born to high-risk mothers, there were additional positive program effects consistent with results from earlier phases of this trial. There were few program effects for boys. Eckenrode J, Campa M, Luckey D, Henderson C, Cole R, Kitzman H, Anson E, Sidora-Arcoleo K, Powers J, Olds D. Long-term effects of prenatal and infancy nurse home visitation on the life course of youths: 19-year follow-up of a randomized trial. Arch Pediatr Adolesc Med. 2010; 164(1): 9-15.

Comparison of the Behavioral and Cardiovascular Effects of Intranasal and Oral d-amphetamine in Healthy Human Subjects Recent reports indicate an increase in intranasal use of prescription oral stimulant medication. However, there do not appear to be any published clinical studies that have characterized the behavioral and cardiovascular effects of intranasally administered d-amphetamine, which is commonly prescribed for Attention Deficit Hyperactivity Disorder. In this study, a range of d-amphetamine doses (0, 16, 24, and 32 mg/70 kg) were administered as an intranasal solution delivered using a mucosal atomization device. Equal oral doses were included for comparison. Assessments were conducted before and at regular intervals for 3 hours following drug administration and included self-reported drug-effect questionnaires, cardiovascular indices, a performance task, and 2 measures of impulsivity. d-Amphetamine produced prototypical stimulant effects (eg, increased subject ratings of Stimulated and Like Drug, elevated heart rate and blood pressure, and improved rate and accuracy on the digit symbol substitution task) irrespective of dose, but the onset of these effects was generally earlier following intranasal administration, with significant effects emerging 15 to 30 minutes after intranasal dosing and 45 to 60 minutes after oral dosing. These results demonstrate that intranasal administration of d-amphetamine results in a more rapid onset compared to oral dosing, which could be associated with the popularity of intranasal prescription stimulant use and an enhanced potential for abuse. Lile J, Babalonis S, Emurian C, Martin C, Wermeling D, Kelly T. Comparison of the behavioral and cardiovascular effects of intranasal and oral d-amphetamine in healthy human subjects. J Clin Pharmacol. 2011; 51(6): 888-898.

Effects of a Family Intervention in Reducing HIV Risk Behaviors among High-Risk Hispanic Adolescents: A Randomized Controlled Trial The objectoive of this trial was to determine the efficacy of a family intervention in reducing human immunodeficiency virus (HIV) risks behaviors among Hispanic delinquent adolescents. The study design was a randomized controlled trial conducted in the Miami-Dade County Public School System and Miami-Dade County's Department of Juvenile Services, Florida. A total of 242 Hispanic delinquent youth aged 12 to 17 years and their primary caregivers completed outcome assessments at baseline and 3 months after intervention. Intervention participants were randomized to either Familias Unidas (120 participants), a Hispanic-specific, family intervention designed to reduce HIV risk behaviors among Hispanic youth, or a community practice control condition (122 participants). Self-reported measures included unprotected sexual behavior, engaging in sex while under the influence of alcohol and/or drugs, number of sexual partners, and incidence of sexually transmitted diseases. Family functioning (e.g., parent-adolescent communication, positive parenting, and parental monitoring) was also assessed via self-report measures. Compared with community practice, Familias Unidas was efficacious in increasing condom use during vaginal and anal sex during the past 90 days, reducing the number of days adolescents were under the influence of drugs or alcohol and had sex without a condom, reducing sexual partners, and preventing unprotected anal sex at the last sexual intercourse. Familias Unidas was also efficacious, relative to community practice, in increasing family functioning and most notably in increasing parent-adolescent communication and positive parenting. These results suggest that culturally tailored, family-centered prevention interventions may be appropriate and efficacious in reducing HIV risk behaviors among Hispanic delinquent adolescents. Prado G, Pantin H, Huang S, Cordova D, Tapia M, Velazquez M, Calfee M, Malcolm S, Arzon M, Villamar J, Jimenez G, Cano N, Brown C, Estrada Y. Effects of a family intervention in reducing hiv risk behaviors among high-risk hispanic adolescents: a randomized controlled trial. Arch Pediatr Adolesc Med. 2011.

Novelty Seeking, Incentive Salience and Acquisition of Cocaine Self-administration in the Rat It has been suggested that incentive salience plays a major role in drug abuse and the development of addiction. Additionally, novelty seeking has been identified as a significant risk factor for drug abuse. However, how differences in the readiness to attribute incentive salience relate to novelty seeking and drug abuse vulnerability has not been explored. The present experiments examined how individual differences in incentive salience attribution relate to novelty seeking and acquisition of cocaine self-administration in a preclinical model. Rats were first assessed in an inescapable novelty task and a novelty place preference task (measures of novelty seeking), followed by a Pavlovian conditioned approach task for food (a measure of incentive salience attribution). Rats then were trained to self-administer cocaine (0.3 or 1.0 mg/kg/infusion) using an autoshaping procedure. The results demonstrate that animals that attributed incentive salience to a food-associated cue were higher novelty seekers and acquired cocaine self-administration more quickly at the lower dose. The results suggest that novelty-seeking behavior may be a mediator of incentive salience attribution and that incentive salience magnitude may be an indicator of drug reward. Beckmann J, Marusich J, Gipson C, Bardo M. Novelty seeking, incentive salience and acquisition of cocaine self-administration in the rat. Behav Brain Res. 2011; 216(1): 159-165.

A Clinic-based Motivational Intervention Improves Condom Use among Subgroups of Youth Living with HIV More than 50% of youth living with HIV (YLH) have unprotected sex. In previous studies, the authors reported effects of a motivational interviewing-based multirisk reduction intervention, "Healthy Choices" in improving motivation, depression, and viral load in YLH. In this study, they report the effect of the intervention on increasing condom use. Six waves of longitudinal data ($n = 142$) across a period from baseline through 15 months postintervention were analyzed. The developmental trajectory modeling method was used for program effect evaluation. The three groups detected with distinct sexual risks were: Persistent low sexual risk (PLSR), delayed high sexual risk, and high and growing sexual risk with regard to levels and time trajectories of condom use throughout the trial. Receiving Healthy Choices increased the likelihood to be in the PLSR group (63% vs. 32%, $p < .01$) and reduced the likelihood to be in the delayed high sexual risk group (16% vs. 50%, $p < .05$). Receiving the intervention was also associated with progressive reductions in no-condom sex for PLSR youth (adjusted $^2 = -.325$, $p < .01$) and high and growing sexual risk youth (adjusted $^2 = -.364$, $p < .01$). The motivational interviewing-based program Healthy Choices, when delivered in clinic settings, can prevent unprotected sex in subgroups of YLH, although more intensive interventions may be needed to change risk trajectories among those at highest risk of transmitting the AIDS virus. Developmental trajectory analysis provides an alternative approach to evaluate program effects for study samples that contain distinct subgroups. Chen X, Murphy D, Naar-King S, Parsons J, Parsons J. A clinic-based motivational intervention improves condom use among subgroups of youth living with HIV. J Adolesc Health. 2011; 49(2): 193-198.

The Role of Maternal Early-life and Later-life Risk Factors on Offspring Low Birth Weight: Findings from a Three-generational Study This study examined three research questions: (1) Is there an association between maternal early-life economic disadvantage and the birth weight of later-born offspring? (2) Is there an association between maternal abuse in childhood and the birth weight of later-born offspring? (3) To what extent are these early-life risks mediated through adolescent and adult substance use, mental and physical health status, and adult socioeconomic status (SES)? Analyses used structural equation modeling to examine data from two longitudinal studies, which included three generations. The first generation (G1) and

the second generation (G2) were enrolled in the Seattle Social Development Project (SSDP), and the third generation (G3) was enrolled in the SSDP Intergenerational Project. Data for the study (N = 136) focused on (G2) mothers enrolled in the SSDP and their children (G3). Analyses revealed that G2 low childhood SES predicted G3 offspring birth weight. Early childhood abuse among G2 respondents predicted G3 offspring birth weight through a mediated pathway including G2 adolescent substance use and G2 prenatal substance use. Birth weight was unrelated to maternal adult SES, depression, or obesity. To the authors' knowledge, this is the first study to identify the effect of maternal early-life risks of low childhood SES and child maltreatment on later-born offspring birth weight. These findings have far-reaching effects on the cumulative risk associated with early-life economic disadvantage and childhood maltreatment. Such findings encourage policies and interventions that enhance child health at birth by taking the mother's own early-life and development into account. Gavin A, Hill K, Hawkins J, Maas C. The role of maternal early-life and later-life risk factors on offspring low birth weight: findings from a three-generational study. J Adolesc Health. 2011; 49(2): 166-171.

Sustained Decreases in Risk Exposure and Youth Problem Behaviors after Installation of the Communities That Care Prevention System in a Randomized Trial The purpose of this study was to test whether the Communities That Care (CTC) prevention system reduced levels of risk and adolescent problem behaviors community-wide 6 years after installation of CTC and 1 year after study-provided resources ended. Using a community randomized trial design, 24 small towns in 7 states, matched within state, were randomly assigned to control or intervention condition in 2003. A panel of 4407 fifth-grade students was surveyed annually through 10th grade from 2004 to 2009. A coalition of community stakeholders received training and technical assistance to install CTC, used epidemiologic data to identify elevated risk factors and depressed protective factors in the community, and implemented programs to address their community's elevated risks from a menu of tested and effective programs for youths aged 10 to 14 years, their families, and schools. Outcomes were levels of risk and incidence and prevalence of tobacco, alcohol, and other drug use; delinquency; and violent behavior by grade 10. Mean levels of targeted risks increased less rapidly between grades 5 and 10 in CTC than in control communities and were significantly lower in CTC than control communities in grade 10. The incidence of delinquent behavior, alcohol use, and cigarette use and the prevalence of current cigarette use and past-year delinquent and violent behavior were significantly lower in CTC than in control communities in grade 10. Using the CTC system can produce enduring reductions in community-wide levels of risk factors and problem behaviors among adolescents beyond the years of supported implementation, potentially contributing to long-term public health benefits. Hawkins J, Oesterle S, Brown E, Monahan K, Abbott R, Arthur M, Catalano R. Sustained decreases in risk exposure and youth problem behaviors after installation of the Communities That Care Prevention System in a randomized trial. Arch Pediatr Adolesc Med. 2011; epub ahead of print.

Observational Measure of Implementation Progress in Community Based Settings: The Stages of Implementation Completion (SIC) An increasingly large body of research is focused on designing and testing strategies to improve knowledge about how to embed evidence-based programs (EBP) into community settings. Development of strategies for overcoming barriers and increasing the effectiveness and pace of implementation is a high priority. Yet, there are few research tools that measure the implementation process itself. The Stages of Implementation Completion (SIC) is an observation-based measure that is used to track the time to achievement of key implementation milestones in an EBP being implemented in 51 counties in 53 sites (two

counties have two sites) in two states in the United States. The SIC was developed in the context of a randomized trial comparing the effectiveness of two implementation strategies: community development teams (experimental condition) and individualized implementation (control condition). Fifty-one counties were randomized to experimental or control conditions for implementation of multidimensional treatment foster care (MTFC), an alternative to group/residential care placement for children and adolescents. Progress through eight implementation stages was tracked by noting dates of completion of specific activities in each stage. Activities were tailored to the strategies for implementing the specific EBP. Preliminary data showed that several counties ceased progress during pre-implementation and that there was a high degree of variability among sites in the duration scores per stage and on the proportion of activities that were completed in each stage. Progress through activities and stages for three example counties is shown. By assessing the attainment time of each stage and the proportion of activities completed, the SIC measure can be used to track and compare the effectiveness of various implementation strategies. Data from the SIC will provide sites with relevant information on the time and resources needed to implement MTFC during various phases of implementation. With some modifications, the SIC could be appropriate for use in evaluating implementation strategies in head-to-head randomized implementation trials and as a monitoring tool for rolling out other EBPs. Chamberlain P, Brown C, Saldana L. Observational measure of implementation progress in community based settings: the stages of implementation completion (SIC). Implement Sci. 2011; 6(1): 116-124.

Effects of Communities That Care on the Adoption and Implementation Fidelity of Evidence-Based Prevention Programs in Communities: Results from a Randomized Controlled Trial This paper describes findings from the Community Youth Development Study (CYDS), a randomized controlled trial of the Communities That Care (CTC) prevention system, on the adoption and implementation fidelity of science-based prevention programming in 24 communities. Data were collected using the Community Resource Documentation (CRD), which entailed a multi-tiered sampling process and phone and web-based surveys with directors of community-based agencies and coalitions, school principals, service providers, and teachers. Four years after the initiation of the CTC prevention system, the results indicated increased use of tested, effective prevention programs in the 12 CTC intervention communities compared to the 12 control communities, and significant differences favoring the intervention communities in the numbers of children and families participating in these programs. Few significant differences were found regarding implementation quality; respondents from both intervention and control communities reported high rates of implementation fidelity across the services provided. Fagan A, Arthur M, Hanson K, Briney J, Hawkins J. Effects of Communities That Care on the adoption and implementation fidelity of evidence-based prevention programs in communities: results from a randomized controlled trial. Prev Sci. 2011; 12(3): 223-234.

Decision-Making Style and Gender Moderation of the Self-Efficacy-Condom Use Link among Adolescents and Young Adults: Informing Targeted STI/HIV Prevention Programs The objective of this study was to test the moderating effects of decision-making style and gender on the relationship between condom use self-efficacy (CUSE) and condom use behavior among sexually active adolescents and young adults. This was a cross-sectional study conducted in twenty-four continuation high schools in California. Data were collected between February 2008 to June 2009 from a sample of 1304 sexually active adolescents and young adults. The mean (SD) age of the participants was 16.8 (0.9) years, 41% were female, and the ethnicity frequencies were Hispanic, 65%; mixed, 13%; white, 11%; black, 6%; and other, 5%. The tools

used were CUSE, decision-making-self-confidence, and decision-making-approach. The main outcome measured was condom use during the most recent sexual intercourse (termed last sex). Forty-five percent of sexually active participants used condoms at last sex. Decision-making-self-confidence and decision-making-approach significantly moderated the effect of CUSE on condom use. The positive relationship between CUSE and condom use was relatively stronger for males and females reporting high vs low decision-making-self-confidence. Among females, the relationship between CUSE and condom use at last sex was weaker for those reporting high vs low decision-making-approach. Both of these effects were observed at high levels of CUSE. Programs for sexually transmitted infection/human immunodeficiency virus prevention including CUSE content may increase adolescent and young adult condom use by targeting interventions to decision-making style and gender. Black D, Sun P, Rohrbach L, Sussman S. Decision-making style and gender moderation of the self-efficacy-condom use link among adolescents and young adults: Informing targeted STI/HIV prevention programs. Arch Pediatr Adolesc Med. 2011; 165(4): 320-325.

Foster Placement Disruptions Associated with Problem Behavior: Mitigating a Threshold Effect Placement disruptions have adverse effects on foster children. Identifying reliable predictors of placement disruptions might assist in the allocation of services to prevent disruptions. There were two objectives in this study: (a) to replicate a prior finding that the number of daily child problem behaviors at entry into a new foster home predicts subsequent placement disruptions in foster preschoolers and (b) to determine whether this association is mitigated by a treatment foster care intervention. Problem behavior and placement disruptions were examined in 60 children in regular foster care (age range = 3.10-5.91 years [M = 4.34, SD = 0.83], 58.3% male, 93.4% Caucasian) and 57 children in a treatment foster care program (age range = 3.01-6.78 years [M = 4.54, SD = 0.86], 49.1% male, 82.5% Caucasian). Using the Parent Daily Report Checklist (Chamberlain & Reid, 1987), a brief telephone interview, foster caregivers reported problem behavior 6 times over 3 months. Placement disruptions were tracked over 12 months. The regular foster care children with 5 or fewer problem behaviors were at low risk for disruption, but their risk increased 10% for each additional behavior ($p = .013$). The intervention appeared to mitigate this "threshold effect"; number of problem behaviors did not predict risk of placement disruption in the treatment foster care group ($p = .63$). These findings replicate previous evidence linking child problem behavior to placement disruptions and further highlight the need for early preventative interventions. Fisher P, Stoolmiller M, Mannering A, Takahashi A, Chamberlain P. Foster placement disruptions associated with problem behavior: mitigating a threshold effect. J Consult Clin Psychol. 2011; 79(4): 481-487.

The Effect of the PROSPER Partnership Model on Cultivating Local Stakeholder Knowledge of Evidence-Based Programs: A Five-Year Longitudinal Study of 28 Communities A substantial challenge in improving public health is how to facilitate the local adoption of evidence-based interventions (EBIs). To do so, an important step is to build local stakeholders ' knowledge and decision-making skills regarding the adoption and implementation of EBIs. One EBI delivery system, called PROSPER (PROmoting School-community-university Partnerships to Enhance Resilience), has effectively mobilized community prevention efforts, implemented prevention programming with quality, and consequently decreased youth substance abuse. While these results are encouraging, another objective is to increase local stakeholder knowledge of best practices for adoption, implementation and evaluation of EBIs. Using a mixed methods approach, the authors assessed local stakeholder knowledge of these best practices over 5 years, in 28 intervention and control communities. Results indicated that the PROSPER

partnership model led to significant increases in expert knowledge regarding the selection, implementation, and evaluation of evidence-based interventions. Findings illustrate the limited programming knowledge possessed by members of local prevention efforts, the difficulty of complete knowledge transfer, and highlight one method for cultivating that knowledge. Crowley D, Greenberg M, Feinberg M, Spoth R, Redmond C. The effect of the PROSPER Partnership Model on cultivating local stakeholder knowledge of evidence-based programs: a five-year longitudinal study of 28 communities. Prev Sci. 2011; epub ahead of print.

Economic Analysis of Methamphetamine Prevention Effects and Employer Costs The goal of this research was to evaluate economically three interventions designed to prevent substance use in general populations of adolescents, specifically focusing on the prevention of methamphetamine use and its subsequent benefits to employers. In a randomized, controlled trial, three preventive interventions were delivered to 6th- or 7th-grade youth in 58 Iowa school districts, with 905 of these youth (449 girls) providing follow-up assessments as 12th graders. Intervention conditions included the family-focused Iowa Strengthening Families Program (ISFP), the school-based Life Skills Training (LST) program, and a combined condition of both the Strengthening Families Program: For Parents and Youth 10-14 (SFP10- 14; an ISFP revision) plus LST (LST + SFP10-14). Analyses based on intervention costs, 12th-grade methamphetamine use rates, and methamphetamine- related employer costs yielded estimates of intervention cost, cost-effectiveness, benefit-cost ratio, and net benefit. The ISFP lowered methamphetamine use by 3.9%, cost $25,385 to prevent each case, and had a benefit-cost ratio of 3.84, yielding a net benefit of $2,813 per youth. The LST program reduced methamphetamine use by 2.5%, required $5,122 per prevented case, and had a benefit-cost ratio of 19.04, netting $2,273 per youth. The combined LST + SFP10-14 prevention condition lowered methamphetamine use rates by 1.8%, cost $62,697 to prevent each case, had a benefit-cost ratio of 1.56, and netted $620 per youth. Findings were robust after varying a number of key parameters across a range of plausible values. Substance use prevention programming is economically feasible, particularly for effective interventions that have lower per person treatment delivery costs. (J. Stud. Alcohol Drugs, 72, 577-585, 2011). Guyll M, Spoth R, Max Crowley D. Economic analysis of methamphetamine prevention effects and employer costs. J Stud Alcohol Drugs. 2011; 72(4): 577-585.

The Developmental Impact of Two First Grade Preventive Interventions on Aggressive/Disruptive Behavior in Childhood and Adolescence: An Application of Latent Transition Growth Mixture Modeling The authors examine the impact of two universal preventive interventions in first grade on the growth of aggressive/disruptive behavior in grades 1-3 and 6-12 through the application of a latent transition growth mixture model (LT-GMM). Both the classroom-centered and family-centered interventions were designed to reduce the risk for later conduct problems by enhancing the child behavior management practices of teachers and parents, respectively. They first modeled growth trajectories in each of the two time periods with separate GMMs. They then associated latent trajectory classes of aggressive/disruptive behavior across the two time periods using a transition model for the corresponding latent class variables. Subsequently, they tested whether the interventions had direct effects on trajectory class membership in grades 1-3 and 6-12. For males, both the classroom-centered and family-centered interventions had significant direct effects on trajectory class membership in grades 6-12, whereas only the classroom-centered intervention had a significant effect on class membership in grades 1-3. Significant direct effects for females were confined to grades 1-3 for the classroom-centered intervention. Further analyses revealed that both the classroom-centered

and family-centered intervention males were significantly more likely than control males to transition from the high trajectory class in grades 1-3 to a low class in grades 6-12. Effects for females in classroom-centered interventions went in the hypothesized direction but did not reach significance. Petras H, Masyn K, Ialongo N. The developmental impact of two first grade preventive interventions on aggressive/disruptive behavior in childhood and adolescence: an application of latent transition growth mixture modeling. Prev Sci. 2011; 12(3): 300-313.

The Effect of Two Elementary School-based Prevention Interventions on Being Offered Tobacco and the Transition to Smoking This study sought to more precisely delineate the mechanisms by which two early elementary school-based, universal (i.e., applied to the entire population regardless of risk status) preventive interventions increased survival to first tobacco cigarette smoked. Specifically, the authors examined whether the interventions' effect on survival to first use was via the reduction of offers to smoke and/or through preventing the transition from first offer to smoking. A total of 678 urban first-graders were assigned randomly to the classroom-centered (CC), or the family-school partnership (FSP), or a control classroom condition. Youth were followed annually until 1 year beyond their anticipated high school graduation (mean age <18 years). Discrete-time survival analyses on 628 youth evaluated the impact of the CC and FSP interventions on first tobacco offer and initial tobacco smoking once offered. The risk of being offered tobacco was reduced among both CC and FSP intervention groups relative to the control group, although the reduction was only statistically significant for the CC intervention. Neither intervention condition reduced the transition to smoking once offered tobacco to smoke. The CC intervention appeared to have its effect on survival to first cigarette smoked by delaying the first offer to smoke. Preventive interventions focused on refusal skills during the middle school years may be necessary to reduce the likelihood of the transition to smoking once offered. Wang Y, Storr C, Green K, Zhu S, Stuart E, Lynne-Landsman S, Clemans K, Petras H, Kellam S, Ialongo N. The effect of two elementary school-based prevention interventions on being offered tobacco and the transition to smoking. Drug Alcohol Depend. 2011.

Preliminary Support for Multidimensional Treatment Foster Care in Reducing Substance Use in Delinquent Boys Although effective outpatient treatments have been identified for the well-documented negative outcomes associated with delinquency and substance use, effective treatments for youths in out-of-home care are rare. In this study, 12- and 18-month substance use outcomes were examined for a sample of 79 boys who were randomly assigned to Multidimensional Treatment Foster Care (experimental condition) or to group care (comparison condition). The boys in the experimental condition had lower levels of self-reported drug use at 12 months and lower levels of tobacco, marijuana, and other drug use at 18 months. Limitations and future directions are discussed. Smith D, Chamberlain P, Eddy J. Preliminary support for multidimensional treatment foster care in reducing substance use in delinquent boys. J Child Adolesc Subst Abuse. 2010; 19(4): 343-358.

Couple-Based HIV Prevention for Low-Income Drug Users from New York City: A Randomized Controlled Trial to Reduce Dual Risks Dual threats of injection drug use and risky sexual practices continue to increase transmission of HIV and other sexually transmitted Infections (STIs) among drug-using couples in low-income communities in the United States. Two hypotheses were tested: (1) "intervention effect"-whether the HIV risk-reduction intervention provided to the couple or individual partners would be more efficacious in decreasing number of unprotected sexual acts and having a lower cumulative incidence of

biologically confirmed STIs over the 12-month follow-up period compared with the attention control condition; and (2) "modality effect"-whether the HIV risk-reduction intervention would be more likely to decrease the number of unprotected sexual acts and have a lower cumulative STI incidence when delivered to a couple compared with the same intervention delivered to an individual. Using a randomized controlled trial, 282 HIV-negative drug-using couples (564 individuals) were randomly assigned to receive either of the following: (1) couple-based risk reduction; (2) individual-based HIV risk reduction, or (3) couple-based wellness promotion, which served as an attention control condition. Over 12-month follow-up, there was a 30% reduction in the incidence rate of unprotected acts of intercourse with the study partners compared with participants in the attention control arm. Moreover, over 12-month follow-up there was a 29% reduction in the same outcome in the couple arm compared with the individual arm with a 41% reduction at the 12-month follow-up. A couple-based approach that addresses drug and sexual risks and targets low-income active drug users may help curb the HIV epidemic. El-Bassel N, Gilbert L, Wu E, Witte S, Chang M, Hill J, Remien R. Couple-based HIV prevention for low-income drug users from New York City: A randomized controlled trial to reduce dual risks. J Acquir Immune Defic Syndr. 2011; 58(2): 198-206.

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 J, Criss M, Laird R, Shaw D, Pettit G, Bates J, Dodge K. Reciprocal relations between parents' physical discipline and children 's externalizing behavior during middle childhood and adolescence. Dev Psychopathol. 2011; 23(1): 225-238.

Prefrontal Cortex and Drug Abuse Vulnerability: Translation to Prevention and Treatment Interventions Vulnerability to drug abuse is related to both reward seeking and impulsivity, two constructs thought to have a biological basis in the prefrontal cortex (PFC). This review addresses similarities and differences in neuroanatomy, neurochemistry and behavior associated with PFC function in rodents and humans. Emphasis is placed on monoamine and amino acid neurotransmitter systems located in anatomically distinct subregions: medial prefrontal cortex (mPFC); lateral prefrontal cortex (lPFC); anterior cingulate cortex (ACC); and orbitofrontal cortex (OFC). While there are complex interconnections and overlapping functions among these regions, each is thought to be involved in various functions related to health-related risk behaviors and drug abuse vulnerability. Among the various functions implicated, evidence suggests that mPFC is involved in reward processing, attention and drug reinstatement; lPFC is involved in decision-making, behavioral inhibition and attentional gating; ACC is involved in

attention, emotional processing and self-monitoring; and OFC is involved in behavioral inhibition, signaling of expected outcomes and reward/punishment sensitivity. Individual differences (e.g., age and sex) influence functioning of these regions, which, in turn, impacts drug abuse vulnerability. Implications for the development of drug abuse prevention and treatment strategies aimed at engaging PFC inhibitory processes that may reduce risk-related behaviors are discussed, including the design of effective public service announcements, cognitive exercises, physical activity, direct current stimulation, feedback control training and pharmacotherapies. A major challenge in drug abuse prevention and treatment rests with improving intervention strategies aimed at strengthening PFC inhibitory systems among at-risk individuals. Perry J, Joseph J, Jiang Y, Zimmerman R, Kelly T, Darna M, Huettl P, Dwoskin L, Bardo M. Prefrontal cortex and drug abuse vulnerability: translation to prevention and treatment interventions. Brain Res Rev. 2011; 65(2): 124-149.

A Comparison of the Associations of Caffeine and Cigarette Use with Depressive and ADHD Symptoms in a Sample of Young Adult Smokers This study examined the relationship between psychiatric symptoms and nicotine, caffeine, alcohol, and marijuana use in young adult smokers. Young adult smokers completed self-report measures of nicotine, caffeine, alcohol and marijuana use, Conner 's Adult ADHD (Attention-Deficit/Hyperactivity Disorder) Rating Scale-Short Version (CAARS-SS), Beck Depression and Anxiety Inventories (BDI and BAI), and provided a breath carbon monoxide (CO) sample. Self-reported cigarette use was positively correlated with carbon monoxide, CAARS-SS and the BDI levels. Caffeine intake was correlated with CAARS-SS, BAI and BDI levels and emerged as the more significant predictor of BDI, BAI and CAARS-SS scores when regressed with cigarette use. Caffeine use is associated with psychiatric symptoms in young adult cigarette smokers and should be considered in future research. Dosh T, Helmbrecht T, Anestis J, Guenthner G, Kelly T, Martin C. A Comparison of the associations of caffeine and cigarette use with depressive and ADHD symptoms in a sample of young adult smokers. J Addict Med. 2010; 4(1): 52-54.

Effects of a Social-emotional and Character Development Program on the Trajectory of Behaviors associated with Social-emotional and Character Development: Findings from Three Randomized Trials The effects of a school-based social-emotional and character development program, Positive Action, on the developmental trajectory of social-emotional and character-related behaviors was evaluated using data from three school-based randomized trials in elementary schools. Results come from 1) 4 years of data from students in 20 Hawai 'i schools, 2) 3 years of data from students in 14 schools in Chicago and 3) 3 years of data from students in 8 schools in a southeastern state. Random intercept, multilevel, growth-curve analyses showed that students in both control and Positive Action schools exhibited a general decline in the number of positive behaviors associated with social-emotional and character development that were endorsed. However, the Positive Action intervention significantly reduced these declines in all three trials. Taken together, these analyses 1) give insight into the normative trajectory of behaviors associated with social-emotional and character development and 2) provide evidence for the effectiveness of Positive Action in helping children maintain a relatively beneficial developmental trajectory. Washburn I, Acock A, Vuchinich S, Snyder F, Li K, Ji P, Day J, Dubois D, Flay B. Effects of a social-emotional and character development program on the trajectory of behaviors associated with social-emotional and character development: findings from three randomized trials. Prev Sci. 2011; 12(3): 314-323.

Natural Mentoring Processes Deter Externalizing Problems among Rural African American Emerging Adults: A Prospective Analysis A 3-wave model linking natural mentoring relationships to externalizing behavior was tested with 345 rural African American emerging adults in their final year of high school. Structural equation models were executed linking multi-informant reports of mentor-emerging adult relationship quality with youths' externalizing behavior 18 months later. Consistent with the authors' primary hypotheses, emerging adults whose relationships with their natural mentors were characterized by instrumental and emotional support and affectively positive interactions reported lower levels of anger, rule-breaking behavior, and aggression. These effects emerged independent of the influences of family support and youth gender. Two intrapersonal processes, a future orientation and self-regulation, emerged as mediators of the influence of natural mentoring relationships. The influence of natural mentors was most pronounced for emerging adults experiencing high levels of life stress. Kogan S, Brody G, Chen Y. Natural Mentoring Processes Deter Externalizing Problems Among Rural African American Emerging Adults: A Prospective Analysis. Am J Community Psychol. 2011; online first.

HIV Risk Profiles among HIV-positive, Methamphetamine-using Men Who Have Sex with Both Men and Women This study examined demographic characteristics, sexual risk behaviors, sexual beliefs, and substance use patterns in HIV-positive, methamphetamine-using men who have sex with both men and women (MSMW) (n = 50) as compared to men who have sex with men only (MSM) (n = 150). Separate logistic regressions were conducted to predict group membership. In the final model, of 12 variables, eight were independently associated with group membership. Factors independently associated with MSMW were acquiring HIV through injection drug use, being an injection drug user, using hallucinogens, using crack, being less likely to have sex at a bathhouse, being less likely to be the receptive partner when high on methamphetamine, having greater intentions to use condoms for oral sex, and having more negative attitudes about HIV disclosure. These results suggest that, among HIV-positive methamphetamine users, MSMW differ significantly from MSM in terms of their HIV risk behaviors. Studies of gay men and HIV often also include bisexual men, grouping them all together as MSM, which may obscure important differences between MSMW and MSM. It is important that future studies consider MSM and MSMW separately in order to expand our knowledge about differential HIV prevention needs for both groups. This study showed that there were important differences in primary and secondary prevention needs of MSM and MSMW. These findings have implications for both primary and secondary HIV prevention among these high-risk populations. Nakamura N, Semple SJ, Strathdee SA, Patterson TL. HIV risk profiles among HIV-positive, methamphetamine-using men who have sex with both men and women. Arch Sex Behav. 2011; EPub.

One-year Outcomes of a Drug Abuse Prevention Program for Older Teens and Emerging Adults: Evaluating a Motivational Interviewing Booster Component The present study tested the efficacy of motivational interviewing-based booster sessions for Project Toward No Drug Abuse (TND), a 12-session school-based curriculum targeting youth at risk for drug abuse. In addition, generalization of effects to risky sexual behavior was assessed. The 1-year outcomes evaluation of the project is presented. A total of 24 schools were randomized to one of three conditions: standard care control (SCC), TND classroom program only (TND-only), and TND plus motivational interviewing booster (TND + MI). A total of 1186 participants completed baseline and 1-year follow-up surveys. Following the classroom program, youth in the TND + MI condition received up to 3 sessions of MI in person or by telephone. Effects were examined

on 30-day cigarette, alcohol, marijuana, and hard drug use, as well as measures of risky sexual behavior (number of sex partners, condom use, having sex while using drugs or alcohol). Collapsed across the 2 program conditions, results showed significant reductions in alcohol use, hard drug use, and cigarette smoking relative to controls. These effects held for an overall substance use index. The MI booster component failed to achieve significant incremental effects above and beyond the TND classroom program. No effects were found on risky sexual behavior. While the program effects of previous studies were replicated, the study failed to demonstrate that an adequately implemented MI booster was of incremental value at 1-year follow-up. (PsycINFO Database Record (c) 2011 APA, all rights reserved). Sussman S, Sun P, Rohrbach L, Spruijt-Metz D. One-year outcomes of a drug abuse prevention program for older teens and emerging adults: Evaluating a motivational interviewing booster component. Health Psychol. 2011.

Positive Childhood Experiences and Positive Adult Functioning: Prosocial Continuity and the Role of Adolescent Substance Use The purpose of this study was to examine positive childhood experiences as predictors of positive adult functioning, including civic involvement, productivity and responsibility, interpersonal connection, and physical exercise; and to examine adolescent substance use as a mediator of prosocial continuity. A total of 429 rural participants were interviewed across seven waves from age 11 to 22 years. Structural equation models examined the relationship between positive childhood experiences and adult functioning, with adolescent substance use added to each model as a possible mediating mechanism. Positive childhood experiences predicted significantly better adult functioning for each model, even after accounting for adolescent substance use. Positive childhood experiences also consistently predicted significantly less adolescent substance use. In turn, adolescent substance use predicted significantly less civic involvement and less productivity and responsibility, but was not associated with interpersonal connection or physical exercise when accounting for childhood experiences. Results were largely consistent across gender and levels of family income. Findings show the enduring importance of positive childhood experiences in predicting positive functioning in early adulthood. Although adolescent substance use increased risk for poorer functioning in important domains of adult life, results suggest that positive experiences in late childhood continued to have a significant prosocial effect into young adulthood. The study also highlights the late elementary grades as a time when parents, teachers, and others can potentially have a large influence in proactively providing prosocial opportunities for children. Kosterman R, Mason W, Haggerty K, Hawkins J, Spoth R, Redmond C. Positive childhood experiences and positive adult functioning: prosocial continuity and the role of adolescent substance use. J Adolesc Health. 2011; 49(2): 180-186.

Behavioral and Emotional Regulation and Adolescent Substance Use Problems: A Test of Moderation Effects in a Dual-process Model In a structural model, the authors tested how relations of predictors to level of adolescent substance use (tobacco, alcohol, marijuana), and to substance-related impaired-control and behavior problems, are moderated by good self-control and poor regulation in behavioral and emotional domains. The participants were a sample of 1,116 public high-school students. In a multiple-group analysis for good self-control, the paths from negative life events to substance use level and from level to behavior problems were lower among persons scoring higher on good behavioral self-control. In a multiple-group analysis for poor regulation, the paths from negative life events and peer use to level of substance use were greater among persons scoring higher on poor behavioral (but not emotional) regulation; an inverse path from academic competence to level was greater among persons scoring higher on

both aspects of poor regulation. Paths from level to impaired-control and behavior problems were greater among persons scoring higher on both poor behavioral and poor emotional regulation. Theoretical implications concerning the role of behavioral and emotional regulation in moderation effects are discussed. Wills T, Pokhrel P, Morehouse E, Fenster B. Behavioral and emotional regulation and adolescent substance use problems: a test of moderation effects in a dual-process model. Psychol Addict Behav. 2011; 25(2): 279-292.

Bullying at Elementary School and Problem Behaviour in Young Adulthood: A Study of Bullying, Violence and Substance Use from Age 11 to Age 21 The main aim of this paper is to investigate to what extent self-reported bullying at Grade 5 predicts later violence, heavy drinking and marijuana use at age 21. Univariate and multivariate associations between bullying and later outcomes were examined based on a longitudinal community sample of 957 young people from the Raising Healthy Children project. Childhood bullying was significantly associated with violence, heavy drinking and marijuana use at age 21. These associations held up after controlling for prior risk factors. Childhood bullying had unique associations with risk of later violence and substance use among young adults. Early intervention to prevent childhood bullying may also reduce other adverse outcomes later in life. Kim M, Catalano R, Haggerty K, Abbott R. Bullying at elementary school and problem behaviour in young adulthood: a study of bullying, violence and substance use from age 11 to age 21. Crim Behav Ment Health. 2011; 21 (2): 136-144.

Preventing Internalizing and Externalizing Problems in Girls in Foster Care as They Enter Middle School: Impact of an Intervention Girls in foster care have been shown to be at risk for emotional and behavioral problems, especially during the preadolescent and adolescent years. Based on these findings and on the lack of research-based preventive interventions for such youths, the current study examined the impact of an intervention targeting the prevention of internalizing and externalizing problems for girls in foster care prior to middle school entry. Study participants included 100 girls in state-supported foster homes who were randomly assigned to an intervention condition or to a control condition (foster care services as usual). The intervention girls were hypothesized to have fewer internalizing problems, fewer externalizing problems, and more prosocial behavior at 6-months post-baseline compared to the control girls. The results confirmed the hypotheses for internalizing and externalizing problems, but not for prosocial behavior. Limitations and future directions are discussed. Smith D, Leve L, Chamberlain P. Preventing internalizing and externalizing problems in girls in foster care as they enter middle school: impact of an intervention. Prev Sci. 2011; 12(3): 269-277.

A Short-term Longitudinal Analysis of Friendship Selection on Early Adolescent Substance Use There is a strong empirical connection between individual and peer substance use during adolescence. The determination of whether this level of covariation reflects influence or selection is obscured by both the design and measurement strategies used. This present study utilizes a short-term longitudinal design with bi-monthly assessments to address the following two hypotheses: a) Adolescents select friends on the basis of their substance use, and b) New friend substance use predicts changes in future use. French Canadian adolescents (n = 143) were interviewed on their friendship networks and substance use behaviors (e.g., tobacco, alcohol and marijuana) four times during a school year. Cross-lag panel models revealed that adolescents who use substances tend to select new friends who use. Moreover, once in the network, these new friends also contribute to changes in the adolescents' substance use. These findings are relevant to understanding the multiple functions of adolescent substance use. Poulin F, Kiesner J,

Pedersen S, Dishion T. A short-term longitudinal analysis of friendship selection on early adolescent substance use. J Adolesc. 2011; 34(2): 249-256.

Observed Parenting Behavior with Teens: Measurement Invariance and Predictive Validity across Race Previous reports supporting measurement equality between European American and African American families have often focused on self-reported risk factors or observed parent behavior with young children. This study examines equality of measurement of observer ratings of parenting behavior with adolescents during structured tasks; mean levels of observed parenting; and predictive validity of teen self-reports of antisocial behaviors and beliefs using a sample of 163 African American and 168 European American families. Multiple-group confirmatory factor analyses supported measurement invariance across ethnic groups for four measures of observed parenting behavior: prosocial rewards, psychological costs, antisocial rewards, and problem solving. Some mean-level differences were found: African American parents exhibited lower levels of prosocial rewards, higher levels of psychological costs, and lower problem solving when compared to European Americans. No significant mean difference was found in rewards for antisocial behavior. Multigroup structural equation models suggested comparable relationships across race (predictive validity) between parenting constructs and youth antisocial constructs (i.e., drug initiation, positive drug attitudes, antisocial attitudes, problem behaviors) in all but one of the tested relationships. This study adds to existing evidence that family-based interventions targeting parenting behaviors can be generalized to African American families. Skinner M, Mackenzie E, Haggerty K, Hill K, Roberson K. Observed parenting behavior with teens: measurement invariance and predictive validity across race. Cultur Divers Ethnic Minor Psychol. 2011; 17(3): 252-260.

Helping Military Families through the Deployment Process: Strategies to Support Parenting Recent studies have highlighted the impact of deployment on military families and children and the corresponding need for interventions to support them. Historically, however, little emphasis has been placed on family-based interventions in general, and parenting interventions in particular, with returning service members. This paper provides an overview of research on the associations between combat deployment, parental adjustment of service members and spouses, parenting impairments, and children's adjustment problems, and provides a social interaction learning framework for research and practice to support parenting among military families affected by a parent's deployment. The authors then describe the Parent Management Training-Oregon model (PMTO) a family of interventions that improves parenting practices and child adjustment in highly stressed families, and briefly present work on an adaptation of PMTO for use in military families (After Deployment: Adaptive Parenting Tools, or ADAPT). The article concludes with PMTO-based recommendations for clinicians providing parenting support to military families. Gewirtz A, Erbes C, Polusny M, Forgatch M, Degarmo D. Helping military families through the deployment process: strategies to support parenting. Prof Psychol Res Pr. 2011; 42(1): 56-62.

Reducing Substance Use and HIV Health Disparities among Hispanic Youth in the U.S.A.: The Familias Unidas Program of Research Preventing/reducing substance use and HIV among Hispanic youth is essential to eliminating the health disparities that exist between Hispanics and other segments of the population. The objective of this article was to describe a program of research involving Familias Unidas, a Hispanic-specific, parent-centered intervention, aimed at reducing substance use and HIV health disparities among Hispanic youth. This article focused on the theoretical foundation of the intervention, the empirical research

supporting the theoretical model, the intervention model itself, the findings of the program of research, and the translation of this intervention into community practice. Prado G, Pantin H. reducing substance use and hiv health disparities among Hispanic youth in the U.S.A.: The Familias Unidas Program of Research. Interv Psicosoc. 2011; 20(1): 63-73.

A Longitudinal Examination of Early Adolescence Ethnic Identity Trajectories Early adolescence is marked by transitions for adolescents, and is also a time for identity exploration. Ethnic identity is an essential component of youths' sense of self. In this study the authors examined the trajectories of ethnic identity for adolescents from ethnic minority backgrounds during a 4-year period. Six latent class trajectories were identified in the study: the majority of adolescents (41.8%) displayed growth in ethnic identity over 4 years, followed by 30.1% whose high levels of ethnic identity remained stable, then by those who experienced moderate decreases in ethnic identity (10.8%). Another class of adolescents (7.3%) showed significant declines in ethnic identity level, followed by 5.5% of adolescents with significant increases, and finally by 4.5% of adolescents with low stable levels of ethnic identity during this developmental period. The classes differed by ethnicity, and adolescents with increasing high levels of ethnic identity reported better parent-child relationships. Findings and implications are discussed. Huang C, Stormshak E. A Longitudinal examination of early adolescence ethnic identity trajectories. Cultur Divers Ethnic Minor Psychol. 2011; 17(3): 261-270.

Pathways to Sexual Risk Taking among Female Adolescent Detainees Sexual risk taking among female delinquents represents a significant public health problem. Research is needed to understand the pathways leading to sexual risk taking among this population. This study sought to address this issue by identifying and testing two pathways from child maltreatment to non-condom use among 329 White and 484 African American female adolescent detainees: a relational pathway and a substance use coping pathway. The relational pathway indicated that child maltreatment would be related to non-condom use via depressive self-concept and condom use self-efficacy. The substance use coping pathway suggested that depressive self-concept and alcohol-based expectancies for sexual enhancement would mediate the relationship between child maltreatment and non-condom use. As hypothesized, the relational pathway variables were associated with one another in the expected directions; however, evidence of mediation was not found. Support for mediation was found for the substance use coping pathway. Exploratory across group comparison analysis indicated that the relational pathway was significant for White girls whereas the substance use coping pathway was significant for African American girls. Limitations and implications for future research are discussed. Lopez V, Kopak A, Robillard A, Gillmore M, Holliday R, Braithwaite R. Pathways to sexual risk taking among female adolescent detainees. J Youth Adolesc. 2011; 40(8): 945-957.

Problem Profiles of At-Risk Youth in Two Service Programs: A Multi-Group, Exploratory Latent Class Analysis Baseline data collected in two brief intervention projects (BI-Court and Truancy Project) were used to assess similarities and differences in subgroups of at-risk youth. Classifications of these subgroups were based on their psychosocial characteristics (e.g., substance use). Multi-group latent class analysis (LCA) identified two BI-Court subgroups of youth, and three Truant subgroups. These classes can be viewed as differing along two dimensions, substance use involvement and emotional/behavioral issues. Equality tests of means across the latent classes for BI-Court and Truancy Project youths found significant differences that were consistent with their problem group classification. These findings highlight the importance of quality assessments and allocating appropriate services based on problem profiles

of at-risk youth. Dembo R, Briones-Robinson R, Ungaro R, Karas L, Gulledge L, Greenbaum P, Schmeidler J, Winters K, Belenko S. Problem profiles of at-risk youth in two service programs: a multi-group, exploratory latent class analysis. Crim Justice Behav. 2011; 38(10): 988-1008.

Benzodiazepine Dependence among Multidrug Users in the Club Scene Benzodiazepines (BZs) are among the most frequently prescribed drugs with the potential for abuse. Young adults ages 18-29 report the highest rates of BZ misuse in the United States. The majority of club drug users are also in this age group, and BZ misuse is prevalent in the nightclub scene. BZ dependence, however, is not well documented. This paper examines BZ dependence and its correlates among multidrug users in South Florida's nightclub scene. Data were drawn from structured interviews with men and women (N=521) who reported regular attendance at large dance clubs and recent use of both club drugs and BZs. Prevalences of BZ-related problems were 7.9% for BZ dependence, 22.6% BZ abuse, and 25% BZ abuse and/or dependence. In bivariate logistic regression models, heavy cocaine use (OR 2.27; 95% CI 1.18, 4.38), severe mental distress (OR 2.63; 95% CI 1.33, 5.21), and childhood victimization history (OR 2.43; 95% CI 1.10, 5.38) were associated with BZ dependence. Heavy cocaine use (OR 2.14; 95% CI 1.10, 4.18) and severe mental distress (OR 2.16; 95% CI 1.07, 4.37) survived as predictors in the multivariate model. BZ misuse is widespread among multidrug users in the club scene, who also exhibit high levels of other health and social problems. BZ dependence appears to be more prevalent in this sample than in other populations described in the literature. Recommendations for intervention and additional research are described. Kurtz S, Surratt H, Levi-Minzi M, Mooss A. Benzodiazepine dependence among multidrug users in the club scene. Drug Alcohol Depend. 2011.

Linking Impulsivity and Inhibitory Control Using Manual and Oculomotor Response Inhibition Tasks Separate cognitive processes govern the inhibitory control of manual and oculomotor movements. Despite this fundamental distinction, little is known about how these inhibitory control processes relate to more complex domains of behavioral functioning. This study sought to determine how these inhibitory control mechanisms relate to broadly defined domains of impulsive behavior. Thirty adults with attention-deficit/hyperactivity disorder (ADHD) and 28 comparison adults performed behavioral measures of inhibitory control and completed impulsivity inventories. Results suggest that oculomotor inhibitory control, but not manual inhibitory control, is related to specific domains of self-reported impulsivity. This finding was limited to the ADHD group; no significant relations between inhibitory control and impulsivity were found in comparison adults. These results highlight the heterogeneity of inhibitory control processes and their differential relations to different facets of impulsivity. Roberts W, Fillmore M, Milich R. Linking impulsivity and inhibitory control using manual and oculomotor response inhibition tasks. Acta Psychol (Amst). 2011.

Joint Modeling of Longitudinal Data in Multiple Behavioral Change Multiple behavioral change is an exciting and evolving research area, albeit one that presents analytic challenges to investigators. This manuscript considers the problem of modeling jointly trajectories for two or more possibly non-normally distributed dependent variables, such as marijuana smoking and risky sexual activity, collected longitudinally. Of particular scientific interest is applying such modeling to elucidate the nature of the interaction, if any, between an intervention and personal characteristics, such as sensation seeking and impulsivity. The authors describe three analytic approaches: generalized linear mixed modeling, group-based trajectory modeling, and latent growth curve modeling. In particular, the authors identify the strengths and weaknesses of these

analytic approaches and assess their impact (or lack thereof) on the psychological and behavioral science literature. The authors also compare what investigators have been doing analytically versus what they might want to be doing in the future and discuss the implications for basic and translational research. Charnigo R, Kryscio R, Bardo M, Lynam D, Zimmerman R. Joint modeling of longitudinal data in multiple behavioral change. Eval Health Prof. 2011; 34 (2): 181-200.

Do Different Facets of Impulsivity Predict Different Types of Aggression? This study examined the relations between impulsivity-related traits (as assessed by the UPPS-P Impulsive Behavior Scale) and aggressive behaviors. Results indicated that UPPS-P Lack of Premeditation and Sensation Seeking were important in predicting general violence. In contrast, UPPS-P Urgency was most useful in predicting intimate partner violence. To further explore relations between intimate partner violence and Urgency, a measure of autonomic response to pleasant and aversive stimuli and facets of Neuroticism from the NEO PI-R were used as control variables. Autonomic responsivity was correlated with intimate partner violence at the zero-order level, and predicted significant variance in intimate partner violence in regression equations. However, UPPS-P Urgency was able to account for unique variance in intimate partner violence, above and beyond measures of Neuroticism and arousal. Implications regarding the use of a multifaceted conceptualization of impulsivity in the prediction of different types of violent behavior are discussed. Derefinko K, DeWall C, Metze A, Walsh E, Lynam D. Do different facets of impulsivity predict different types of aggression? Aggress Behav. 2011; 37(3): 223-233.

Reporting Rape in a National Sample of College Women Studies indicate that a small percentage of rapes are reported to law enforcement officials. Research also suggests that rapes perpetrated by a stranger are more likely to be reported and that rapes involving drugs and/or alcohol are less likely to be reported. College women represent a unique and understudied population with regard to reporting rape. In the current study, the authors interviewed a national sample of 2,000 college women about rape experiences in 2006. Only 11.5% of college women in the sample reported their most recent/only rape experience to authorities, with only 2.7% of rapes involving drugs and/or alcohol reported. Minority status (ie, nonwhite race) was associated with lower likelihood of reporting, whereas sustaining injuries during the rape was associated with increased likelihood of reporting. Reporting, particularly for rapes involving drugs and alcohol, is low among college women. Implications for policy are discussed. Wolitzky-Taylor K, Resnick H, Amstadter A, McCauley J, Ruggiero K, Kilpatrick D. Reporting rape in a national sample of college women. J Am Coll Health. 2011; 59(7): 582-587.

A Multivariate Assessment of Individual Differences in Sensation Seeking and Impulsivity as Predictors of Amphetamine Self-administration and Prefrontal Dopamine Function in Rats Drug abuse vulnerability has been linked to sensation seeking (behaviors likely to produce rewards) and impulsivity (behaviors occurring without foresight). Since previous preclinical work has been limited primarily to using single tasks as predictor variables, the present study determined if measuring multiple tasks of sensation seeking and impulsivity would be useful in predicting amphetamine self-administration in rats. Multiple tasks were also used as predictor variables of dopamine transporter function in the medial prefrontal and orbitofrontal cortexes, as these neural systems have been implicated in sensation seeking and impulsivity. Rats were tested on six behavioral tasks as predictor variables to evaluate sensation seeking (locomotor activity, novelty place preference, and sucrose reinforcement on a progressive ratio schedule) and impulsivity (delay discounting, cued go/no-go, and passive avoidance), followed by

d-amphetamine self-administration (0.0056-0.1 mg/kg infusion) and kinetic analysis of dopamine transporter function as outcome variables. The combination of these predictor variables into a multivariate approach failed to yield any clear relationship among predictor and outcome measures. Using multivariate approaches to understand the relation between individual predictor and outcome variables in preclinical models may be hindered by alterations in behavior due to training and thus, the relation between various individual differences in behavior and drug self-administration may be better assessed using a univariate approach in which a only a single task is used as the predictor variable. Marusich J, Darna M, Charnigo R, Dwoskin L, Bardo M. A Multivariate assessment of individual differences in sensation seeking and impulsivity as predictors of amphetamine self-administration and prefrontal dopamine function in rats. Exp Clin Psychopharmacol. 2011; 19 (4): 275-284.

Going through the Rites of Passage: Timing and Transition of Menarche, Childhood Sexual Abuse, and Anxiety Symptoms in Girls Menarche is a discrete, transitional event that holds considerable personal, social, biological, and developmental significance. The present longitudinal study examined both the transition and timing of menarche on the trajectory of anxiety in girls with histories of childhood maltreatment (N = 93; 63% European American, 14% multiracial, 10% Latino, 9% African American, and 4% Native American). The authors hypothesized that because menarche is a novel, unfamiliar experience, girls would show greater anxiety around the time of menarche. The anxiety-provoking nature of menarche may be accentuated among earlier-maturing girls and girls with histories of childhood sexual abuse. Results indicated that earlier-maturing girls were more anxious in the pre- and peri-menarche periods than their later-maturing peers; however, their anxiety declined after menarche. Childhood sexual abuse was associated with heightened anxiety throughout this transition. The developmental significance of the timing and transition of menarche in relation to childhood sexual abuse and anxiety is discussed. Natsuaki M, Leve L, Mendle J. Going Through the rites of passage: Timing and transition of menarche, childhood sexual abuse, and anxiety symptoms in girls. J Youth Adolesc. 2011; 40(10): 1357-1370.

Understanding Early-onset Drug and Alcohol Outcomes among Youth Research on adolescents focuses increasingly on features of the family in predicting and preventing illicit substance use. Multivariate analyses of data from the National Survey of Parents and Youth (N=4173) revealed numerous significant differences on risk variables associated with family structure on adolescent drug-related perceptions and substance use. Youth from dual-parent households were least likely to use drugs and were monitored more closely than single-parent youth ($p<0.001$). A path analytic model estimated to illuminate linkages among theoretically implicated variables revealed that family income and child's gender ($p<0.001$), along with family structure ($p<0.05$), affected parental monitoring, but not parental warmth. Monitoring and warmth, in turn, predicted adolescents' social and interpersonal perceptions of drug use ($p<0.001$), and both variables anticipated adolescents' actual drug use one year later ($p<0.001$). Results reconfirm the importance of parental monitoring and warmth and demonstrate the link between these variables, adolescents' social and intrapersonal beliefs, and their use of illicit substances. Hemovich V, Lac A, Crano W. Understanding early-onset drug and alcohol outcomes among youth: the role of family structure, social factors, and interpersonal perceptions of use. Psychol Health Med. 2011; 16(3): 249-267.

Middle School Friendships and Academic Achievement in Early Adolescence: A Longitudinal Analysis Early adolescence is a critical transition period for the maintenance of academic achievement. One factor that school systems often fail to take into account is the influence of friends on academic achievement during middle school. This study investigated the influence of friends' characteristics on change in academic achievement from Grade 6 through 8, and the role of students ' own characteristics as moderators of this relationship. The sample included 1,278 participants (698 girls). Linear regressions suggest that students with academically engaged friends may achieve to levels higher than expected in Grade 8. However, when considering the significant, negative influence of friends ' problem behavior, the role of friend's school engagement became nonsignificant. Low-achieving girls who had high-achieving friends in Grade 6 had lower academic achievement than expected by Grade 8. In contrast, high-achieving girls seemed to benefit from having high-achieving friends. Implications for theory and prevention efforts targeting young adolescents are discussed. Véronneau M, Dishion T. Middle school friendships and academic achievement in early adolescence: a longitudinal analysis. J Early Adolesc. 2011; 31(1): 99-124.

Examining the Protective Effects of Brand Equity in the keepin' it REAL Substance Use Prevention Curriculum While branding appears to be an effective health prevention strategy, it is less clear how successful brands have protective effects. To better understand the role of branding in health prevention and promotion, it is necessary to examine how the persuasive mechanisms of branding function in health campaigns (e.g., modeling socially desirable behaviors). Using cross-sectional data (n = 709), the current study uncovered the mechanisms explaining branding's effects on adolescent substance use in a school-based substance use intervention, the keepin' it REAL (kiR) curriculum. Consistent with the authors' predictions, a confirmatory factor analysis suggested that kiR brand equity had a higher order, multidimensional factor structure. In addition, a path analysis revealed that brand equity affected adolescent substance use directly and through the predicted social cognitive processes, including refusal efficacy and resistance skills. Thus, it is concluded that kiR brand equity serves as a protective factor for adolescent substance use. Practical implications, research limitations, and future directions are discussed. Lee J, Hecht M. Examining the protective effects of brand equity in the keepin' it real substance use prevention curriculum. Health Commun. 2011; 26(7): 605-614.

Predicting Program Start-Up Using the Stages of Implementation Measure Recent efforts to better understand the process of implementation have been hampered by a lack of tools available to define and measure implementation progress. The Stages of Implementation Completion (SIC) was developed as part of an implementation trial of MTFC in 53 sites, and identifies the duration of time spent on implementation activities and the proportion of activities completed. This article examines the ability of the first three stages of the SIC (Engagement, Consideration of Feasibility, Readiness Planning) to predict successful program start-up. Results suggest that completing SIC stages completely, yet relatively quickly, predicts the likelihood of successful implementation. Saldana L, Chamberlain P, Wang W, Hendricks Brown C. Predicting program start-up using the stages of implementation measure. Adm Policy Ment Health. 2011; epub ahead of print.

Comparison of a Theory-based (AIDS Risk Reduction Model) Cognitive Behavioral Intervention versus Enhanced Counseling for Abused Ethnic Minority Adolescent Women: Results of a Randomized Control Trial Ethnic minority adolescent women with a history of sexual or physical abuse and sexually transmitted infections represent a vulnerable population at risk for HIV. Community-based interventions for behavior modification and subsequent risk reduction have not been effective among these women. The objectives of this study were to evaluate the effects of a theory-based (AIDS Risk Reduction Model) cognitive behavioral intervention model versus enhanced counseling for abused ethnic minority adolescent women on infection with sexually transmitted infection at 6 and 12 months follow-up. The study design was a controlled randomized trial with longitudinal follow-up conducted in a Southwestern United States, Metropolitan community-based clinic. Study participants were Mexican-and-African American adolescent women aged 14-18 years with a history of abuse or sexually transmitted infection seeking sexual health care. Extensive preliminary study for intervention development was conducted including individual interviews, focus groups, secondary data analysis, pre-testing and feasibility testing for modification of an evidence-based intervention prior to testing in the randomized controlled trial. Following informed consents for participation in the trial, detailed interviews concerning demographics, abuse history, sexual risk behavior, sexual health and physical exams were obtained. Randomization into either control or intervention groups was conducted. Intervention participants received workshop, support group and individual counseling sessions. Control participants received abuse and enhanced clinical counseling. Follow-up including detailed interview and physical exam was conducted at 6 and 12 months following study entry to assess for infection. Intention to treat analysis was conducted to assess intervention effects using chi-square and multiple regression models. 409 Mexican-(n=342) and African-(n=67) American adolescent women with abuse and sexually transmitted infection histories were enrolled; 90% intervention group attendance; longitudinal follow-up at 6 (93%) and 12 (94%) months. Intervention (n=199) versus control (n=210) group participants experienced fewer infections at 0-6 (0% versus 6.6%, p=.001), 6-12 (3.6% versus 7.8%, p=.005, CI 95% lower-upper .001-.386) and 0-12 (4.8% versus 13.2%, p=.002, CI 95% lower-upper, .002-.531) month intervals. A cognitive behavioral intervention specifically designed for ethnic minority adolescent women with a history of abuse and sexually transmitted infection was effective for prevention of infection. These results provide evidence for development of evidence-based interventions for sexually transmitted infection/HIV. Implications include translation to community-clinic-based settings for prevention of adverse outcomes regarding sexual health of adolescent women. Champion JD, Collins JL. Comparison of a theory-based (AIDS Risk Reduction Model) cognitive behavioral intervention versus enhanced counseling for abused ethnic minority adolescent women on infection with sexually transmitted infection: results of a randomized controlled trial. Int J Nurs Stud. 2011.

Self-Verification as a Mediator of Mothers' Self-fulfilling Effects on Adolescents' Educational Attainment This research examined whether self-verification acts as a general mediational process of self-fulfilling prophecies. The authors tested this hypothesis by examining whether self-verification processes mediated self-fulfilling prophecy effects within a different context and with a different belief and a different outcome than has been used in prior research. Results of longitudinal data obtained from mothers and their adolescents (N=332) indicated that mothers' beliefs about their adolescents' educational outcomes had a significant indirect effect on adolescents' academic attainment through adolescents' educational aspirations. This effect, observed over a 6-year span, provided evidence that mothers' self-fulfilling effects occurred, in part, because mothers' false beliefs influenced their adolescents' own educational aspirations,

which adolescents then self-verified through their educational attainment. The theoretical and applied implications of these findings are discussed. Scherr K, Madon S, Guyll M, Willard J, Spoth R. Self-verification as a mediator of mothers' self-fulfilling effects on adolescents' educational attainment. Pers Soc Psychol Bull. 2011; 37(5): 587-600.

Enrolling and Engaging High-Risk Youth and Families in Commuity-Based, Brief Intervention Services Increasing interest has been shown in Brief Interventions for troubled persons, including those with substance abuse problems. Most of the published literature on this topic has focused on adults, and on the efficacy of these interventions. Few of these studies have examined the critical issues of enrollment and engagement in Brief Intervention services. The present paper seeks to address the shortcomings in the current literature by reporting on our experiences implementing NIDA funded, Brief Intervention projects involving truant and diversion program youth. Dembo R, Gulledge L, Robinson R, Winters K. Enrolling and engaging high-risk youth and families in community-based, brief intervention services. J Child Adolesc Subst Abuse. 2011; 20(4): 330-335.

Popularity Trajectories and Substance Use in Early Adolescence This paper introduces new longitudinal network data from the "Promoting School-Community-University Partnerships to Enhance Resilience" or "PROSPER" peers' project. In 28 communities, grade-level sociometric friendship nominations were collected from two cohorts of middle school students as they moved from 6(th), to 9(th) grade. As an illustration and description of these longitudinal network data, this paper describes the school popularity structure, changes in popularity position, and suggests linkages between popularity trajectory and substance use. In the cross-section, the authors find that the network is consistent with a hierarchical social organization, but exhibits considerable relational change in both particular friends and position at the individual level. They find that both the base level of popularity and the variability of popularity trajectories effect substance use. Moody J, Brynildsen W, Osgood D, Feinberg M, Gest S. Popularity trajectories and substance use in early adolescence. Soc Networks. 2011; 33(2): 101-112.

Prereading Deficits in Children in Foster Care Reading skills are core competencies in children's readiness to learn and may be particularly important for children in foster care, who are at risk for academic difficulties and higher rates of special education placement. In this study, prereading skills (phonological awareness, alphabetic knowledge, and oral language ability) and kindergarten performance of 63 children in foster care were examined just prior to and during the fall of kindergarten. The children exhibited prereading deficits with average prereading scores that fell at the 30(th) to 40(th) percentile. Variations in prereading skills (particularly phonological awareness) predicted kindergarten teacher ratings of early literacy skills in a multivariate path analysis. These findings highlight the need for interventions focused on prereading skills for children in foster care. Pears K, Heywood C, Kim H, Fisher P. Prereading deficits in children in foster care. School Psych Rev. 2011; 40(1): 140-148.

Context of Sexual Risk Behaviour among Abused Ethnic Minority Adolescent Women Evidence suggests that multiple influences on sexual behaviour of adolescents exist, ranging from relationships with significant others including sexual or physical abuse and childhood molestation to substances used prior to sex and environmental circumstances such as sex work. This study aims to describe associations between childhood molestation and sexual risk behaviour. African American and Mexican American adolescent women aged 14-18 years (n=562) with sexually transmitted infection (STI) or abuse histories and enrolled in a randomized

controlled trial of behavioural interventions were interviewed via self-report concerning sexual risk behaviour, abuse and childhood molestation at study entry. Sexual (59%), physical (77%) and psychological (82%) abuse and childhood molestation (25%) were self-reported without differences by ethnicity. Adolescents reporting childhood molestation experienced more forms of sexual, physical and psychological abuse than others and higher incidences of STI. Fewer attended school; however, more had arrests, convictions, incarcerations and probations. Stressors including depression, running away, thoughts of death and suicide were highest for those reporting childhood molestation. Those reporting childhood molestation engaged in higher sexual risk behaviours than adolescents experiencing other forms of sexual or physical abuse (lifetime partners, bisexual relationships, anal and group sex, sex with friends with benefits, sex for money, concurrent partners, drug use including multiple substances, alcohol use and alcohol problems). These adolescents reported 'getting high ' and having sex when out of control as reasons for sex with multiple partners. Interventions for abused adolescent women necessitate a focus on associations between childhood molestation and a multiplicity of sexual risk behaviours for prevention of abuse, substance use and sex work, STI/human immunodeficiency virus (HIV) and sequelae. Champion J. Context of sexual risk behaviour among abused ethnic minority adolescent women. Int Nurs Rev. 2011; 58(1): 61-67.

The Path to Intervention: Community Partnerships and Development of a Cognitive Behavioral Intervention for Ethnic Minority Adolescent Females Reproductive health needs for ethnic minority adolescents are a national priority given the population growth of minority adolescents in the United States. United States census reports predict minority adolescents will comprise one-third of all young persons' less than 20 years of age early in the twenty-first century. Developing culturally sensitive interventions for minority adolescents includes ecological assessments of cultural priorities, community resources, disease burden, and socioeconomic conditions. These assessments must be accomplished in partnership with the local community. Understanding reproductive health needs necessarily includes an evaluation of the absence of reproductive health, namely, the prevalence of sexually transmitted infection (STI), sexual or physical abuse, unplanned pregnancy, and the risk factors that contribute to such adverse outcomes. This article describes the methodological processes utilized to conduct an ecological assessment of a community including the health, economic, and psychosocial status of, and resources available to, a target population prior to the implementation of a community-based, cognitive behavioral intervention to reduce STI, abuse, and unplanned pregnancy. Champion J, Collins J. The path to intervention: Community Partnerships and development of a cognitive behavioral intervention for ethnic minority adolescent females. Issues Ment Health Nurs. 2010; 31(11): 739-747.

Principles for Establishing Trust When Developing a Substance Abuse Intervention with a Native American Community This article traces the development of a research project with a Native American community. Four principles were used to guide the development of the "Community Partnership to Affect Cherokee Adolescent Substance Abuse" project using a community-based participatory research approach. The principles suggest that establishing trust is key when developing and conducting research with a Native American community. Lowe J, Riggs C, Henson J. Principles for establishing trust when developing a substance abuse intervention with a Native American community. Creat Nurs. 2011; 17(2): 68-73.

Associations between Early Life Stress, Child Maltreatment, and Pubertal Development among Girls in Foster Care The present study investigated pubertal development in girls with maltreatment histories (*N*=100), assessed at 4 time points over 2 years, beginning in the spring of their final year of elementary school. This sample is unique in that participants were subject to an unusual level of environmental risk early in life and resided in foster care at the start of the study. Analyses replicated the previously established association between sexual abuse and earlier onset of maturation and earlier age at menarche. Physical abuse was related to a more rapid tempo of pubertal development across the period assessed. These results strengthen previous investigations of childhood maltreatment and puberty, highlighting the complexity and specificity of early life experiences for later development. Mendle J, Leve LD, Van Ryzin M, Natsuaki MN, Ge X. Associations between early life stress, child maltreatment, and pubertal development among girls in foster care. J Res Adolesc. 2011.

Validity Evidence for the Security Scale as a Measure of Perceived Attachment Security in Adolescence In this study, the validity of a self-report measure of children's perceived attachment security (the Kerns Security Scale) was tested using adolescents. With regards to predictive validity, the Security Scale was significantly associated with (1) observed mother-adolescent interactions during conflict and (2) parent- and teacher-rated social competence. With regards to convergent validity, the Security Scale was significantly associated with all subscales of the Adult Attachment Scale (i.e., Depend, Anxiety, and Close) as measured 3 years later. Further, these links were found even after controlling for mother-child relationship quality as assessed by the Inventory of Parent and Peer Attachment (IPPA), and chi-square difference tests indicated that the Security Scale was generally a stronger predictor as compared to the IPPA. These results suggest that the Security Scale can be used to assess perceived attachment security across both childhood and adolescence, and thus could contribute significantly to developmental research during this period. Van Ryzin M, Leve L. Validity evidence for the security scale as a measure of perceived attachment security in adolescence. J Adolesc. 2011.

CLINICAL NEUROSCIENCE RESEARCH

The Galanin Receptor 1 Gene Associates with Tobacco Craving in Smokers Seeking Cessation Treatment Craving for tobacco is a major challenge for people with nicotine dependence (ND) who try to quit smoking. Galanin (GAL) and its receptors (GALRs) can alter addiction-related behaviors and are therefore good candidates for modulators of behavioral parameters associated with smoking. The authors performed a genetic association study in 486 subjects (432 European American, EA) recruited for smoking cessation trials. Twenty-six candidate genes for ND-related phenotypes were selected based on the literature. Subjects were assessed using the Minnesota Withdrawal Scale (MWS), which included a specific item for craving, the Fagerström Scale of Nicotine Dependence (FTND), and other ND-related instruments. One single-nucleotide polymorphism (SNP) in GALR1, rs2717162, significantly associated with severity of craving in EA samples ($p=6.48 \times 10(-6)$) and in the combined sample ($p=9.23 \times 10(-6)$). Individuals with TT and TC genotypes had significantly higher craving scores than CC subjects. The authors also observed that SNPs in the CHRNA5 locus, rs16969968 and rs684513, which have been associated with ND-related phenotypes in previous studies, were nominally associated with FTND scores, although these results did not meet Bonferroni-adjusted criteria for experiment-wide significance. These findings suggest that variation at GALR1 associates with differences in the severity of past craving for tobacco among smokers motivated to quit. Taken together with preclinical evidence, these results, if replicated, suggest that GAL and GALRs may be useful therapeutic targets for the pharmacological treatment of ND. These results also confirm previously reported associations between variation at CHRNA5 and ND. Lori A, Tang Y, O'Malley S, Picciotto MR, Wu R, Conneely KN, Cubells JF. The galanin receptor 1 gene associates with tobacco craving in smokers seeking cessation treatment. Neuropsychopharmacology. 2011 Jun; 36(7): 1412-1420.

fMRI Brain Activation During a Delay Discounting Task in HIV-positive Adults with and without Cocaine Dependence Cocaine use is associated with poorer HIV clinical outcomes and may contribute to neurobiological impairments associated with impulsive decision making. This study examined the effect of cocaine dependence on brain activation during a delay discounting task involving choices between smaller immediate rewards and larger delayed ones. Participants were 39 HIV-positive adults on antiretroviral therapy who had current cocaine dependence ("active," $n = 15$), past cocaine dependence ("recovered," $n = 13$), or no lifetime substance dependence ("naïve," $n = 11$). Based on responses on a traditional delay discounting task, three types of choices were individualized for presentation during functional magnetic resonance imaging: hard (similarly valued), easy (disparately valued), and no (single option). Active participants had significantly smaller increases in activation than naïve participants during hard versus easy choices bilaterally in the precentral gyrus and anterior cingulate cortex and in the right frontal pole (including dorsolateral, ventrolateral, and orbitofrontal cortex). During hard and easy choices relative to no choices, active participants had smaller increases in activation compared to naïve participants in frontoparietal cortical regions. These deficits in the executive network during delay discounting choices may contribute to impulsive decision making among HIV-positive cocaine users, with implications for risk behaviors associated with disease transmission and progression. Meade CS, Lowen SB, MacLean RR, Key MD, Scott E. Lukas SE. fMRI brain activation during a delay discounting task in HIV-positive adults with and without cocaine dependence. Psychiatry Res.: Neuroimaging. 2011 Jun 30; 192(3): 167-175.

Impact of HIV and a History of Marijuana Dependence on Procedural Learning among Individuals with a History of Substance Dependence Marijuana (MJ) use and HIV infection are both associated with neurocognitive deficits, yet there is little research to date examining their interactions, specifically how they pertain to procedural learning (PL). The authors examined a sample of 86 individuals with a history of dependence for multiple substances who underwent a comprehensive evaluation including measures of mental health, substance use history, and three measures of PL: the photoelectric Rotary Pursuit Task (RPT), the Star Mirror Tracing Task (SMT), and the Weather Prediction Task (WPT). They found that a positive HIV serostatus and a history of marijuana dependence were both independently associated with overall poorer performance on the SMT and RPT in this sample of individuals with a history of dependence for multiple substances. Rate of improvement across trial blocks did not differ as a function of HIV serostatus or history of marijuana dependence. Although they found no significant HIV × MJ interaction for any of the PL tasks, they did observe evidence of additive negative effects from HIV and a history of marijuana dependence on overall performance on the SMT and RPT, but not the WPT. The findings suggest that complex motor skills are adversely affected among abstinent polysubstance users with a history of marijuana dependence and that such deficits are compounded by HIV. Gonzalez R, Schuster RM, Vassileva J, Martin EM. Impact of HIV and a history of marijuana dependence on procedural learning among individuals with a history of substance dependence. J Clin Exptl Neuropsych. 2011 Apr 8; 33(7): 735-752.

Effect of Stress and Bupropion on Craving, Withdrawal Symptoms, and Mood in Smokers Studies suggest that in smokers attempting to quit smoking, the occurrence of stressful events is associated with smoking relapse. The purpose of this study was to determine the effect of bupropion (an agent known to increase smoking cessation rates) on the craving, withdrawal, and mood response to stressful tasks administered in a laboratory setting. Response to three tasks (a speech, math, and cold pressor task) was measured in 65 smokers during *ad libitum* smoking. Smokers were then randomized to either bupropion or placebo. Fourteen days after starting medication, 43 subjects (28 receiving bupropion and 15 receiving placebo) quit smoking and laboratory procedures were repeated on the third day of abstinence. Prior to cessation, stressors presented in a laboratory setting increased craving, nicotine withdrawal symptoms, and subjective distress but decreased positive affect. Thirty minutes of relaxation after the stressors did not result in these measures returning to pre-stress levels. During the nicotine withdrawal period, stress-induced responses were generally smaller than during the pre-cessation period. Bupropion (relative to placebo) reduced overall levels of craving and withdrawal symptoms but did not have significant effects on response to stress during the nicotine withdrawal period. This study demonstrates that stress results in sustained increases in craving and withdrawal symptoms and changes in mood symptoms and that bupropion affects overall levels of these symptoms. Further research is needed to determine if modifying response to stress is predictive of an effective treatment for facilitating smoking cessation. Kotlyar M, Drone D, Thuras P, Hatsukami DK, Brauer L, Adson DE, al'Absi M. Effect of stress and bupropion on craving, withdrawal symptoms, and mood in smokers. Nicotine Tob Res. 2011; 13(6): 492-497.

Caudolateral Orbitofrontal Regional Cerebral Blood Flow is Decreased in Abstinent Cocaine-addicted Subjects in Two Separate Cohorts The orbitofrontal cortex (OFC) is crucial for the inhibition of extraneous stimuli, evaluation of aversive information and emotional regulation—all behaviors impaired in cocaine addiction. Previous studies suggest that cocaine-addicted subjects have decreased basal activity in the OFC. In this study, the authors examined

regional cerebral blood flow (rCBF) during a saline infusion in two independent populations of abstinent cocaine- (and mostly nicotine-) addicted (n = 33 and 26) and healthy control (n = 35 and 20) men and women. Isolated rCBF decreases ($P < 0.001$) were observed in the left caudolateral OFC, as well as left superior temporal cortex, in cocaine-addicted subjects relative to controls in both cohorts and bilaterally in the combined cohort. An anatomically defined region of the caudolateral OFC showed similar findings which were evident in both male and female addicted subjects. The reliability of these findings across two cohorts reveals a functional disruption in the lateral OFC, a brain region implicated in the evaluation of behavior-terminating stimuli. This may contribute to an addicted individual's persistent drug use despite negative consequences. Adinoff B, Braud J, Michael D. Devous MD, Thomas S, Harris TS. Caudolateral orbitofrontal regional cerebral blood flow is decreased in abstinent cocaine-addicted subjects in two separate cohorts. Addict Biol. 2011 Nov 29. [Epub ahead of print].

***GABRA2* and *KIBRA* Genotypes Predict Early Relapse to Substance Use** Numerous single nucleotide polymorphisms (SNPs) within different genes have been associated with alcohol and drug involvement or known risk factors for involvement, such as impaired cognitive control. The ability of these SNPs to predict re-involvement, defined here as abstinence failure during treatment, has not been thoroughly tested. The authors studied a small sample (n = 146; 49% female) of residential substance abuse treatment program patients who had maintained 2–6 months of abstinence. They were followed for 4 months thereafter for the purpose of counting days until the first abstinence violation. The analysis used logistic and Cox regression methods to evaluate the contributions of age; sex; number of intake alcohol, drug use, and depression symptoms; and either *GABRA2*, *CHRM2*, *ANKK1*, *BDNF*, or *KIBRA* SNP genotypes to outcome. *GABRA2* and *KIBRA* genotypes, as well as the number of intake drug abuse problems and a younger age, were associated with an increased risk of relapse. Importantly, these genotypes were found to add value to relapse prediction: the χ^2 statistic evaluating their residual contribution, after age and the number of previous drug use problems were entered, was significant. Genetic analyses may add value to outcome prediction. Future studies should evaluate the sensitivity and specificity of *GABRA2* and *KIBRA* genotypes for this purpose in other racial/ethnic groups and treatment settings. Bauer L, Covault J, Gelernter J. *GABRA2* and *KIBRA* genotypes predict early relapse to substance use. Drug Alcohol Depend. 2011 Nov 29. [Epub ahead of print].

Evidence for Chronically Altered Serotonin Function in the Cerebral Cortex of Female 3,4-Methylenedioxymethamphetamine Polydrug Users MDMA (3,4-methylenedioxymeth-amphetamine, 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 research 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. The design 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) participated. The main exclusion criteria were nondrug-related *DSM-IV* Axis I psychiatric disorders and

general medical illness. The main outcome measure was cortical serotonin$_{2A}$ receptor non-displaceable binding potential (serotonin$_{2A}$BP$_{ND}$) 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-methylenedioxymeth-amphetamine polydrug users. Arch Gen Psychiat. 2011 Dec 5. [Epub ahead of print].

Cannabis Cue-elicited Craving and the Reward Neurocircuitry Cue-elicited craving or the intense desire to consume a substance following exposure to a conditioned drug cue is one of the primary behavioral symptoms of substance use disorders (SUDs). While the concept of cue-elicited craving is well characterized in alcohol and other substances of abuse, only recently has it been described in cannabis. A review of the extant literature has established that cue-elicited craving is a powerful reinforcer that contributes to drug-seeking for cannabis. Further, emergent research has begun to identify the neurobiological systems and neural mechanisms associated with this behavior. What research shows is that while theories of THC's effects on the dopaminergic-reward system remain divergent, cannabis cues elicit neural activation in the brain's reward network. Filbey FM, DeWitt SJ. Cannabis cue-elicited craving and the reward neurocircuitry. Prog Neuro-psychopharm & Biol Psychiat. 2011. [Epub ahead of print].

Prescription Opioid Analgesics Rapidly Change the Human Brain Chronic opioid exposure is known to produce neuroplastic changes in animals; however, it is not known if opioids used over short periods of time and at analgesic dosages can similarly change brain structure in humans. In this longitudinal, magnetic resonance imaging study, 10 individuals with chronic low back pain were administered oral morphine daily for 1 month. High-resolution anatomical images of the brain were acquired immediately before and after the morphine administration period. Regional changes in gray matter volume were assessed on the whole brain using tensor-based morphometry, and those significant regional changes were then independently tested for correlation with morphine dosage. Thirteen regions evidenced significant volumetric change, and degree of change in several of the regions was correlated with morphine dosage. Dosage-correlated volumetric decrease was observed primarily in the right amygdala. Dosage-correlated volumetric increase was seen in the right hypothalamus, left inferior frontal gyrus, right ventral posterior cingulate, and right caudal pons. Follow-up scans that were conducted an average of 4.7 months after cessation of opioids demonstrated many of the morphine-induced changes to be persistent. In a separate study, 9 individuals consuming blinded placebo capsules for 6 weeks evidenced no significant morphologic changes over time. The results add to a growing body of literature showing that opioid exposure causes structural and functional changes in reward- and

affect-processing circuitry. Morphologic changes occur rapidly in humans during new exposure to prescription opioid analgesics. Further research is needed to determine the clinical impact of those opioid-induced gray matter changes. Younger JW, Chu LF, D'Arcy NT, Trott KE, Jastrzab LE, Mackey SC. Prescription opioid analgesics rapidly change the human brain. Pain. 2011 Aug; 152(8): 1803-1810.

The Catechol-O-Methyltransferase (COMT) Val/met Polymorphism Affects Brain Responses to Repeated Painful Stimuli Despite the explosion of interest in the genetic underpinnings of individual differences in pain sensitivity, conflicting findings have emerged for most of the identified "pain genes". Perhaps the prime example of this inconsistency is represented by catechol-O-methyltransferase (COMT), as its substantial association to pain sensitivity has been reported in various studies, but rejected in several others. In line with findings from behavioral studies, the authors hypothesized that the effect of COMT on pain processing would become apparent only when the pain system was adequately challenged (i.e., after repeated pain stimulation). In the present study, they used functional Magnetic Resonance Imaging (fMRI) to investigate the brain response to heat pain stimuli in 54 subjects genotyped for the common COMT val158met polymorphism (val/val=n 22, val/met=n 20, met/met=n 12). Met/met subjects exhibited stronger pain-related fMRI signals than val/val in several brain structures, including the periaqueductal gray matter, lingual gyrus, cerebellum, hippocampal formation and precuneus. These effects were observed only for high intensity pain stimuli after repeated administration. In spite of the authors' relatively small sample size, their results suggest that COMT appears to affect pain processing. These data demonstrate that the effect of COMT on pain processing can be detected in presence of 1) a sufficiently robust challenge to the pain system to detect a genotype effect, and/or 2) the recruitment of pain-dampening compensatory mechanisms by the putatively more pain sensitive met homozygotes. These findings may help explain the inconsistencies in reported findings of the impact of COMT in pain regulation. Loggia ML, Jensen K, Gollub RL, Wasan AD, Edwards RR, Kong J. The Catechol-O-Methyltransferase (COMT) valmet polymorphism affects brain responses to repeated painful stimuli. PLoS One. 2011; 6(11): e27764.

Machine Learning Patterns of Human Brain Reactivity Permits Objective Assessment of Thermal Pain Pain often exists in the absence of observable injury; therefore, the gold standard for pain assessment has long been self-report. Because the inability to verbally communicate can prevent effective pain management, research efforts have focused on the development of a tool that accurately assesses pain without depending on self-report. Those previous efforts have not proven successful at substituting self-report with a clinically valid, physiology-based measure of pain. Recent neuroimaging data suggest that functional magnetic resonance imaging (fMRI) and support vector machine (SVM) learning can be jointly used to accurately assess cognitive states. Therefore, the authors hypothesized that an SVM trained on fMRI data can assess pain in the absence of self-report. In fMRI experiments, 24 individuals were presented painful and nonpainful thermal stimuli. Using eight individuals, the authors trained a linear SVM to distinguish these stimuli using whole-brain patterns of activity. The authors assessed the performance of this trained SVM model by testing it on 16 individuals whose data were not used for training. The whole-brain SVM was 81% accurate at distinguishing painful from non-painful stimuli ($p<0.0000001$). Using distance from the SVM hyperplane as a confidence measure, accuracy was further increased to 84%, albeit at the expense of excluding 15% of the stimuli that were the most difficult to classify. Overall performance of the SVM was primarily affected by activity in pain-processing regions of the brain including the primary somatosensory cortex,

secondary somatosensory cortex, insular cortex, primary motor cortex, and cingulate cortex. Region of interest (ROI) analyses revealed that whole-brain patterns of activity led to more accurate classification than localized activity from individual brain regions. These findings demonstrate that fMRI with SVM learning can assess pain without requiring any communication from the person being tested. The authors outline tasks that should be completed to advance this approach toward use in clinical settings. Brown JE, Chatterjee N, Younger J, Mackey S. Towards a physiology-based measure of pain: patterns of human brain activity distinguish painful from non-painful thermal stimulation. PLoS One. 2011; 6(9):e24124. [Epub 2011 Sep 13].

Strategy-Dependent Dissociation of the Neural Correlates Involved in Pain Modulation
Cognitive strategies are a set of psychologic behaviors used to modulate one's perception or interpretation of a sensation or situation. Although the effectiveness of each cognitive strategy seems to differ between individuals, they are commonly used clinically to help patients with chronic pain cope with their condition. The neural basis of commonly used cognitive strategies is not well understood. Understanding the neural correlates that underlie these strategies will enhance understanding of the analgesic network of the brain and the cognitive modulation of pain. The current study examines patterns of brain activation during two common cognitive strategies, external focus of attention and reappraisal, in patients with chronic pain using functional magnetic resonance imaging. Behavioral results revealed inter-individual variability in the effectiveness of one strategy versus another in the patients. Functional magnetic resonance imaging revealed distinct patterns of activity when the two strategies were used. During external focus of attention, activity was observed mainly in cortical areas including the postcentral gyrus, inferior parietal lobule, middle occipital gyrus, and precentral gyrus. The use of reappraisal evoked activity in the thalamus and amygdala in addition to cortical regions. Only one area, the postcentral gyrus, was observed to be active during both strategies. The results of this study suggest that different cognitive behavioral strategies recruit different brain regions to perform the same task: pain modulation. Lawrence JM, Hoeft F, Sheau KE, Mackey SC. Strategy-dependent dissociation of the neural correlates involved in pain modulation. Anesthesiology. 2011 Oct; 15(4): 844-851.

Neural Correlates of Chronic Low Back Pain The varying nature of chronic pain (CP) is difficult to correlate to neural activity using typical functional magnetic resonance imaging methods. Arterial spin labeling is a perfusion-based imaging technique allowing the absolute quantification of regional cerebral blood flow, which is a surrogate measure of neuronal activity. Subjects with chronic low back and radicular pain and matched healthy normal subjects, undergoing identical procedures, participated in three sessions: a characterization and training session and two arterial spin labeling sessions. In the first imaging session, CP (if any) was exacerbated using clinical maneuvers; in the second session, noxious heat was applied to the affected leg dermatome, the intensity of which was matched to the pain intensity level of the CP exacerbations for each back pain subject. The clinically significant worsening of ongoing CP ($\leq$ 30%, n = 16) was associated with significant regional blood flow increases (6-10 mm/100 g of tissue/min, P less than 0.01) within brain regions known to activate with experimental pain (somatosensory, prefrontal, and insular cortices) and in other structures observed less frequently in experimental pain studies, such as the superior parietal lobule (part of the dorsal attention network). This effect is specific to changes in ongoing CP as it is observed during worsening CP, but it is not observed after thermal pain application, or in matched, pain-free healthy controls. The findings demonstrate the use of arterial spin labeling to investigate the neural processing of

CP, and these findings are a step forward in the quest for objective biomarkers of the chronic pain experience. Wasan AD, Loggia ML, Chen LQ, Napadow V, Kong J, Gollub RL. Neural correlates of chronic low back pain measured by arterial spin labeling. Anesthesiology. 2011 Aug; 115(2): 364-374.

Elevated Pain Sensitivity in Chronic Pain Patients at Risk for Opioid Misuse This study employed quantitative sensory testing (QST) to evaluate pain responses in chronic spinal pain patients at low risk and high risk for opioid misuse, with risk classification based on scores on the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R). Patients were further sub-grouped according to current use of prescription opioids. Of the 276 chronic pain patients tested, approximately 65% were taking opioids; a median split was used to further categorize these patients as being on lower or higher doses of opioids. The high-risk group (n = 161) reported higher levels of clinical pain, had lower pressure and thermal pain thresholds at multiple body sites, had lower heat pain tolerance, and rated repetitive mechanical stimuli as more painful relative to the low-risk group (n = 115; P's < .01). In contrast, QST measures did not differ across opioid groups. Multiple linear regression analysis suggested that indices of pain-related distress (i.e., anxiety and catastrophizing about pain) were also predictive of hyperalgesia, particularly in patients taking opioids. Collectively, regardless of opioid status, the high-risk group was hyperalgesic relative to the low-risk group; future opioid treatment studies may benefit from the classification of opioid risk, and the examination of pain sensitivity and other factors that differentiate high- and low-risk groups. This study demonstrates that chronic spinal pain patients at high risk for misuse of prescription opioids are more pain-sensitive than low-risk patients, whether or not they are currently taking opioids. Indices of pain-related distress were important predictors of pain sensitivity, particularly among those patients taking opioids for pain. Edwards RR, Wasan AD, Michna E, Greenbaum S, Ross E, Jamison RN. Elevated pain sensitivity in chronic pain patients at risk for opioid misuse. J Pain. 2011 Sep; 2(9): 953-963.

Prevalence and Psychiatric Correlates of Pain Interference The study examined gender differences in the associations of levels of pain interference and psychiatric disorders among a nationally representative sample of adult men and women. The Chi-square tests and multinomial logistic regression analyses were performed on data obtained from the National Epidemiologic Survey on Alcohol and Related Conditions from 42,750 adult respondents (48% men; 52% women), who were categorized according to three levels of pain interference (i.e., no or low pain interference [NPI], moderate pain interference [MPI], severe pain interference [SPI]). The results show that female respondents in comparison to male respondents were more likely to exhibit moderate ($p < 0.001$) or severe pain interference ($p < 0.001$). Levels of pain interference were associated with past-year Axis I and lifetime Axis II psychiatric disorders in both male and female respondents ($p < 0.05$), with the largest odds typically observed in association with moderate or severe pain interference. A stronger relationship between MPI and alcohol abuse or dependence (OR = 1.61, $p < 0.05$) was observed in male participants as compared to female ones, while a stronger relationship between SPI and drug abuse or dependence (OR = 0.57, $P < 0.05$) was observed in female respondents as compared to male ones. The study concludes that levels of pain interference are associated with the prevalence of Axis I and Axis II psychiatric disorders in both men and women. Differences in the patterns of co-occurring substance-related disorders between levels of pain interference in male and female respondents indicate the importance of considering gender-related factors associated with levels of pain interference in developing improved mental health prevention and treatment strategies. Barry

DT, Pilver C, Potenza MN, Desai RA. Prevalence and psychiatric correlates of pain interference among men and women in the general population. J Psychiatr Res. 2012 Jan; 46(1): 118-127.

Group-based Strategies for Stress Reduction in Methadone Maintenance Treatment: What Do Patients Want? The study assessed methadone maintenance treatment (MMT) patients' willingness to use, and perceived efficacy of, conventional and unconventional group stress reduction treatments. A survey was administered to 150 MMT patients. Levels of treatment willingness and perceived efficacy for both conventional and unconventional treatments were relatively high; however, ratings for conventional interventions were, on average, significantly higher than those for unconventional ones. The highest rated conventional and unconventional treatments in terms of willingness and perceived efficacy were nutrition and spiritual counseling, respectively, whereas the lowest rated conventional and unconventional group treatments were anger management and visualization training, respectively. White race was a significant predictor of lower willingness to try conventional and unconventional group therapies and lower perceived efficacy of unconventional group treatment, whereas female sex and older age were significant predictors of higher levels of willingness to try unconventional group treatment. Higher levels of substance use problems were associated with increased willingness to try conventional group treatment. Higher levels of anxiety emerged as a significant independent predictor of treatment willingness and perceived efficacy for both conventional and unconventional group treatments. The study concludes that the relatively high levels of treatment willingness and perceived efficacy of conventional and unconventional group stress reduction treatments point to the feasibility of offering these interventions in MMT and suggest that, in particular, high levels of anxiety are associated with greater treatment willingness and perceived treatment efficacy. Barry DT, Beitel M, Breuer T, Cutter CJ, Savant J, Peters S, Schottenfeld RS, Rounsaville BJ. Group-based strategies for stress reduction in methadone maintenance treatment: what do patients want? J Addict Med. 2011 Sep; 5(3): 181-187.

Large-scale Automated Synthesis of Human Functional Neuroimaging Data The rapid growth of the literature on neuroimaging in humans has led to major advances in our understanding of human brain function but has also made it increasingly difficult to aggregate and synthesize neuroimaging findings. Here the authors describe and validate an automated brain-mapping framework that uses text-mining, meta-analysis and machine-learning techniques to generate a large database of mappings between neural and cognitive states. They show that this approach can be used to automatically conduct large-scale, high-quality neuroimaging meta-analyses, address long-standing inferential problems in the neuroimaging literature and support accurate 'decoding' of broad cognitive states from brain activity in both entire studies and individual human subjects. Collectively, these results have validated a powerful and generative framework for synthesizing human neuroimaging data on an unprecedented scale. Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD. Large-scale automated synthesis of human functional neuroimaging data. Nat Methods. 2011 Jun 26; 8(8): 665-670.

Dissociating Neural Correlates of Action Monitoring and Metacognition of Agency Judgments of agency refer to people's self-reflective assessments concerning their own control: their assessments of the extent to which they themselves are responsible for an action. These self-reflective metacognitive judgments can be distinguished from action monitoring, which involves the detection of the divergence (or lack of divergence) between observed states and expected states. Presumably, people form judgments of agency by metacognitively reflecting on the output of their action monitoring and then consciously inferring the extent to which they

caused the action in question. Although a number of previous imaging studies have been directed at action monitoring, none have assessed judgments of agency as a potentially separate process. The present fMRI study used an agency paradigm that not only allowed the authors to examine the brain activity associated with action monitoring but that also enabled them to investigate those regions associated with metacognition of agency. Regarding action monitoring, The authors found that being "out of control" during the task (i.e., detection of a discrepancy between observed and expected states) was associated with increased brain activity in the right TPJ, whereas being "in control" was associated with increased activity in the pre-SMA, rostral cingulate zone, and dorsal striatum (regions linked to self-initiated action). In contrast, when participants made self-reflective metacognitive judgments about the extent of their own control (i.e., judgments of agency) compared with when they made judgments that were not about control (i.e., judgments of performance), increased activity was observed in the anterior PFC, a region associated with self-reflective processing. These results indicate that action monitoring is dissociable from people's conscious self-attributions of control. Miele DB, Wager TD, Mitchell JP, Metcalfe J. Dissociating neural correlates of action monitoring and metacognition of agency. J Cogn Neurosci. 2011 Nov; 23(11): 3620-3636.

The Behavioral Economics and Neuroeconomics of Reinforcer Pathologies: Implications for Etiology and Treatment of Addiction The current paper presents a novel approach to understanding and treating addiction. Drawing from work in behavioral economics and developments in the new field of neuroeconomics, the authors describe addiction as pathological patterns of responding resulting from the persistently high valuation of a reinforcer and/or an excessive preference for the immediate consumption of that reinforcer. They further suggest that, as indicated by the competing neurobehavioral decision systems theory, these patterns of pathological choice and consumption result from an imbalance between two distinct neurobehavioral systems. Specifically, pathological patterns of responding result from hyperactivity in the evolutionarily older impulsive system (which values immediate and low-cost reinforcers) and/or hypoactivity in the more recently evolved executive system (which is involved in the valuation of delayed reinforcers). This approach is then used to explain five phenomena that we believe any adequate theory of addiction must address. Bickel WK, Jarmolowicz DP, Mueller ET, Gatchalian KM. The behavioral economics and neuroeconomics of reinforcer pathologies: implications for etiology and treatment of addiction. Curr Psychiatry Rep. 2011 Oct; 13(5): 406-415.

Single- and Cross-commodity Discounting Among Cocaine Addicts: the Commodity and its Temporal Location Determine Discounting Rate Intertemporal choice has provided important insights into understanding addiction, predicted drug-dependence status, and outcomes of treatment interventions. However, such analyses have largely been based on the choice of a single commodity available either immediately or later (e.g., money now vs. money later). In real life, important choices for those with addiction depend on making decisions across commodities, such as between drug and non-drug reinforcers. To date, no published study has systematically evaluated intertemporal choice using all combinations of a drug and a non-drug commodity. In this study, the authors examine the interaction between intertemporal choice and commodity type in the decision-making process of cocaine-dependent individuals. This study of 47 treatment-seeking cocaine addicts analyzes intertemporal choices of two commodities (equated amounts of cocaine and money), specifically between cocaine now vs. cocaine later (C-C), money now vs. money later (M-M), cocaine now vs. money later (C-M), and money now vs. cocaine later (M-C). The results indicate that cocaine addicts discounted significantly more in the C-C condition

than in M-M (P = 0.032), consistent with previous reports. Importantly, the two cross-commodity discounting conditions produced different results. Discounting in C-M was intermediate to the C-C and M-M rates, while the greatest degree of discounting occurred in M-C. These data indicate that the menu of commodities offered alter discounting rates in intertemporal choice and that the greatest rate is obtained when the drug is the later available commodity. Implications for understanding intertemporal choices and addiction are addressed. Bickel WK, Landes RD, Christensen DR, Jackson L, Jones BA, Kurth-Nelson Z, Redish AD. Single- and cross-commodity discounting among cocaine addicts: the commodity and its temporal location determine discounting rate. Psychopharm. (Berl). 2011 Sep; 217(2): 177-187.

A Mechanism for Reducing Delay Discounting by Altering Temporal Attention Rewards that are not immediately available are discounted compared to rewards that are immediately available. The more a person discounts a delayed reward, the more likely that person is to have a range of behavioral problems, including clinical disorders. This latter observation has motivated the search for interventions that reduce discounting. One surprisingly simple method to reduce discounting is an "explicit-zero" reframing that states default or null outcomes. Reframing a classical discounting choice as "something now but nothing later" versus "nothing now but more later" decreases discount rates. However, it is not clear how this "explicit-zero" framing intervention works. The present studies delineate and test two possible mechanisms to explain the phenomenon. One mechanism proposes that the explicit-zero framing creates the impression of an improving sequence, thereby enhancing the present value of the delayed reward. A second possible mechanism posits an increase in attention allocation to temporally distant reward representations. In four experiments, the authors distinguish between these two hypothesized mechanisms and conclude that the temporal attention hypothesis is superior for explaining their results. They propose a model of temporal attention whereby framing affects intertemporal preferences by modifying present bias. Radu PT, Yi R, Bickel WK, Gross JJ, McClure SM. A mechanism for reducing delay discounting by altering temporal attention. J Exp Anal Behav. 2011 Nov; 96(3): 363-385.

APOE ε 4 Allele and CSF APOE on Cognition in HIV-Infected Subjects The significance of the cerebrospinal fluid (CSF) Apolipoprotein E (APOE) level and whether it might have differential effects on brain function due to the presence of APOE ε 4 allele(s) in HIV-infected patients are unknown. However, APOE ε 4 allele has been associated with greater incidence of HIV-associated dementia and accelerated progression of HIV infection. Here, the authors show further evidence for the role of APOE ε 4 in promoting cognitive impairment. They measured the APOE levels in the CSF of HIV-infected individuals. HIV+ subjects showed lower CSF APOE proteins than SN controls (-19%, p= 0.03). While SN subjects with or without ε 4 allele showed no difference in CSF APOE levels, ε 4+ HIV+ subjects had similar levels to the SN subjects but higher levels than ε 4- HIV+ subjects (+34%, p= 0.01). Furthermore, while HIV+ subjects with ε 2 or ε 3 allele(s) showed a positive relationship between their CSF APOE levels and cognitive performance on the speed of processing domain (r= +0.35, p= 0.05), ε 4+ HIV+ subjects, in contrast, exhibited a negative relationship such that those with higher levels of CSF APOE(4) performed worse on the HIV Dementia Scale (r= -0.61, p= 0.02), had lower Global Cognitive Scores (r= -0.57, p= 0.03), and had poorer performance on tests involving learning (ε 4 allele x [APOE] interaction, p = 0.01). These findings also suggest that the relatively higher levels of CSF APOE in ε 4+ HIV+ (having primarily APOE4 isoforms) may negatively impact the brain and lead to poorer cognitive outcomes, while those individuals without the ε 4 allele (with

primarily APOE2 or APOE3 isoforms) may show compensatory responses that lead to better cognitive performance. Andres MA, Feger U, Nath A, Munsaka S, Jiang CS, Chang L. APOE ε 4 allele and CSF APOE on cognition in HIV-infected subjects. J Neuroimmune Pharmacol. 2011 Sep; 6(3): 389-398.

Impact of Apolipoprotein E ε4 and HIV on Cognition and Brain Atrophy: Antagonistic Pleiotropy and Premature Brain Aging The apolipoprotein E (APOE) ε4 allele may accelerate the progression of HIV disease, and increase the risk for developing HIV-associated neurocognitive disorder (HAND). Whether APOEε4 allele(s) and age may influence brain atrophy in HIV patients is unknown and was evaluated. Automated morphometry on magnetic resonance images, using FreeSurfer analyses, neuropsychological testing and APOE genotyping were performed in 139 subjects [70 seronegative controls (SN); 69 clinically-stable HIV subjects]. Compared to SN, HIV subjects had smaller volumes throughout the brain regardless of their HAND status. Compared to APOEε4- subjects, SN controls with APOEε4 had better memory and larger global brain volumes (cerebral white matter and cortex) while HIV subjects with the APOEε4 allele(s) had poorer cognition (verbal fluency, learning, executive function and memory) and smaller cerebral and cerebellar white matter and subcortical structures. Further stratification of age showed that younger (<50 years) APOEε4+SN subjects had larger putamen and cerebral white matter, while younger APOEε4+HIV subjects had poorer performance on verbal fluency and smaller brain volumes [3-way (HIV-status×APOEε4×Age) interaction-p-values=0.005 to 0.03]. These findings suggest that APOEε4 allele(s) may show antagonistic pleiotropy on cognition and brain atrophy in SN controls, but may lead to premature aging with neurodegeneration in younger HIV patients prior to the development of HAND. Potential mechanisms for such interactions may include stronger neuro-inflammation or greater amyloid deposition in younger HIV subjects with APOEε4 allele(s). Early screening for the APOEε4 allele and brain atrophy with morphometry may guide neuro-protective intervention of cognitively normal HIV subjects prior to the development of HAND. Longitudinal follow-up studies and larger sample sizes are needed to validate these cross-sectional results. Chang L, Andres M, Sadino J, Jiang CS, Nakama H, Miller E, Ernst T. Impact of apolipoprotein E ε4 and HIV on cognition and brain atrophy: antagonistic pleiotropy and premature brain aging. Neuroimage. 2011 Oct 15; 58(4): 1017-1027.

Altered Brain Activation during Visuomotor Integration in Chronic Active Cannabis Users: Relationship to Cortisol Levels 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.

Diagnosing Symptomatic HIV-Associated Neurocognitive Disorders: Self-Report Versus Performance-Based Assessment of Everyday Functioning Three types of HIV-associated neurocognitive disorders (HAND) exist that are distinguished by presence and severity of impairment in cognitive and everyday functioning. Although well-validated neurocognitive measures exist, determining impairment in everyday functioning remains a challenge. The authors aim to determine whether Self-Report measures of everyday functioning are as effective in characterizing HAND as Performance-Based measures. They assessed 674 HIV-infected participants with a comprehensive neurocognitive battery; 233 met criteria for a HAND diagnosis by having at least mild neurocognitive impairment. Functional decline was measured via Self-Report and Performance-Based measures. HAND diagnoses were determined according to published criteria using three approaches to assess functional decline: (1) Self-Report measures only, (2) Performance-Based measures only, and (3) Dual-method combining Self-Report and Performance-Based measures. The Dual-method classified the most symptomatic HAND, compared to either singular method. Singular method classifications were 76% concordant with each other. Participants classified as Performance-Based functionally impaired were more likely to be unemployed and more immune-suppressed, whereas those classified as Self-Report functionally impaired had more depressive symptoms. Multimodal methods of assessing everyday functioning facilitate detection of symptomatic HAND. Singular Performance-Based classifications were associated with objective functional and disease-related factors; reliance on Self-Report classifications may be biased by depressive symptoms. Blackstone K, Moore DJ, Heaton RK, Franklin DR, Woods SP, Clifford DB, Collier AC, Marra CM, Gelman BB, McArthur JC, Morgello S, Simpson DM, Rivera-Mindt M, Deutsch R, Ellis RJ, Hampton Atkinson J, Grant I. Diagnosing symptomatic HIV-associated neurocognitive disorders: self-report versus performance-based assessment of everyday functioning. J Int Neuropsychol Soc. 2012 Jan; 18(1): 79-88.

Self-Generation Enhances Verbal Recall in Individuals Infected with HIV Despite the prevalence of HIV-associated episodic memory impairment and its adverse functional impact, there are no empirically validated cognitive rehabilitation strategies for HIV-infected persons. The present study examined the self-generation approach, which is theorized to enhance new learning by elaborating and deepening encoding. Participants included 54 HIV-infected and 46 seronegative individuals, who learned paired word associates in both self-generated and didactic encoding experimental conditions. Results revealed main effects of HIV serostatus and encoding condition, but no interaction. Planned comparisons showed that both groups recalled significantly more words learned in the self-generation condition, and that HIV+ individuals recalled fewer words overall compared to their seronegative counterparts at delayed recall. Importantly, HIV+ participants with clinical memory impairment evidenced similar benefits of self-generation compared to unimpaired HIV+ subjects. Self-generation strategies may improve verbal recall in individuals with HIV infection and may, therefore, be an appropriate and potentially effective cognitive rehabilitation tool in this population. Weber E, Woods SP, Kellogg E, Grant I, Basso MR. The HIV Neurobehavioral Research Program (HNRP) Group.

Self-generation enhances verbal recall in individuals infected with HIV. J Int Neuropsychol Soc. 2012 Jan; 18(1): 128-133.

An Examination of the Age-Prospective Memory Paradox in HIV-Infected Adults The age-prospective memory (PM) paradox asserts that, despite evidence of age-associated PM deficits on laboratory tasks, older adults perform comparably to (or better than) young adults on naturalistic PM tasks. This study examined the age-PM paradox in older HIV-infected individuals, who represent a growing epidemic and may be at heightened risk for adverse neurocognitive and everyday functioning outcomes. Participants included 88 older (50+ years) and 53 younger (≤40 years) HIV-infected individuals as well as 54 older and 59 younger seronegative adults who completed both laboratory and naturalistic time-based PM tasks. Similar interactions were observed in both the seropositive and the seronegative samples, such that the older participants demonstrated significantly lower laboratory-based PM than the younger groups, but not on the naturalistic PM trial. Secondary analyses within the HIV+ sample revealed that naturalistic task success was indirectly associated with greater self-reported use of PM-based and external compensatory strategies in the daily lives of older, but not younger, HIV+ adults. Study findings suggest that, although older HIV-infected adults exhibit moderate PM deficits on laboratory measures versus their younger counterparts, such impairments are paradoxically not evident on ecologically relevant naturalistic PM activities in daily life, perhaps related to effective utilization compensatory strategies. Weber E, Woods SP, Delano-Wood L, Bondi MW, Gilbert PE, Grant I, The HIV Neurobehavioral Research Program HNRP Group. An examination of the age-prospective memory paradox in HIV-infected adults. J Clin Exp Neuropsychol. 2011 Dec; 33(10): 1108-1118.

Clinical Variables Identify Seronegative HCV Co-Infection in HIV-Infected Individuals A substantial number of people living with HIV (PLWH) are co-infected with Hepatitis C Virus (HCV) but have a negative screening HCV antibody test (seronegative HCV infection, or SN-HCV). This study is designed to identify a concise set of clinical variables that could be used to improve case finding for SN-HCV co-infection among PLWH. Two hundred HIV-infected participants of the CHARTER study were selected based on 7 clinical variables associated with HCV infection but were HCV seronegative. Data were analyzed using Fisher's exact tests, receiver-operating characteristic (ROC) curves, and logistic regression. Twenty-six (13%) participants had detectable HCV RNA. SN-HCV was associated with a history of IDU, elevated ALT and AST, low platelets, black ethnicity, and undetectable HIV RNA in plasma. Each of these clinical variables, except for abnormal AST, remained independently associated with SN-HCV in a multivariate logistic regression analysis. A composite risk score correctly identified SN-HCV with sensitivity up to 85% and specificity up to 88%. It concludes that in a substantial minority of PLWH, seronegative HCV viremia can be predicted by a small number of clinical variables. These findings, after validation in an unselected cohort, could help focus screening in those at highest risk. Bharti AR, Letendre SL, Wolfson T, Clifford D, Collier AC, Gelman B, McArthur J, Marra C, McCutchan A, Morgello S, Simpson D, Ellis RJ, Grant I. Clinical variables identify seronegative HCV co-infection in HIV-infected individuals. J Clin Virol. 2011 Dec; 52(4): 328-332.

Family History of Dementia Predicts Worse Neuropsychological Functioning Among HIV-Infected Persons HIV-negative individuals with a family history of dementia (FHD) are more likely to develop dementia than those without FHD. Whether FHD increases risk for neuropsychological (NP) impairment in HIV+ persons is unknown. As part of a multisite study into HIV-associated neurocognitive disorders (HAND), the authors captured FHD with a free-response, self-report question, and assessed NP performance with a comprehensive battery of tests. The authors examined HIV+ persons with (N=190) and without (N=916) self-reported FHD. Despite the fact that the FHD group had factors typically associated with better NP performance (e.g., higher CD4 counts and estimated verbal IQ), persons with FHD had significantly worse NP ability than those without FHD as measured by a Global Deficit Score. Thus, FHD appears to be a risk factor for HAND; the mechanism(s) underlying how FHD contributes to NP impairment among HIV+ persons warrants study. Moore DJ, Arce M, Moseley S, McCutchan JA, Marquie-Beck J, Franklin DR, Vaida F, Achim CL, McArthur J, Morgello S, Simpson DM, Gelman BB, Collier AC, Marra CM, Clifford DB, Heaton RK, Grant I; Charter Group and HNRC Group. Family history of dementia predicts worse neuropsychological functioning among HIV-infected persons. J Neuropsychiatry Clin Neurosci. 2011 Summer; 23(3): 316-323.

CD4 Nadir is a Predictor of HIV Neurocognitive Impairment in the Era of Combination Antiretroviral Therapy Despite immune recovery in individuals on combination antiretroviral therapy (CART), the frequency of HIV-associated neurocognitive disorders (HANDs) remains high. Immune recovery is typically achieved after initiation of ART from the nadir, or the lowest historical CD4. The present study evaluated the probability of neuropsychological impairment (NPI) and HAND as a function of CD4 nadir in an HIV-positive cohort. One thousand five hundred and twenty-five HIV-positive participants enrolled in CNS HIV Antiretroviral Therapy Effects Research, a multisite, observational study that completed comprehensive neurobehavioral and neuro-medical evaluations, including a neurocognitive test battery covering seven cognitive domains. Among impaired individuals, HAND was diagnosed if NPI could not be attributed to comorbidities. CD4 nadir was obtained by self-report or observation. Potential modifiers of the relationship between CD4 nadir and HAND, including demographic and HIV disease characteristics, were assessed in univariate and multivariate analyses. The median CD4 nadir (cells/μl) was 172, and 52% had NPI. Among impaired participants, 603 (75%) had HAND. Higher CD4 nadirs were associated with lower odds of NPI such that for every 5-unit increase in square-root CD4 nadir, the odds of NPI were reduced by 10%. In 589 virally suppressed participants on ART, higher CD4 nadir was associated with lower odds of NPI after adjusting for demographic and clinical factors. The study concluded that as the risk of NPI was lowest in patients whose CD4 cell count was never allowed to fall to low levels before CART initiation, our findings suggest that initiation of CART as early as possible might reduce the risk of developing HAND, the most common source of NPI among HIV-infected individuals. Ellis RJ, Badiee J, Vaida F, Letendre S, Heaton RK, Clifford D, Collier AC, Gelman B, McArthur J, Morgello S, McCutchan JA, Grant I; CHARTER Group. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. AIDS. 2011 Sep 10; 25(14): 1747-1751.

Neurocognitive Impact of Substance Use in HIV Infection The study aims to determine how serious a confound substance use (SU) might be in studies on HIV-associated neurocognitive disorder (HAND). The relationship of SU history to neurocognitive impairment (NCI) is tested in participants enrolled in the Central Nervous System HIV Antiretroviral Therapy Effects Research study. After excluding cases with behavioral evidence of acute intoxication and histories of factors that independently could account for NCI (e.g., stroke), baseline demographic, medical, SU, and neurocognitive data were analyzed from 399 participants. Potential SU risk for NCI was determined by the following criteria: lifetime SU Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnosis, self-report of marked lifetime SU, or positive urine toxicology. Participants were divided into 3 groups as follows: no SU (n = 134), non-syndromic SU (n = 131), syndromic SU (n = 134) and matched on literacy level, nadir CD4, and depressive symptoms. Although approximately 50% of the participants were diagnosed with HAND, a multivariate analysis of covariance of neurocognitive summary scores, covarying for urine toxicology, revealed no significant effect of SU status. Correlational analyses indicated weak associations between lifetime heroin dosage and poor recall and working memory and between cannabis and cocaine use and better verbal fluency. The study concluded that these data indicate that HIV neurocognitive effects are seen at about the same frequency in those with and without historic substance abuse in cases that are equated on other factors that might contribute to NCI. Therefore, studies on neuroAIDS and its treatment need not exclude such cases. However, the effects of acute SU and current SU disorders on HAND require further study. Byrd DA, Fellows RP, Morgello S, Franklin D, Heaton RK, Deutsch R, Atkinson JH, Clifford DB, Collier AC, Marra CM, Gelman B, McCutchan JA, Duarte NA, Simpson DM, McArthur J, Grant I, CHARTER Group. Neurocognitive impact of substance use in HIV infection. J Acquir Immune Defic Syndr. 2011 Oct1; 58(2): 54-62.

Intraindividual Variability in HIV Infection: Evidence for Greater Neurocognitive Dispersion in Older HIV Seropositive Adults Both the prevalence and incidence of HIV infection among older adults are on the rise. Older adults are at increased risk of HIV-associated neurocognitive disorders, which have historically been characterized as an inconsistent or "spotty" pattern of deficits. Dispersion is a form of intra-individual variability (IIV) that is defined as within-person variability in performance across domains and has been associated with poorer neurocognitive functioning and incipient decline among healthy older adults. To the authors' knowledge, no studies have yet examined dispersion in an aging HIV-infected sample. For the current study they examined the hypothesis that age and HIV infection have synergistic effects on dispersion across a battery of clinical and experimental cognitive tasks. Their well-characterized sample comprised 126 HIV-seropositive individuals (HIV+) and 40 HIV-seronegative comparison individuals (HIV-), all of whom were administered a comprehensive neuropsychological battery. Consistent with the authors' hypothesis, an age by HIV serostatus interaction was observed, with the older HIV+ group demonstrating a higher level of dispersion relative to older HIV- and younger HIV+ individuals, even when potentially confounding demographic and medical factors were controlled. These results demonstrate that older HIV+ adults produce greater dispersion, or intra-individual variability in performance across a range of tests, which may be reflective of cognitive dyscontrol to which this population is vulnerable, perhaps driven by the combined effects of aging and HIV infection on prefronto-striatal systems. Morgan EE, Woods SP, Delano-Wood L, Bondi MW, Grant I, HIV Neurobehavioral Research Program (HNRP) Group. Intraindividual variability in HIV infection: evidence for greater neurocognitive dispersion in older HIV seropositive adults. Neuropsychology. 2011 Sep; 25(5): 645-654.

Clinical Factors Related to Brain Structure in HIV: The CHARTER Study Despite the widening use of combination antiretroviral therapy (ART), neurocognitive impairment remains common among HIV-infected (HIV+) individuals. Associations between HIV-related neuromedical variables and magnetic resonance imaging indices of brain structural integrity may provide insight into the neural bases for these symptoms. A diverse HIV+ sample (n = 251) was studied through the CNS HIV Antiretroviral Therapy Effects Research initiative. Multi-channel image analysis produced volumes of ventricular and sulcal cerebrospinal fluid (CSF), cortical and subcortical gray matter, total cerebral white matter, and abnormal white matter. Cross-sectional analyses employed a series of multiple linear regressions to model each structural volume as a function of severity of prior immune-suppression (CD4 nadir), current CD4 count, presence of detectable CSF HIV RNA, and presence of HCV antibodies; secondary analyses examined plasma HIV RNA, estimated duration of HIV infection, and cumulative exposure to ART. Lower CD4 nadir was related to most measures of the structural brain damage. Higher current CD4, unexpectedly, correlated with lower white and subcortical gray and increased CSF. Detectable CSF HIV RNA was related to less total white matter. HCV coinfection was associated with more abnormal white matter. Longer exposure to ART was associated with lower white matter and higher sulcal CSF. HIV neuromedical factors, including lower nadir, higher current CD4 levels, and detectable HIV RNA, were associated with white matter damage and variability in subcortical volumes. Brain structural integrity in HIV likely reflects dynamic effects of current immune status and HIV replication, superimposed on residual effects associated with severe prior immunosuppression. Jernigan TL, Archibald SL, Fennema-Notestine C, Taylor MJ, Theilmann RJ, Julaton MD, Notestine RJ, Wolfson T, Letendre SL, Ellis RJ, Heaton RK, Gamst AC, Franklin DR Jr, Clifford DB, Collier AC, Gelman BB, Marra C, McArthur JC, McCutchan JA, Morgello S, Simpson DM, Grant I; CHARTER Group. Clinical factors related to brain structure in HIV: the CHARTER study. J Neurovirol. 2011 Jun; 17(3): 248-257.

HIV and Chronic Methamphetamine Dependence Affect Cerebral Blood Flow Human immunodeficiency virus (HIV) and methamphetamine (METH) dependence are independently associated with neuronal dysfunction. The coupling between cerebral blood flow (CBF) and neuronal activity is the basis of many task-based functional neuroimaging techniques. The authors examined the interaction between HIV infection and a previous history of METH dependence on CBF within the lenticular nuclei (LN). Twenty-four HIV-/METH-, eight HIV-/METH+, 24 HIV+/METH-, and 15 HIV+/METH+ participants performed a finger tapping paradigm. A multiple regression analysis of covariance assessed associations and two-way interactions between CBF and HIV serostatus and/or previous history of METH dependence. HIV+ individuals had a trend towards a lower baseline CBF (-10%, $p = 0.07$) and greater CBF changes for the functional task (+32%, $p = 0.01$) than HIV- subjects. Individuals with a previous history of METH dependence had a lower baseline CBF (-16%, $p = 0.007$) and greater CBF changes for a functional task (+33%, $p = 0.02$). However, no interaction existed between HIV serostatus and previous history of METH dependence for either baseline CBF ($p = 0.53$) or CBF changes for a functional task ($p = 0.10$). In addition, CBF and volume in the LN were not correlated. A possible additive relationship could exist between HIV infection and a history of METH dependence on CBF with a previous history of METH dependence having a larger contribution. Abnormalities in CBF could serve as a surrogate measure for assessing the chronic effects of HIV and previous METH dependence on brain function. Ances BM, Vaida F, Cherner M, Yeh MJ, Liang CL, Gardner C, Grant I, Ellis RJ, Buxton RB; HIV Neurobehavioral Research

Center (HNRC) Group. HIV and chronic methamphetamine dependence affect cerebral blood flow. J Neuroimmune Pharmacol. 2011 Sep; 6(3): 409-419.

A Neuropsychological Investigation of Multitasking in HIV Infection: Implications for Everyday Functioning A subset of individuals with HIV-associated neurocognitive impairment experience related deficits in "real world" functioning (i.e., independently performing instrumental activities of daily living [IADL]). While performance-based tests of everyday functioning are reasonably sensitive to HIV-associated IADL declines, questions remain regarding the extent to which these tests' highly structured nature fully captures the inherent complexities of daily life. The aim of this study was to assess the predictive and ecological validity of a novel multitasking measure in HIV infection. Participants included 60 individuals with HIV infection (HIV+) and 25 demographically comparable seronegative adults (HIV-). Participants were administered a comprehensive neuropsychological battery, questionnaires assessing mood and everyday functioning, and a novel standardized test of multitasking, which involved balancing the demands of four interconnected performance-based functional tasks (i.e., financial management, cooking, medication management, and telephone communication). The study revealed that HIV+ individuals demonstrated significantly worse overall performance, fewer simultaneous task attempts, and increased errors on the multitasking test as compared to the HIV- group. Within the HIV+ sample, multitasking impairments were modestly associated with deficits on standard neuropsychological measures of executive functions, episodic memory, attention/working memory, and information processing speed, providing preliminary evidence for convergent validity. More importantly, multivariate prediction models revealed that multitasking deficits were uniquely predictive of IADL dependence beyond the effects of depression and global neurocognitive impairment, with excellent sensitivity (86%), but modest specificity (57%). Taken together, these data indicate that multitasking ability may play an important role in successful everyday functioning in HIV+ individuals. Scott JC, Woods SP, Vigil O, Heaton RK, Schweinsburg BC, Ellis RJ, Grant I, Marcotte TD; San Diego HIV Neurobehavioral Research Center (HNRC) Group. A neuropsychological investigation of multitasking in HIV infection: implications for everyday functioning. Neuropsychology. 2011 Jul; 25(4): 511-519.

Prospective Memory Deficits are Associated with Unemployment in Persons Living with HIV Infection This study was to determine whether deficits in prospective memory (i.e., "remembering to remember") confer an increased risk of unemployment in individuals living with chronic HIV infection. Fifty-nine Unemployed and 49 Employed individuals with HIV infection underwent comprehensive neuropsychological and medical evaluations, including measures of prospective memory. The Unemployed participants demonstrated significantly lower performance on time- and event-based prospective memory, which was primarily characterized by errors of omission. Importantly, prospective memory impairment was an independent predictor of unemployment when considered alongside other neurocognitive abilities, mood disturbance, and HIV disease severity. It was concluded that prospective memory impairment is a salient predictor of unemployment in persons living with HIV infection and might be considered in screening for unemployment risk and developing vocational rehabilitation plans. Woods SP, Weber E, Weisz BM, Twamley EW, Grant I; HIV Neurobehavioral Research Programs Group. Prospective memory deficits are associated with unemployment in persons living with HIV infection. Rehabil Psychol. 2011 Feb; 56(1):77-84.

Normative Data and Validation of a Regression Based Summary Score for Assessing Meaningful Neuropsychological Change Reliable detection and quantification of longitudinal cognitive change are of considerable importance in many neurological disorders, particularly to monitor central nervous system effects of disease progression and treatment. In the current study, the authors developed normative data for repeated neuropsychological (NP) assessments (6 testings) using a modified standard regression-based (SRB) approach in a sample that includes both HIV-uninfected (HIV-, N = 172) and neuromedically stable HIV-infected (HIV+, N = 124) individuals. Prior analyses indicated no differences in NP change between the infected and uninfected participants. The norms for change included correction for factors found to significantly affect follow-up performance, using hierarchical regression. The most robust and consistent predictors of follow-up performance were the prior performance on the same test (which contributed in all models) and a measure of prior overall NP competence (predictor in 97% of all models). Demographic variables were predictors in 10-46% of all models and in small amounts; while test-retest interval contributed in only 6% of all models. Based on the regression equations, standardized change scores (z scores) were computed for each test measure at each interval; these z scores were then averaged to create a total battery change score. An independent sample of HIV- participants who had completed 8 of the 15 tests was used to validate a bridged summary change score. The normative data are available in an electronic format by e-mail request to the first author. Correction for practice effects based on normative data improved the consistency of NP impairment classification in a clinically stable longitudinal cohort after baseline. Cysique LA, Franklin D Jr, Abramson I, Ellis RJ, Letendre S, Collier A, Clifford D, Gelman B, McArthur J, Morgello S, Simpson D, McCutchan JA, Grant I, Heaton RK, CHARTER Group, HNRC Group. Normative data and validation of a regression based summary score for assessing meaningful neuropsychological change. J Clin Exp Neuropsychol. 2011 Jun; 33(5): 505-522.

Smoking Withdrawal Symptoms Are More Severe Among Smokers with ADHD and Independent of ADHD Symptom Change Smokers with attention deficit hyperactivity disorder (ADHD) have greater difficulty quitting than those without ADHD, but preliminary data (McClernon, Kollins, Lutz, Fitzgerald, Murray, Redman, et al., 2008) suggest equivalent severity of withdrawal symptoms following brief abstinence. The objective of this study was to characterize the differential effects of intermediate term smoking abstinence on self-reported withdrawal and ADHD symptoms in adult smokers with and without ADHD. Forty adult (50% female), non-treatment seeking moderate-to-heavy smokers with and without ADHD were enrolled in a 12-day quit study in which monetary incentives were provided for maintaining biologically verified abstinence. Self-reported withdrawal, mood, and ADHD symptoms were measured pre- and post-quitting. The study revealed that ADHD and controls did not vary on smoking or demographic variables. Significant Group × Session interactions were observed across a broad range of withdrawal symptoms and were generally characterized by greater withdrawal severity among ADHD smokers, particularly during the first 5 days of abstinence. In addition, Group × Sex × Session interactions were observed for craving, somatic symptoms, negative affect, and habit withdrawal; these interactions were driven by greater withdrawal severity among females with ADHD. Group × Session interactions were not observed for ADHD symptom scales. In conclusion, this study suggests that smokers with ADHD, and ADHD females in particular, experience greater withdrawal severity during early abstinence-independent of effects on ADHD symptoms. Whereas additional research is needed to pinpoint mechanisms, these findings suggest that smoking cessation interventions targeted at smokers with ADHD should address their more severe withdrawal symptoms following quitting.

McClernon FJ, Van Voorhees EE, English J, Hallyburton M, Holdaway A, Kollins SH. Smoking withdrawal symptoms are more severe among smokers with ADHD and independent of ADHD symptom change: results from a 12-day contingency-managed abstinence trial. Nicotine Tob Res. 2011 Sep; 13(9): 784-792.

A CHRNA5 Allele Related to Nicotine Addiction and Schizophrenia Schizophrenia and nicotine addiction are both highly heritable phenotypes. Because individuals with schizophrenia have a higher rate of smoking than those in the general population, one could hypothesize that genes associated with smoking might be overrepresented in schizophrenia and thus help explain their increased smoking incidence. Although a number of genes have been proposed to explain the increased smoking risk in schizophrenia, none of them have been consistently linked to smoking and schizophrenia, and thus difficult to explain the increased smoking in schizophrenia. A functional smoking-related nicotinic acetylcholine receptor α5 subunit gene (CHRNA5) nonsynonymous single nucleotide polymorphism (SNP) rs16969968 (Asp398Asn) has recently been discovered and replicated. As such, the authors tested whether this variant contributes to smoking in schizophrenia in a sample of 313 schizophrenia patients and 525 controls. The Asp398Asn risk allele is significantly associated with smoking severity independently in schizophrenia patient smokers (P = 0.001) and control smokers (P = 0.029). Furthermore, the same risk allele is significantly associated with schizophrenia in both Caucasian (P = 0.022) and African-American (P = 0.006) nonsmoker schizophrenia patients compared with control nonsmokers. Intriguingly, this SNP was not significantly associated with smoking status (smokers vs. nonsmokers) in either schizophrenia patients or controls. Therefore, this study identifies a genetic variant that is simultaneously linked to smoking and schizophrenia in the same cohort, but whether this SNP contributes to the increased smoking prevalence in schizophrenia patients requires additional studies. Hong LE, Yang X, Wonodi I, Hodgkinson CA, Goldman D, Stine OC, Stein ES, Thaker GK. A CHRNA5 allele related to nicotine addiction and schizophrenia. Genes Brain Behav. 2011 Jul; 10(5): 530-535.

Neurobiological and Cognitive Effects of Moderate-dose Treatment with Varenicline in Smokers and Nonsmokers with Schizophrenia or Schizoaffective Disorder The administration of nicotine transiently improves many neurobiological and cognitive functions in schizophrenia and schizoaffective disorder. It is not yet clear which nicotinic acetylcholine receptor (nAChR) subtype or subtypes are responsible for these seemingly pervasive nicotinic effects in schizophrenia and schizoaffective disorder. Because α4β2 is a key nAChR subtype for nicotinic actions, the authors investigated the effect of varenicline tartrate, a relatively specific α4β2 partial agonist and antagonist, on key biomarkers that are associated with schizophrenia and are previously shown to be responsive to nicotinic challenge in humans. A double-blind, parrandomized, placebo-controlled trial of patients with schizophrenia or schizoaffective disorder to examine the effects of varenicline on biomarkers at 2 weeks (short-term treatment) and 8 weeks (long-term treatment), using a slow titration and moderate dosing strategy for retaining α4β2-specific effects while minimizing adverse effects. Participants are a total of 69 smoking and nonsmoking patients at Outpatient clinics; 64 patients completed week 2, and 59 patients completed week 8. Prepulse inhibition, sensory gating, antisaccade, spatial working memory, eye tracking, processing speed, and sustained attention. A moderate dose of varenicline (1) significantly reduced the P50 sensory gating deficit in nonsmokers after long-term treatment (P = .006), (2) reduced startle reactivity (P = .02) regardless of baseline smoking status, and (3) improved executive function by reducing the antisaccadic error rate (P = .03) regardless of smoking status. A moderate dose of varenicline had no significant effect on spatial working

memory, predictive and maintenance pursuit measures, processing speed, or sustained attention by Conners' Continuous Performance Test. Clinically, there was no evidence of exacerbation of psychiatric symptoms, psychosis, depression, or suicidality using a gradual titration (1-mg daily dose). In conclusion, moderate-dose treatment with varenicline has a unique treatment profile on core schizophrenia-related biomarkers. Further development is warranted for specific nAChR compounds and dosing and duration strategies to target subgroups of schizophrenic patients with specific biological deficits. Hong LE, Thaker GK, McMahon RP, Summerfelt A, Rachbeisel J, Fuller RL, Wonodi I, Buchanan RW, Myers C, Heishman SJ, Yang J, Nye A. Effects of moderate-dose treatment with varenicline on neurobiological and cognitive biomarkers in smokers and nonsmokers with schizophrenia or schizoaffective disorder. Arch Gen Psychiatry. 2011 Dec; 68(12): 1195-1206.

Short-Term Meditation Increases Network Efficiency of the Anterior Cingulate Cortex

Previous studies have found that short-term integrative body-mind training (IBMT) has positive effects on the brain structure and function in the anterior cingulate cortex. Here, the authors determined whether 11 h of IBMT alters topological properties of the anterior cingulate cortex in brain functional networks. They applied network analysis to resting-state functional connectivity between 90 cortical and subcortical regions before and after IBMT and relaxation training. The results demonstrated a significant increase in the network efficiency and connectivity of the anterior cingulate cortex after IBMT, but not after relaxation training. These findings indicated that the change in network topology might occur by altering the brain or psychological state. IBMT might be an intervention tool for improvement of self-regulation. Xue S, Tang YY, Posner MI. Short-term meditation increases network efficiency of the anterior cingulated cortex. Neuroreport. 2011 Aug 24; 22(12): 570-574.

Strategizing Over Risky Choice Options Reduces Risk-taking and Striatal Activation

Cognitive strategies typically involved in regulating negative emotions have recently been shown to also be effective with positive emotions associated with monetary rewards. However, it is less clear how these strategies influence behavior, such as preferences expressed during decision-making under risk, and the underlying neural circuitry. That is, can the effective use of emotion regulation strategies during presentation of a reward-conditioned stimulus influence decision-making under risk and neural structures involved in reward processing such as the striatum? To investigate this question, the authors asked participants to engage in imagery-focused regulation strategies during the presentation of a cue that preceded a financial decision-making phase. During the decision phase, participants then made a choice between a risky and a safe monetary lottery. Participants who successfully used cognitive regulation, as assessed by subjective ratings about perceived success and facility in implementation of strategies, made fewer risky choices in comparison with trials where decisions were made in the absence of cognitive regulation. Additionally, BOLD responses in the striatum were attenuated during decision-making as a function of successful emotion regulation. These findings suggest that exerting cognitive control over emotional responses can modulate neural responses associated with reward processing (e.g., striatum) and promote more goal-directed decision-making (e.g., less risky choices), illustrating the potential importance of cognitive strategies in curbing risk-seeking behaviors before they become maladaptive (e.g., substance abuse). Martin LN, Delgado MR. The influence of emotion regulation on decision-making under risk. J Cogn Neurosci. 2011 Sep; 23(9): 2569-2581.

Getting to Make a Choice Itself Activates Reward Neurocircuitry Research suggests that the exercise of control is desirable and adaptive, but the precise mechanisms underlying the affective value of control are not well understood. The study reported here characterized the affective experience of personal control by examining the neural substrates recruited when individuals anticipate the opportunity to make a choice--in other words, when they anticipate the means for exercising control. The authors used an experimental paradigm that probed the value of having a choice. Participants reported liking cues that predicted a future opportunity to make a choice more than cues that predicted no choice. The anticipation of choice itself was associated with increased activity in corticostriatal regions, particularly the ventral striatum, involved in affective and motivational processes. This study is the first direct examination of the affective value of having the opportunity to choose. These findings have important implications for understanding the role of perception of control, and choice itself, in self-regulatory processes. Leotti LA, Delgado MR. The inherent reward of choice. Psychol Sci. 2011 Oct; 22(10): 1310-1318.

Deficits in Default Mode Network Activity Precede 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): e51-57.

Acute Modafinil Disproportionately Improves Attention and Inhibitory Control in the Most Heavy-using Methamphetamine-Dependent Subjects Individuals who are methamphetamine dependent exhibit higher rates of cognitive dysfunction than healthy people who do not use methamphetamine, and this dysfunction may have a negative effect on the success of behavioral treatments for the disorder. Therefore, a medication that improves cognition, such as modafinil (Provigil), may serve as a useful adjunct to behavioral treatments for methamphetamine dependence. Although cognitive-enhancing effects of modafinil have been reported in several populations, little is known about the effects of modafinil in methamphetamine-dependent individuals. The authors thus sought to evaluate the effects of

modafinil on the cognitive performance of methamphetamine-dependent and healthy individuals. Seventeen healthy subjects and 24 methamphetamine-dependent subjects participated in this randomized, double-blind, placebo-controlled, crossover study. Effects of modafinil (200 mg, single oral dose) were assessed on participants' performance on tests of inhibitory control, working memory, and processing speed/attention. Across subjects, modafinil improved performance on a test of sustained attention, with no significant improvement on any other cognitive tests. However, within the methamphetamine-dependent group only, participants with a high baseline frequency of methamphetamine use demonstrated a greater effect of modafinil on tests of inhibitory control and processing speed than those participants with low baseline use of methamphetamine. Although modafinil produced limited effects across all participants, methamphetamine-dependent participants with a high baseline use of methamphetamine demonstrated significant cognitive improvement on modafinil relative to those with low baseline methamphetamine use. These results add to the findings from a clinical trial that suggested that modafinil may be particularly useful in methamphetamine-dependent subjects who use the drug frequently. Dean AC, Sevak RJ, Monterosso JR, Hellemann G, Sugar CA, London ED. Acute modafinil effects on attention and inhibitory control in methamphetamine-dependent humans. J Stud Alcohol Drugs. 2011 Nov; 72(6): 943-953.

Moderators of the Association Between Brain Activation and Choices of Delay Rewards 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.

Deciding When To "Cash In" When Outcomes Are Continuously Improving: An Escalating Interest Task A first-person shooter video game was adapted for the study of choice between smaller sooner and larger later outcomes. Participants chose when to fire a weapon that increased in damage potential over a 10s interval, an escalating interest situation. Across two experiments, participants demonstrated sensitivity to the nature of the mathematical function that defined the relationship between waiting and damage potential. In Experiment 1, people tended to wait longer when doing so allowed them to eliminate targets more quickly. In Experiment 2,

people tended to wait longer to increase the probability of a constant magnitude outcome than to increase the magnitude of a 100% certain outcome that was matched for the same expected value (i.e., probability times magnitude). The two experiments demonstrated sensitivity to the way in which an outcome improves when the outcome is continuously available. The results also demonstrate that this new video game task is useful for generating sensitivity to delay to reinforcement over time scales that are typically used in nonhuman animal studies. Young ME, Webb TL, Jacobs EA. Deciding when to "cash in" when outcomes are continuously improving: an escalating interest task. Behav Processes. 2011 Oct; 88(2): 101-110.

Neural Correlates of Different Mental Strategies for Resisting Craving in Smokers Craving is a significant factor which can lead to relapse during smoking quit attempts. Attempts to resist urges to smoke during cue-elicited craving have been shown to activate regions in the brain associated with decision-making, anxiety regulation and visual processing. In this study, 32 treatment-seeking, nicotine-dependent smokers viewed blocks of smoking and neutral cues alternating with rest periods during magnetic resonance imaging scanning in a 3T Siemens scanner (Siemens AG, Erlangen, Bavaria, Germany). While viewing cues or control images, participants were instructed either to 'allow yourself to crave' or 'resist craving.' Data were analyzed with FSL 4.1.5, focused on the smoking cues versus neutral cues contrast, using cluster thresholding ($Z > 2.3$ and corrected cluster threshold of $P = 0.05$) at the individual and group levels. During the Crave condition, activation was seen on the left anterior cingulated cortex (LACC), medial prefrontal cortex, left middle cingulate gyrus, bilateral posterior cingulated gyrus and bilateral precuneus, areas associated with attention, decision-making and episodic memory. The LACC and areas of the prefrontal cortex associated with higher executive functioning were activated during the Resist condition. No clear distinctions between group crave and resist analyses as a whole were seen without taking into account specific strategies used to resist the urge to smoke, supporting the idea that craving is associated with some degree of resisting the urge to smoke, and trying to resist is almost always accompanied by some degree of craving. Different strategies for resisting, such as distraction, activated different regions. Understanding the underlying neurobiology of resisting craving to smoke may identify new foci for treatments. Hartwell KJ, Johnson KA, Li X, Myrick H, LeMatty T, George MS, Brady KT. Neural correlates of craving and resisting craving for tobacco in nicotine dependent smokers. Addict Biol. 2011 Oct; 16(4): 654-666.

Responses on a New Sexual Discounting Task Correlate with Real-World HIV Risk Behavior Cocaine dependence is associated with high rates of sexual risk behavior and HIV infection. However, little is known about the responsible mechanism(s). Cocaine-dependent individuals (N=62) completed a novel Sexual Discounting Task assessing decisions between immediate unprotected sex and delayed sex with a condom across four hypothetical partners: most (and least) likely to have a sexually transmitted infection (STI), and most (and least) sexually desirable; a real rewards money delay-discounting task, and self-reported sexual risk behavior using the HIV Risk-Taking Behavior Scale (HRBS). Sexual Discounting Task results were largely systematic and showed a strong effect of delay in decreasing condom use. Sexual discounting (preference for immediate unprotected sex) was significantly greater when making responses for partners judged least (compared to most) likely to have an STI, and for partners judged most (compared to least) desirable. Differences in sexual discounting were significant after controlling for differences in condom use (with no delay) between conditions. Greater discounting in 3 or the 4 Sexual Discounting Task conditions, but not in the money discounting task, was associated with greater self-reported sexual risk behavior as measured by the HRBS.

Results suggest that delay is a critical variable strongly affecting HIV sexual risk behavior, and that the Sexual Discounting Task provides a clinically sensitive measure of this phenomenon that may address a variety of questions about HIV risk in future research. The wealth of behavioral and neurobiological data on delay discounting should be brought to bear on HIV education and prevention. Johnson MW, Bruner NR. The Sexual Discounting Task: HIV risk behavior and the discounting of delayed sexual rewards in cocaine dependence. Drug Alcohol Depend. 2011 Nov 4. [Epub ahead of print].

Cocaine Use Drops 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. Substance use after participation in laboratory studies involving smoked cocaine self-administration. Drug Alcohol Depend. 2012 Jan 1; 120(1-3): 162-167.

Striatal Topography of Probability and Magnitude Information for Decisions Under Uncertainty Most decisions involve some element of uncertainty. When the outcomes of these decisions have different likelihoods of occurrence, the decision-maker must consider both the magnitude of each outcome and the probability of its occurrence, but how do individual decision makers combine the two dimensions of magnitude and probability? Here, the authors approach the problem by separating in time the presentation of magnitude and probability information, and focus the analysis of fMRI activations on the first piece of information only. Thus, they are able to identify distinct neural circuits for the two dimensions without the confounding effect of divided attention or the cognitive operation of combining them. They find that magnitude information correlates with the size of the response of the ventral striatum while probability information correlates with the response in the dorsal striatum. The relative responsiveness of these two striatal regions correlates with the behavioral tendency to weight one more than the other. The results are consistent with a second-order process of information aggregation in which individuals make separate judgments for magnitude and probability and then integrate those judgments. Berns GS, Bell E. Striatal topography of probability and magnitude information for decisions under uncertainty. Neuroimage. 2012 February; 59(4): 3166-3172.

Empirical Evaluation of Diagnostic Criteria for Cannabis Withdrawal Syndrome Cannabis withdrawal occurs in frequent users who quit, but there are no accepted diagnostic criteria for a cannabis withdrawal syndrome (CWS). This study evaluated diagnostic criteria for CWS proposed in DSM-V and two earlier proposals. A convenience sample of 384 adult, non-treatment-seeking lifetime cannabis smokers provided retrospective self-report data on their "most difficult" quit attempt without formal treatment, which was used in this secondary analysis. Prevalence, time of onset, and peak intensity (5-point Likert scale) for 39 withdrawal symptoms (drawn from the literature) were assessed via computer-administered questionnaire. Subject groups were compared using chi-square or ANOVA. Symptom clustering was evaluated with principal components analysis. 40.9% of subjects met the DSM-V criterion of ≥3 symptoms from a list of 7. There were no associations with sex, race, or type of cannabis preparation used. There were significant positive associations between duration or frequency of cannabis use prior to the quit attempt and experiencing CWS. Subjects with CWS had a significantly shorter duration of abstinence. Alternative syndromal criteria (dropping physical symptoms from DSM-V list; requiring ≥2 or ≥4 symptoms from a list of 11) yielded a similar prevalence of CWS and similar associations with prior cannabis use and relapse. The PCA yielded 12 factors, including some symptom clusters not included in DSM-V. Findings support the concurrent and predictive validity of the proposed DSM-V CWS, but suggest that the list of withdrawal symptoms and number required for diagnosis warrant further evaluation. Gorelick DA, Levin KH, Copersino ML, Heishman SJ, Liu F, Boggs DL, Kelly DL. Diagnostic criteria for cannabis withdrawal syndrome. Drug Alcohol Depend. 2011 Dec 7. [Epub ahead of print].

Functional Connectivity Mapping of the Human Precuneus by Resting State fMRI Precuneus responds to a wide range of cognitive processes. Here, the authors examined how the patterns of resting state connectivity may define functional subregions in the precuneus. Using a K-means algorithm to cluster the whole-brain "correlograms" of the precuneus in 225 adult individuals, the authors corroborated the dorsal-anterior, dorsal-posterior, and ventral subregions, each involved in spatially guided behaviors, mental imagery, and episodic memory as well as self-related processing, with the ventral precuneus being part of the default mode network, as described extensively in earlier work. Furthermore, they showed that the lateral/medial volumes of dorsal anterior and dorsal posterior precuneus are each connected with areas of motor execution/attention and motor/visual imagery, respectively. Compared to the ventral precuneus, the dorsal precuneus showed greater connectivity with occipital and posterior parietal cortices, but less connectivity with the medial superior frontal and orbitofrontal gyri, anterior cingulate cortex as well as the parahippocampus. Compared to dorsal-posterior and ventral precuneus, the dorsal-anterior precuneus showed greater connectivity with the somatomotor cortex, as well as the insula, supramarginal, Heschl's, and superior temporal gyri, but less connectivity with the angular gyrus. Compared to ventral and dorsal-anterior precuneus, dorsal-posterior precuneus showed greater connectivity with the middle frontal gyrus. Notably, the precuneus as a whole has negative connectivity with the amygdala and the lateral and inferior orbital frontal gyri. Finally, men and women differed in the connectivity of precuneus. Men and women each showed greater connectivity with the dorsal precuneus in the cuneus and medial thalamus, respectively. Women also showed greater connectivity with ventral precuneus in the hippocampus/parahippocampus, middle/anterior cingulate gyrus, and middle occipital gyrus, compared to men. Taken together, these new findings may provide a useful platform upon which to further investigate sex-specific functional neuroanatomy of the precuneus and to elucidate the pathology of many neurological illnesses. Zhang S, Li CS. Functional connectivity mapping of the human precuneus by resting state fMRI. Neuroimage. 2011 Feb; 59(4): 3548-3562.

CREB-Mediated Alterations in the Amygdala Transcriptome: Coordinated Regulation of Immune Response Genes Following Cocaine The neuronal circuitry underlying stress- and drug-induced reinstatement of cocaine-seeking has been relatively well characterized; however, less is known regarding the long-term molecular changes following cocaine administration that may promote future reinstatement. The transcription factor cAMP response element-binding protein (CREB) is necessary for stress- but not cocaine-induced reinstatement of conditioned reward, suggesting that different molecular mechanisms may underlie these two types of reinstatement. To explore the relationship between this transcription factor and reinstatement, the authors utilized the place-conditioning paradigm to examine alterations in gene expression in the amygdala, a neural substrate critically involved in stress-induced reinstatement, following the development of cocaine reward and subsequent extinction. These findings demonstrate that the amygdala transcriptome was altered by CREB deficiency more than by previous cocaine experience, with an over-representation of genes involved in the immune response. However, a subset of genes involved in stress and immune response demonstrated a drugXgenotype interaction, indicating that cocaine produces different long-term alterations in gene expression depending on the presence or absence of CREB. This profile of gene expression in the context of addiction enhances our understanding of the long-term molecular changes that occur throughout the addiction cycle and identifies novel genes and pathways that might lead to the creation of better therapeutic agents. Ecke LE, Cleck JN, White P, Schug J, Mifflin L, Blendy JA. CREB-mediated alterations in the amygdala transcriptome: coordinated regulation of immune response genes following cocaine. Int J Neuropsychopharmacol. 2011 Sep; 14(8): 1111-1126.

Rare Nonsynonymous Variants in Alpha-4 Nicotinic Acetylcholine Receptor Gene Protect against Nicotine Dependence Several studies report association of alpha-4 nicotinic acetylcholine receptors (encoded by CHRNA4) with nicotine dependence (ND). A meta-analysis of genome-wide linkage studies for ND implicated a single chromosomal region, which includes CHRNA4, as genome-wide significant. After establishing that common variants are unlikely to completely account for this linkage, the authors investigated the distribution of CHRNA4 rare variants by sequencing the coding exons and flanking intronic regions of CHRNA4 in 209 European American (EA) ND cases and 183 EA control subjects. Because most of the rare variants that the authors detected (and all nonsynonymous changes) were in Exon 5, they sequenced Exon 5 in an additional 1000 ND cases and 1000 non-ND comparison subjects, both of which included equal numbers of EAs and African Americans. Comparison subjects had a higher frequency of rare nonsynonymous variants in the Exon 5 region (encoding the large intercellular loop of the α4 subunit; Fisher's Exact Test $p = .009$; association test $p = .009$, odds ratio = .43; weighted-sum method $p = .014$), indicating a protective effect against ND. Considering data from the two stages combined and only nonsynonymous variants predicted to alter protein function, the association was stronger (Fisher's Exact Test $p = .005$; association test $p = .008$, odds ratio = .29; weighted-sum method $p = .005$). Single-photon emission computed tomography imaging results were consistent with functionality. CHRNA4 functional rare variants may reduce ND risk. This is the first demonstration that rare functional variants at a candidate locus protect against substance dependence to the authors' knowledge, suggesting a novel mechanism of substance dependence heritability that is potentially of general importance. Xie P, Kranzler HR, Krauthammer M, Cosgrove KP, Oslin D, Anton RF, Farrer LA, Picciotto MR, Krystal JH, Zhao H, Gelernter J. Rare nonsynonymous variants in alpha-4 nicotinic acetylcholine receptor gene protect against nicotine dependence. Biol Psychiatry. 2011 Sep 15; 70(6): 528-536.

What Can Allostasis Tell Us About Anabolic-Androgenic Steroid Addiction? Anabolic-androgenic steroids (AASs) are synthetic hormones used by individuals who want to look better or perform better in athletics and at the gym. Their use raises an interesting paradox in which drug use is associated with a number of health benefits, but also the possibility of negative health consequences. Existing models of AAS addiction follow the traditional framework of drug abuse and dependence, which suggest that harmful use occurs as a result of the drug's ability to hijack the motivation-reward system. However, AASs, unlike typical drugs of abuse, are not used for acute intoxication effects or euphoria. Rather, AASs are used to affect the body through changes to the musculoskeletal system and the hypothalamic-pituitary-gonadal axis as opposed to stimulating the reward system. The authors offer an allostatic model of AAS addiction to resolve this inconsistency between traditional drug addiction and AAS addiction. This allostatic framework provides a way to (a) incorporate exercise into AAS misuse, (b) identify where AAS use transitions from recreational use into a drug problem, and (c) describe individual differences in vulnerability or resilience to AASs. Implications for this model of AAS addiction are discussed. Hildebrandt T, Yehuda R, Alfano L. What can allostasis tell us about anabolic-androgenic steroid addiction? Dev Psychopathol. 2011 Aug; 23(3): 907-919.

Providing Coaching and Cotinine Results to Preteens to Reduce Their Secondhand Smoke Exposure: A Randomized Trial Secondhand smoke exposure (SHSe) poses health risks to children living with smokers. Most interventions to protect children from SHSe have coached adult smokers. This trial determined whether coaching and cotinine feedback provided to preteens can reduce their SHSe. Two hundred one predominantly low-income families with a resident smoker and a child aged 8 to 13 years who was exposed to two or more cigarettes per day or had a urine cotinine concentration ≥ 2.0 ng/mL were randomized to control or SHSe reduction coaching groups. During eight in-home sessions over 5 months, coaches presented to the child graphic charts of cotinine assay results as performance feedback and provided differential praise and incentives for cotinine reductions. Generalized estimating equations were used to determine the differential change in SHSe over time by group. For the baseline to posttest period, the coaching group had a greater decrease in both urine cotinine concentration ($P = .039$) and reported child SHSe in the number of cigarettes exposed per day (child report, $P = .003$; parent report, $P = .078$). For posttest to month 12 follow-up, no group or group by time differences were obtained, and both groups returned toward baseline. Coaching preteens can reduce their SHSe, although reductions may not be sustained without ongoing counseling, feedback, and incentives. Unlike interventions that coach adults to reduce child SHSe, programs that increase child avoidance of SHSe have the potential to reduce SHSe in all settings in which the child is exposed, without requiring a change in adult smoking behavior. Hovell MF, Wahlgren DR, Liles S, Jones JA, Hughes SC, Matt GE, Ji M, Lessov-Schlaggar CN, Swan GE, Chatfield D, Ding D. Providing coaching and cotinine results to preteens to reduce their secondhand smoke exposure: a randomized trial. Chest. 2011 Sep; 140(3): 681-689.

Nicotine Effects on Default Mode Network During Resting State The default mode network (DMN), one of several resting-state networks (RSN) in the brain, is thought to be involved in self-referential thought, awareness, and episodic memories. Nicotine improves cognitive performance, in part by improving attention. Nicotinic agonists have been shown to decrease activity in regions within DMN and increase activity in regions involved in visual attention during effortful processing of external stimuli. It is unknown if these pharmacological effects also occur in the absence of effortful processing. This study aims to determine if nicotine suppresses activity in default mode and enhances activity in extra-striate RSNs in the absence of

an external visual task. Within-subject, single-blinded, counterbalanced study of 19 non-smoking subjects who had resting functional MRI scans after 7 mg nicotine or placebo patch. Group independent component analysis was performed. The DMN component was identified by spatial correlation with a reference DMN mask. A visual attention component was identified by spatial correlation with an extra-striate mask. Analyses were conducted using statistical parametric mapping. Nicotine was associated with decreased activity in regions within the DMN and increased activity in extra-striate regions. Suppression of DMN and enhancement of extra-striate resting-state activity in the absence of visual stimuli or effortful processing suggest that nicotine's cognitive effects may involve a shift in activity from networks that process internal to those that process external information. This is a potential mechanism by which cholinergic agonists may have a beneficial effect in diseases associated with altered resting-state activity. Tanabe J, Nyberg E, Martin LF, Martin J, Cordes D, Kronberg E, Tregellas JR. Nicotine effects on default mode network during resting state. Psychopharmacology (Berl). 2011 Jul; 216(2): 287-295.

Multimodal Neuroimaging Dissociates Hemodynamic and Electrophysiological Correlates of Error Processing Recognizing errors and adjusting responses are fundamental to adaptive behavior. The error-related negativity (ERN) and error-related functional MRI (fMRI) activation of the dorsal anterior cingulate cortex (dACC) index these processes and are thought to reflect the same neural mechanism. In the present study, the authors evaluated this hypothesis. Although errors elicited robust dACC activation using fMRI, combined electroencephalography and magnetoencephalography data localized the ERN to the posterior cingulate cortex (PCC). ERN amplitude correlated with fMRI activation in both the PCC and dACC, and these two regions showed coordinated activity based on functional connectivity MRI. Finally, increased microstructural integrity of the posterior cingulum bundle, as measured by diffusion tensor imaging, predicted faster error correction. These findings suggest that the PCC generates the ERN and communicates with the dACC to subserve error processing. They challenge current models that view fMRI activation of the dACC as the hemodynamic reflection of the ERN. Agam Y, Hämäläinen MS, Lee AKC, Dyckman KA, Friedman JS, Isom M, Makris N, Manoach DS. Multimodal neuroimaging dissociates hemodynamic and electrophysiological correlates of error processing. Proc. Natl. Acad. Sci. U.S.A. 2011 Oct; 108(42): 17556-17561.

Medial Prefrontal Cortex as an Action-Outcome Predictor The medial prefrontal cortex (mPFC) and especially anterior cingulate cortex is central to higher cognitive function and many clinical disorders, yet its basic function remains in dispute. Various competing theories of mPFC have treated effects of errors, conflict, error likelihood, volatility and reward, using findings from neuroimaging and neurophysiology in humans and monkeys. No single theory has been able to reconcile and account for the variety of findings. Here the authors show that a simple model based on standard learning rules can simulate and unify an unprecedented range of known effects in mPFC. The model reinterprets many known effects and suggests a new view of mPFC, as a region concerned with learning and predicting the likely outcomes of actions, whether good or bad. Cognitive control at the neural level is then seen as a result of evaluating the probable and actual outcomes of one’s actions. Alexander WH, Brown JW. Medial prefrontal cortex as an action-outcome predictor. Nat. Neurosci. 2011 Oct; 14(10): 1338-1344.

Monoamine Oxidase A Binding in the Prefrontal and Anterior Cingulate Cortices During Acute Withdrawal from Heavy Cigarette Smoking Greater prefrontal cortex and anterior cingulate cortex monoamine oxidase A (MAO-A) binding is associated with depressed mood. Substances in cigarette smoke, such as harman, inhibit MAO-A, and cigarette withdrawal is associated with depressed mood. Dysphoria during cigarette withdrawal predicts relapse. It is unknown whether MAO-A binding increases during early cigarette withdrawal. The aims of this study were to measure prefrontal and anterior cingulate cortex MAO-A binding during acute cigarette withdrawal and to assess the relationship with smoking severity, plasma levels of harman, and severity of depression. This was studied via positron emission tomography of healthy control and cigarette-smoking individuals. Twenty-four healthy nonsmoking and 24 otherwise healthy cigarette-smoking individuals underwent positron emission tomography with harmine labeled with carbon 11. Healthy nonsmoking individuals underwent scanning once. Cigarette-smoking individuals underwent scanning after acute withdrawal and after active cigarette smoking. Cigarette smoking was heavy (≥25 cigarettes per day) or moderate (15-24 cigarettes per day). Tertiary care psychiatric hospital. An index of MAO-A density, MAO-A V(T), was measured in the prefrontal and anterior cingulate cortices. In heavy-smoking individuals, prefrontal and anterior cingulate cortex MAO-A V(T) was greater during withdrawal (23.7% and 33.3%, respectively; repeated-measures multivariate analysis of variance, $F(1,22) = 25.58$, $P < .001$). During withdrawal from heavy smoking, prefrontal and anterior cingulate cortex MAO-A V(T) was greater than in healthy controls (25.0% and 25.6%, respectively; multivariate analysis of variance, $F(2,33) = 6.72$, $P = .004$). The difference in MAO-A V(T) in the prefrontal cortex and anterior cingulate cortex between withdrawal and active, heavy smoking covaried with change in plasma harman levels in the prefrontal cortex and anterior cingulate cortex (multivariate analysis of covariance, $F(1,10) = 9.97$, $P = .01$). The change in MAO-A V(T) between withdrawal and active, heavy smoking also covaried with severity of depression (multivariate analysis of covariance, $F(1,10) = 11.91$, $P = .006$). The increase in prefrontal and anterior cingulate cortex MAO-A binding and associated reduction in plasma harman level represent a novel, additional explanation for depressed mood during withdrawal from heavy cigarette smoking. This finding resolves a longstanding paradox regarding the association of cigarette smoking with depression and suicide and argues for additional clinical trials on the effects of MAO-A inhibitors on quitting heavy cigarette smoking. Bacher I, Houle S, Xu X, Zawertailo L, Soliman A, Wilson AA, Selby P, George TP, Sacher J, Miler L, Kish SJ, Rusjan P, Meyer JH. Monoamine oxidase A binding in the prefrontal and anterior cingulate cortices during acute withdrawal from heavy cigarette smoking. Arch. Gen. Psychiatry 2011 Aug; 68(8): 817-826.

Dorsolateral Prefrontal Cortex Drives Mesolimbic Dopaminergic Regions to Initiate Motivated Behavior How does the brain translate information signaling potential rewards into motivation to get them? Motivation to obtain reward is thought to depend on the midbrain [particularly the ventral tegmental area (VTA)], the nucleus accumbens (NAcc), and the dorsolateral prefrontal cortex (dlPFC), but it is not clear how the interactions among these regions relate to reward-motivated behavior. To study the influence of motivation on these reward-responsive regions and on their interactions, the authors used dynamic causal modeling to analyze functional magnetic resonance imaging (fMRI) data from humans performing a simple task designed to isolate reward anticipation. The use of fMRI permitted the simultaneous measurement of multiple brain regions while human participants anticipated and prepared for opportunities to obtain reward, thus allowing characterization of how information about reward changes physiology underlying motivational drive. Furthermore, they modeled the impact of

external reward cues on causal relationships within this network, thus elaborating a link between physiology, connectivity, and motivation. Specifically, these results indicated that dlPFC was the exclusive entry point of information about reward in this network, and that anticipated reward availability caused VTA activation only via its effect on the dlPFC. Anticipated reward thus increased dlPFC activation directly, whereas it influenced VTA and NAcc only indirectly, by enhancing intrinsically weak or inactive pathways from the dlPFC. These findings of a directional prefrontal influence on dopaminergic regions during reward anticipation suggest a model in which the dlPFC integrates and transmits representations of reward to the mesolimbic and mesocortical dopamine systems, thereby initiating motivated behavior. Ballard IC, Murty VP, Carter RM, MacInnes JJ, Huettel SA, Adcock RA. Dorsolateral prefrontal cortex drives mesolimbic dopaminergic regions to initiate motivated behavior. J. Neurosci. 2011 Jul; 31(28): 10340-10346.

Contrasting Behavioral Effects of Acute Nicotine and Chronic Smoking in Detoxified Alcoholics Current literature suggests that acute nicotine administration provides a compensatory mechanism by which alcoholics might alleviate attentional deficits. In contrast, chronic smoking is increasingly recognized as negatively affecting neurobehavioral integrity. These opposing effects have not been simultaneously examined. Thus, the authors sought to a) extend previous work by exploring the effects of acute nicotine effects on vigilance components of attention and replicate previous findings suggesting that treatment-seeking alcoholics experience benefit to a greater extent than do other groups; and b) to examine the impact of chronic smoking on these tasks and across subgroups. Substance abusing participants (N=86) were recruited and subgrouped on the basis of dependency criteria as either alcoholics, alcoholics with co-morbid stimulant dependence, or stimulant dependent individuals. Groups of cigarette-smoking (N=17) and non-smoking (N=22) community controls were recruited as comparison groups. Smoking subjects were assigned a placebo, low, or high dose nicotine patch in a double-blind placebo controlled fashion. Non-smoking controls were administered either a placebo or low dose. Testing occurred after dose stabilization. General linear models indicated greater sensitivity to acute nicotine administration among alcoholics than other groups when controlling for the effect of intensity of smoking history, as reflected by pack-years. Pack-years correlated negatively with performance measures in alcoholics but not stimulant abusing subgroups or smoking controls. Finally, regression analyses demonstrated that pack-years predicted poorer performance only for the alcoholic subgroup. These results support previous work finding a compensatory effect of acute nicotine administration on attentional performance in alcoholics and reinforce the consideration of recent nicotine use as a confound in neurocognitive studies of alcoholics. Of particular interest is the finding that smoking history as reflected in pack-years predicted poorer performance, but only among alcoholics. Further systematic study of these opposing effects among alcoholics and other groups using a broader array of tasks is needed. Boissoneault J, Gilbertson R, Prather R, Nixon SJ. Contrasting behavioral effects of acute nicotine and chronic smoking in detoxified alcoholics. Addict Behav 2011 Dec; 36(12): 1344-1348.

The Relationship Between Posttraumatic Stress Disorder and Smoking Outcome Expectancies Among U.S. Military Veterans Who Served Since September 11, 2001 Posttraumatic stress disorder (PTSD) is associated with increased rates of smoking although little is known regarding the mechanisms underlying this relationship. The current study examined expectations about smoking outcomes among smokers with and without PTSD. The sample included 96 veterans (mean age of 34 years) and included 17% women and 50% racial

minorities. Smoking expectancies were measured with the Smoking Consequences Questionnaire-Adult (Copeland, Brandon, & Quinn, 1995). Consistent with previous work suggesting that smokers with PTSD smoke in an effort to reduce negative affect, unadjusted analyses indicated that smokers with PTSD (n = 38) had higher expectations that smoking reduces negative affect than smokers without PTSD (d = 0.61). Smokers with PTSD also had increased expectancies associated with boredom reduction (d = 0.48), stimulation (d = 0.61), taste/sensorimotor manipulation aspects of smoking (d = 0.73), and social facilitation (d = 0.61). Results of hierarchical linear regression analyses indicated that PTSD symptom severity was uniquely associated with these expectancies beyond the effects of gender and nicotine dependence. More positive beliefs about the consequences of smoking may increase risk of continued smoking among those with PTSD who smoke. Further understanding of smoking expectancies in this group may help in developing interventions tailored for this vulnerable population. Calhoun PS, Levin HF, Dedert EA, Johnson Y, Beckham JC. The relationship between posttraumatic stress disorder and smoking outcome expectancies among U.S. military veterans who served since September 11, 2001. J Trauma Stress 2011 Jun; 24(3): 303-308.

The Effect of Nicotine and Trauma Context on Acoustic Startle in Smokers with and without Posttraumatic Stress Disorder Exaggerated startle response is a prominent feature of posttraumatic stress disorder (PTSD) although results examining differences in the acoustic startle response (ASR) between those with and without PTSD are mixed. One variable that may affect ASR among persons with PTSD is smoking. Individuals with PTSD are more likely to smoke and have greater difficulty quitting smoking. While smokers with PTSD report that smoking provides significant relief of negative affect and PTSD symptoms, the effects of smoking or nicotine deprivation on startle reactivity among smokers with PTSD are unknown. The purposes of the current study were to (1) examine baseline acoustic startle response (ASR) in smokers with and without PTSD under conditions of overnight abstinence, (2) evaluate the effect of smoking on ASR, and (3) evaluate the contextual effects of trauma versus neutral script presentations. METHODS ASR was measured among 48 smokers with and without PTSD in the context of a 2 (group: PTSD vs. non-PTSD) x 2 (context: trauma vs. neutral) x 3 (smoking condition: usual brand cigarette vs. denicotinized cigarette vs. no smoking) design. RESULTS Effects of modest size indicated that (1) PTSD participants demonstrated higher ASR (2) compared to non-PTSD participants, PTSD participants reported greater negative affect following a trauma-related script, and (3) following a trauma-related script and smoking a usual brand cigarette, PTSD participants demonstrated higher ASR. Although many smokers with PTSD report that smoking reduces PTSD symptoms, results suggest that smoking may actually potentiate or maintain an exaggerated startle response. Calhoun PS, Wagner HR, McClernon FJ, Lee S, Dennis MF, Vrana SR, Clancy CP, Collie CF, Johnson YC, Beckham JC. The effect of nicotine and trauma context on acoustic startle in smokers with and without posttraumatic stress disorder. Psychopharmacology (Berl.) 2011 May; 215(2): 379-389.

Inverted-U-Shaped Dopamine Actions on Human Working Memory and Cognitive Control Brain dopamine (DA) has long been implicated in cognitive control processes, including working memory. However, the precise role of DA in cognition is not well-understood, partly because there is large variability in the response to dopaminergic drugs both across different behaviors and across different individuals. The authors review evidence from a series of studies with experimental animals, healthy humans, and patients with Parkinson's disease, which highlight two important factors that contribute to this large variability. First, the existence of an optimum DA level for cognitive function implicates the need to take into account baseline levels

of DA when isolating the effects of DA. Second, cognitive control is a multifactorial phenomenon, requiring a dynamic balance between cognitive stability and cognitive flexibility. These distinct components might implicate the prefrontal cortex and the striatum, respectively. Manipulating DA will thus have paradoxical consequences for distinct cognitive control processes, depending on distinct basal or optimal levels of DA in different brain regions. Cools R, D'Esposito M. Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol. Psychiatry 2011 Jun; 69(12): 113-125.

Feedback Timing Modulates Brain Systems for Learning in Humans The ability to learn from the consequences of actions--no matter when those consequences take place--is central to adaptive behavior. Despite major advances in understanding how immediate feedback drives learning, it remains unknown precisely how the brain learns from delayed feedback. Here, the authors present converging evidence from neuropsychology and neuroimaging for distinct roles for the striatum and the hippocampus in learning, depending on whether feedback is immediate or delayed. They show that individuals with striatal dysfunction due to Parkinson's disease are impaired at learning when feedback is immediate, but not when feedback is delayed by a few seconds. Using functional imaging (fMRI) combined with computational model-derived analyses, they further demonstrate that healthy individuals show activation in the striatum during learning from immediate feedback and activation in the hippocampus during learning from delayed feedback. Additionally, later episodic memory for delayed feedback events was enhanced, suggesting that engaging distinct neural systems during learning had consequences for the representation of what was learned. Together, these findings provide direct evidence from humans that striatal systems are necessary for learning from immediate feedback and that delaying feedback leads to a shift in learning from the striatum to the hippocampus. The results provide a link between learning impairments in Parkinson's disease and evidence from single-unit recordings demonstrating that the timing of reinforcement modulates activity of midbrain dopamine neurons. Collectively, these findings indicate that relatively small changes in the circumstances under which information is learned can shift learning from one brain system to another. Foerde K, Shohamy D. Feedback timing modulates brain systems for learning in humans. J. Neurosci. 2011 Sep; 31(37): 13157-13167.

Residual Neurocognitive Features of Long-Term Ecstasy Users with Minimal Exposure to other Drugs In field studies assessing cognitive function in illicit ecstasy users, there are several frequent confounding factors that might plausibly bias the findings toward an overestimate of ecstasy-induced neurocognitive toxicity. The authors designed an investigation seeking to minimize these possible sources of bias. They compared illicit ecstasy users and non-users while (1) excluding individuals with significant life-time exposure to other illicit drugs or alcohol; (2) requiring that all participants be members of the "rave" subculture; and (3) testing all participants with breath, urine and hair samples at the time of evaluation to exclude possible surreptitious substance use. They compared groups with adjustment for age, gender, race/ethnicity, family-of-origin variables and childhood history of conduct disorder and attention deficit hyperactivity disorder. They provide significance levels without correction for multiple comparisons. A field study was conducted with fifty-two illicit ecstasy users and 59 non-users, aged 18-45 years using a battery of 15 neuropsychological tests tapping a range of cognitive functions. They found little evidence of decreased cognitive performance in ecstasy users, save for poorer strategic self-regulation, possibly reflecting increased impulsivity. However, this finding might have reflected a pre-morbid attribute of ecstasy users, rather than a residual neurotoxic effect of the drug. In a study designed to minimize limitations found in many prior investigations, the authors failed to

demonstrate marked residual cognitive effects in ecstasy users. This finding contrasts with many previous findings-including the authors'-and emphasizes the need for continued caution in interpreting field studies of cognitive function in illicit ecstasy users. Halpern JH, Sherwood AR, Hudson JI, Gruber S, Kozin D, Pope HG Jr. Residual neurocognitive features of long-term ecstasy users with minimal exposure to other drugs. Addiction 2011 Apr; 106(4): 777-786.

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 Jun; 218(4): 681-692.

Effect of Methamphetamine Dependence on Inhibitory Deficits in a Novel Human Open-Field Paradigm Methamphetamine (MA) is an addictive psychostimulant associated with neurocognitive impairment, including inhibitory deficits characterized by a reduced ability to control responses to stimuli. While various domains of inhibition such as exaggerated novelty seeking and perseveration have been assessed in rodents by quantifying activity in open-field tests, similar models have not been utilized in human substance abusers. The authors recently developed a cross-species translational human open-field paradigm, the human behavior pattern monitor (hBPM), consisting of an unfamiliar room containing novel and engaging objects. Previous work demonstrated that manic bipolar subjects exhibit a disinhibited pattern of behavior in the hBPM characterized by increased object interactions. In the current study, they examined the effect of MA dependence on inhibitory deficits using this paradigm. hBPM activity and object interactions were quantified in 16 abstinent MA-dependent individuals and 18 matched drug-free comparison subjects. The Wisconsin card sorting task (WCST) and the positive and negative syndrome scale (PANSS) were administered to assess executive function and psychopathology. MA-dependent participants exhibited a significant increase in total object interactions, time spent with objects, and perseverative object interactions relative to comparison subjects. Greater object interaction was associated with impaired performance on the WCST, higher PANSS scores, and more frequent MA use in the past year. Abstinent MA-dependent individuals exhibited impaired inhibition in the hBPM, displaying increased interaction with novel stimuli. Utilization of this measure may enable assessment of inhibitory deficits relevant to

drug-seeking behavior and facilitate development of intervention methods to reduce high-risk conduct in this population. Henry BL, Minassian A, van Rhenen M, Young JW, Geyer MA, Perry W. Effect of methamphetamine dependence on inhibitory deficits in a novel human open-field paradigm. Psychopharmacology (Berl.) 2011 Jun; 215(4): 697-707.

Estrogen Shapes Dopamine-Dependent Cognitive Processes: Implications for Women's Health The prefrontal cortex (PFC) is exquisitely sensitive to its neurochemical environment. Minor fluctuations in cortical dopamine (DA) can profoundly alter working memory, a PFC-dependent cognitive function that supports an array of essential human behaviors. Dopamine's action in the PFC follows an inverted U-shaped curve, where an optimal DA level results in maximal function and insufficient or excessive DA impairs PFC function. In animals, 17β-estradiol (the major estrogen in most mammals, referred to henceforth as estradiol) has been shown to enhance DA activity, yet no human study has adequately addressed whether estradiol's impact on cognition occurs by way of modulating specific neurochemical systems. Here the authors examined the effects of endogenous fluctuations in estradiol on working memory in healthy young women as a function of baseline PFC DA [indexed by catechol-O-methyltransferase (COMT) Val(158)Met genotype and, at a finer scale, COMT enzyme activity]. The results demonstrate that estradiol status impacts working memory function and, crucially, the direction of the effect depends on indices of baseline DA. Moreover, consistent with a DA cortical efficiency hypothesis, functional MRI revealed that inferred optimal DA was associated with reduced PFC activity sustained across task blocks and selectively enhanced PFC activity on trials with the greatest demand for cognitive control. The magnitude of PFC activity during high control trials was predictive of an individual's performance. These findings show that although estrogen, considered in isolation, may have unpredictable effects on cognitive performance, its influence is clarified when considered within a larger neuromodulatory framework. Given the clinical prevalence of dopaminergic drugs, understanding the relationship between estrogen and DA is essential for advancing women's health. Jacobs E, D'Esposito M. Estrogen shapes dopamine-dependent cognitive processes: implications for women's health. J. Neurosci 2011 Apr; 31(14): 5286-5293.

The Influence of Emotion Regulation on Decision-Making Under Risk Cognitive strategies typically involved in regulating negative emotions have recently been shown to also be effective with positive emotions associated with monetary rewards. However, it is less clear how these strategies influence behavior, such as preferences expressed during decision-making under risk, and the underlying neural circuitry. That is, can the effective use of emotion regulation strategies during presentation of a reward-conditioned stimulus influence decision-making under risk and neural structures involved in reward processing such as the striatum? To investigate this question, the authors asked participants to engage in imagery-focused regulation strategies during the presentation of a cue that preceded a financial decision-making phase. During the decision phase, participants then made a choice between a risky and a safe monetary lottery. Participants who successfully used cognitive regulation, as assessed by subjective ratings about perceived success and facility in implementation of strategies, made fewer risky choices in comparison with trials where decisions were made in the absence of cognitive regulation. Additionally, BOLD responses in the striatum were attenuated during decision-making as a function of successful emotion regulation. These findings suggest that exerting cognitive control over emotional responses can modulate neural responses associated with reward processing (e.g., striatum) and promote more goal-directed decision-making (e.g., less risky choices), illustrating the potential importance of cognitive strategies in curbing risk-seeking behaviors before they

become maladaptive (e.g., substance abuse). Martin LN, Delgado MR. The influence of emotion regulation on decision-making under risk. J Cogn Neurosci 2011 Sep; 23(9): 2569-2581.

Anterior Cingulate Proton Spectroscopy Glutamate Levels Differ as a Function of Smoking Cessation Outcome Cigarette smoking is the leading preventable cause of death. Unfortunately, the majority of smokers who attempt to quit smoking relapse within weeks. Abnormal dorsal anterior cingulate cortex (dACC) function may contribute to tobacco smoking relapse vulnerability. Growing evidence suggests that glutamate neurotransmission is involved in mediating nicotine dependence. The authors hypothesized that prior to a cessation attempt, dACC glutamate levels would be lower in relapse vulnerable smokers. Proton magnetic resonance spectra (MRS) were obtained from dACC and a control region, the parieto-occipital cortex (POC), using two-dimensional J-resolved MRS at 4T and analyzed using LCModel. Nine nicotine-dependent women were scanned prior to making a quit attempt. Subjects then were divided into two groups; those able to maintain subsequent abstinence aided by nicotine replacement therapy (NRT) and those who slipped while on NRT (smoked any part of a cigarette after attaining at least 24h of abstinence). Slip subjects exhibited significantly reduced dACC MRS glutamate (Glu/Cr) levels ($p<0.03$) compared to abstinent subjects. This effect was not observed in the POC control region. These preliminary findings suggest that dACC Glu levels as measured with MRS may help identify and/or be a biomarker for relapse vulnerable smokers. Future research following up on these findings may help clarify the role of dACC Glu in smoking dependence that may lead to new treatment strategies. Mashhoon Y, Janes AC, Jensen JE, Prescot AP, Pachas G, Renshaw PF, Fava M, Evins AE, Kaufman MJ. Anterior cingulate proton spectroscopy glutamate levels differ as a function of smoking cessation outcome. Prog Neuropsychopharmacol Biol Psychiatry 2011 May; 35(7): 170-1713.

Altered Pain Responses in Abstinent (±)3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") Users (±)3,4-Methylenedioxymethamphetamine (MDMA) is a popular recreational drug that has potential to damage brain serotonin (5-HT) neurons in humans. Brain 5-HT neurons play a role in pain modulation, yet little is known about long-term effects of MDMA on pain function. Notably, MDMA users have been shown to have altered sleep, a phenomenon that can lead to altered pain modulation. This study sought to assess pain processing in MDMA users using objective methods, and explore potential relationships between pain processing and sleep indices. Forty-two abstinent MDMA users and 43 age-matched controls participated in a 5-day inpatient study. Outcome measures included standardized measures of pain, sleep polysomnograms, and power spectral measures of the sleep EEG. When differences in psychophysiological measures of pain were found, the relationship between pain and sleep measures was explored. MDMA users demonstrated lower pressure pain thresholds, increased cold pain ratings, increased pain ratings during testing of diffuse noxious inhibitory control, and decreased Stage 2 sleep. Numerous significant relationships betweesleep and pain measures were identified, but differences in sleep between the two groups wee not found to mediate altered pain perception in MDMA users. The authors conclude that abstinent MDMA users have altered pain perception and sleep architecture. Although pain and sleep outcomes were related, differences in sleep architecture in MDMA users did not mediate altered pain responses. It remains to be determined whether alterations in pain perception in MDMA users are secondary to neurotoxicity of 5-HT-mediated pain pathways or alterations in other brain processes that modulate pain perception. McCann UD, Edwards RR, Smith MT, Kelley K, Wilson M, Sgambati F, Ricaurte G. Altered pain responses in abstinent (±)3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users. Psychopharmacology (Berl.) 2011 Oct; 217(4): 475-484.

Methamphetamine Users Show Greater than Normal Age-Related Cortical Gray Matter Loss Methamphetamine (Meth) abuse continues to be a major illicit drug of abuse. Neuroimaging findings suggest that Meth is neurotoxic and may alter various brain structures, but the effect of Meth on the aging brain has not been studied. The aim was to determine regional volumes of cortical gray matter in the brains of adult Meth users versus healthy control subjects, and their interaction with age and Meth-usage variables. Magnetic resonance imaging (MRI) Research Center located in a university-affiliated hospital. Thirty-four Meth-dependent subjects (21 men and 13 women; ages 33.1 ± 8.9 years), diagnosed according to DSM-IV criteria, and 31 healthy non-Meth user comparison subjects (23 men and 8 women ages 35.7 ± 8.4 years). Regional gray matter volumes were segmented automatically in all subjects and evaluated in relation to age, using high-resolution MRIs at 3.0 Tesla. After adjustment for the effects of cranium size, the Meth users showed enhanced cortical gray matter volume loss with age in the frontal (analysis of covariance interaction $P = 0.02$), occipital (interaction $P = 0.01$), temporal (interaction $P < 0.001$) and the insular lobes (interaction $P = 0.01$) compared to controls, independently of Meth-usage patterns. Additionally, Meth users showed smaller gray matter volumes than control subjects in several subregions (dorsolateral prefrontal: $P = 0.02$; orbitofrontal: $P = 0.03$; prefrontal: $P = 0.047$; superior temporal: $P = 0.04$). Methamphetamine users appear to show increased cortical gray matter loss with age which raises the possibility of accelerated decline in mental functioning. Nakama H, Chang L, Fein G, Shimotsu R, Jiang CS, Ernst T. Methamphetamine users show greater than normal age-related cortical gray matter loss. Addiction 2011 Aug; 106(8): 1474-1483.

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 [11C]-(+)-dihydrotetrabenazine (DTBZ) to assess the in vivo VMAT2 availability in a group of 12 recently abstinent cocaine-dependent subjects and matched healthy comparison subjects. Method:[11C]DTBZ nondisplaceable binding potential (BPND) was measured by kinetic analysis using the arterial input function or, if arterial input was unavailable, by the simplified reference tissue method. [11C]DTBZ BPND 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. American Journal of Psychiatry 2011 Oct; 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) 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 [11C]-(+)-dihydrotetrabenazine (DTBZ) to assess the in vivo VMAT2 availability in a group of 12 recently abstinent cocaine-dependent subjects and matched healthy comparison subjects. [11C]DTBZ nondisplaceable binding potential (BPND) was measured by kinetic analysis using the arterial input function or, if arterial input was unavailable, by the simplified reference tissue method. [11C]DTBZ BPND 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, 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.

Evaluation of Dopamine D2/3 Specific Binding in the Cerebellum for the Positron Emission Tomography Radiotracer [^{11}C]FLB 457: Implications for Measuring Cortical Dopamine Release In a recent positron emission tomography (PET) study, the authors demonstrated the ability to measure amphetamine-induced dopamine (DA) release in the human cortex with the DA D2/3 radioligand [^{11}C]FLB 457. As previous studies in animals have shown that a relatively high fraction of the [^{11}C]FLB 457 signal in the cerebellum represents specific binding to D2/3 receptors, there was concern that the use of the cerebellum as a measure of nonspecific binding (i.e., reference region) to derive [^{11}C]FLB 457 binding potential (BP) (BP(ND)) would bias cortical DA release measurements. Thus, they evaluated the fractional contribution of specific binding to D2/3 receptors in the human cerebellum for [^{11}C]FLB 457. Six healthy human subjects (5M/1F) were studied twice with [^{11}C]FLB 457, once at baseline and again following a single oral dose of 15 mg of aripiprazole, a D2/3 partial agonist. [^{11}C]FLB 457 distribution volume (V(T)) was estimated using kinetic analysis in the cortical regions of interest and potential reference regions. The change in [^{11}C]FLB 457 V(T) following aripiprazole ranged from -33 to -42% in the cortical regions of interest (ROIs). The aripiprazole-induced change in [^{11}C]FLB 457 V(T) in three potential reference regions suggests significant specific binding the cerebellum (CER, -17 ± 12%), but not pons (PON, -10 ± 10%) and centrum semiovale (CESVL, -3 ± 12%). Nevertheless, a reanalysis of the published [^{11}C]FLB 457 test-retest and amphetamine studies suggests that the use of the PON V(T) and CESVL V(T) as an estimate of nonspecific binding to derive [^{11}C]FLB 457 BP(ND) in DA release studies is unlikely to be successful because it leads to less reproducible outcome measures, which in turn diminishes the ability to measure DA release in the cortex. D2/3 blocking studies with aripiprazole and [^{11}C]FLB 457 suggest specific binding to D2/3 receptors in the cerebellum. These data also suggest that the

contribution of specific binding to D2/3 receptors in the cerebellum is lower than that in the cortical ROIs and that CER V(T) is mostly representative of nonspecific binding. Nevertheless, caution is advised when using reference tissue methods that rely solely on the cerebellum signal as an input function to quantify [^{11}C]FLB 457 BP(ND). Narendran R, Mason NS, Chen C-M, Himes M, Keating P, May MA, Rabiner EA, Laruelle M, Mathis CA, Frankle WG. Evaluation of dopamine D2/3 specific binding in the cerebellum for the positron emission tomography radiotracer [^{11}C]FLB 457: implications for measuring cortical dopamine release. Synapse 2011 Oct; 65(10): 991-997.

Relationship between Genetic Variation in the Glutaminase Gene GLS1 and Brain Glutamine/Glutamate Ratio Measured In Vivo Abnormalities in glutamatergic neurotransmission are implicated in several psychiatric disorders, but in vivo neurochemical studies of the glutamate (Glu) system have been hampered by a lack of adequate probes. By contrast, glutamine (Gln) and Glu can be quantified separately in proton magnetic resonance spectroscopy studies in vivo. Accumulating evidence suggests that the Gln/Glu ratio is a putative index of glutamatergic neurotransmission but interpretation of changes in the Gln/Glu ratio depends on the conditions of the system, including ammonia levels. Here, the authors explored whether variation in GLS1 (the gene encoding the brain isoform of glutaminase, which catalyzes Gln-to-Glu conversion) is associated with Gln/Glu measured in vivo in two brain regions (anterior cingulate cortex, parieto-occipital cortex). A specific haplotype of four single nucleotide polymorphisms within GLS1 was significantly associated with Gln/Glu in the parieto-occipital cortex in an magnetic resonance spectroscopy-genetics dataset optimized for Gln/Glu detection (n = 42). This finding was replicated in a second magnetic resonance spectroscopy dataset that was optimized for γ-aminobutyric acid detection where Gln and Glu measurements could still be extracted (n = 40). These findings suggest that genetic variation in a key component of glutamatergic machinery is associated with a putative in vivo index of glutamatergic neurotransmission. Thus, GLS1 genotype might provide insight into normal brain function and into the pathophysiology of many psychiatric conditions where glutamatergic neurotransmission has been implicated. It might also serve as a biomarker for predicting response to existing and novel therapeutic interventions in psychiatry that target glutamatergic neurotransmission. Öngür D, Haddad S, Prescot AP, Jensen JE, Siburian R, Cohen BM, Renshaw PF, Smoller JW. Relationship between genetic variation in the glutaminase gene GLS1 and brain glutamine/glutamate ratio measured in vivo. Biol. Psychiatry 2011 Jul; 70(2): 169-174.

Impact of Reward and Punishment Motivation on Behavior Monitoring as Indexed by the Error-Related Negativity The error-related negativity (ERN) is thought to index a neural behavior monitoring system with its source in anterior cingulate cortex (ACC). While ACC is involved in a wide variety of cognitive and emotional tasks, there is debate as to what aspects of ACC function are indexed by the ERN. In one model the ERN indexes purely cognitive function, responding to mismatch between intended and executed actions. Another model posits that the ERN is more emotionally driven, elicited when an action is inconsistent with motivational goals. If the ERN indexes mismatch between intended and executed actions, then it should be insensitive to motivational valence, e.g. reward or punishment; in contrast if the ERN indexes the evaluation of responses relative to goals, then it might respond differentially under differing motivational valence. This study used a flanker task motivated by potential reward and potential punishment on different trials and also examined the N2 and P3 to the imperative stimulus, the response Pe, and the FRN and P3 to the outcome feedback to assess the impact of motivation valence on other stages of information processing in this choice reaction time task. Participants

were slower on punishment motivated trials and both the N2 and ERN were larger on punishment motivated trials, indicating that loss aversion has an impact on multiple stages of information processing including behavior monitoring. Potts GF. Impact of reward and punishment motivation on behavior monitoring as indexed by the error-related negativity. Int J Psychophysiol 2011 Sep; 81(3): 324-331.

Premotor Functional Connectivity Predicts Impulsivity in Juvenile Offenders Teenagers are often impulsive. In some cases this is a phase of normal development; in other cases impulsivity contributes to criminal behavior. Using functional magnetic resonance imaging, the authors examined resting-state functional connectivity among brain systems and behavioral measures of impulsivity in 107 juveniles incarcerated in a high-security facility. In less-impulsive juveniles and normal controls, motor planning regions were correlated with brain networks associated with spatial attention and executive control. In more-impulsive juveniles, these same regions correlated with the default-mode network, a constellation of brain areas associated with spontaneous, unconstrained, self-referential cognition. The strength of these brain-behavior relationships was sufficient to predict impulsivity scores at the individual level. These data suggest that increased functional connectivity of motor-planning regions with networks subserving unconstrained, self-referential cognition, rather than those subserving executive control, heightens the predisposition to impulsive behavior in juvenile offenders. To further explore the relationship between impulsivity and neural development, the authors studied functional connectivity in the same motor-planning regions in 95 typically developing individuals across a wide age span. The change in functional connectivity with age mirrored that of impulsivity: younger subjects tended to exhibit functional connectivity similar to the more-impulsive incarcerated juveniles, whereas older subjects exhibited a less-impulsive pattern. This observation suggests that impulsivity in the offender population is a consequence of a delay in typical development, rather than a distinct abnormality. Shannon BJ, Raichle ME, Snyder AZ, Fair DA, Mills KL, Zhang D, Bache K, Calhoun VD, Nigg JT, Nagel BJ, Stevens AA, Kiehl KA. Premotor functional connectivity predicts impulsivity in juvenile offenders. Proc. Natl. Acad. Sci. U.S.A. 2011 Jul; 108(27): 11241-11245.

Extended Characterization of the Serotonin 2A (5-HT2A) Receptor-Selective PET Radiotracer 11C-MDL100907 in Humans: Quantitative Analysis, Test-Retest Reproducibility, and Vulnerability to Endogenous 5-HT Tone Scanning properties and analytic methodology of the 5-HT2A receptor-selective positron emission tomography (PET) tracer 11C-MDL100907 have been partially characterized in previous reports. The authors present an extended characterization in healthy human subjects. 64 11C-MDL100907 PET scans with metabolite-corrected arterial input function were performed in 39 healthy adults (18-55 years). 12 subjects were scanned twice (duration 150 min) to provide data on plasma analysis, model order estimation, and stability and test-retest characteristics of outcome measures. All other scans were 90 min duration. 3 subjects completed scanning at baseline and following 5-HT2A receptor antagonist medication (risperidone or ciproheptadine) to provide definitive data on the suitability of the cerebellum as reference region. 10 subjects were scanned under reduced 5-HT and control conditions using rapid tryptophan depletion to investigate vulnerability to competition with endogenous 5-HT. 13 subjects were scanned as controls in clinical protocols. Pooled data were used to analyze the relationship between tracer injected mass and receptor occupancy, and age-related decline in 5-HT2A receptors. Optimum analytic method was a 2-tissue compartment model with arterial input function. However, basis function implementation of SRTM may be suitable for measuring between-group differences non-invasively and warrants

further investigation. Scan duration of 90 min achieved stable outcome measures in all cortical regions except orbitofrontal which required 120 min. Binding potential (BPP and BPND) test-retest variability was very good (7-11%) in neocortical regions other than orbitofrontal, and moderately good (14-20%) in orbitofrontal cortex and medial temporal lobe. Saturation occupancy of 5-HT2A receptors by risperidone validates the use of the cerebellum as a region devoid of specific binding for the purposes of PET. The authors advocate a mass limit of 4.6 μg to remain below 5% receptor occupancy. 11C-MDL100907 specific binding is not vulnerable to competition with endogenous 5-HT in humans. Paradoxical decreases in BPND were found in right prefrontal cortex following reduced 5-HT, possibly representing receptor internalization. Mean age-related decline in brain 5-HT2A receptors was 14.0±5.0% per decade, and higher in prefrontal regions. Our data confirm and extend support for 11C-MDL100907 as a PET tracer with very favorable properties for quantifying 5-HT2A receptors in the human brain. Talbot PS, Slifstein M, Hwang D-R, Huang Y, Scher E, Abi-Dargham A, Laruelle M. Extended characterization of the serotonin 2A (5-HT2A) receptor-selective PET radiotracer 11C-MDL100907 in humans: quantitative analysis, test-retest reproducibility, and vulnerability to endogenous 5-HT tone. Neuroimage 2012 Jan; 59(1): 271-285.

Negative Reinforcement Learning is Affected in Substance Dependence Negative reinforcement results in behavior to escape or avoid an aversive outcome. Withdrawal symptoms are purported to be negative reinforcers in perpetuating substance dependence, but little is known about negative reinforcement learning in this population. The purpose of this study was to examine reinforcement learning in substance dependent individuals (SDI), with an emphasis on assessing negative reinforcement learning. The authors modified the Iowa Gambling Task to separately assess positive and negative reinforcement. They hypothesized that SDI would show differences in negative reinforcement learning compared to controls and we investigated whether learning differed as a function of the relative magnitude or frequency of the reinforcer. Thirty subjects dependent on psychostimulants were compared with 28 community controls on a decision making task that manipulated outcome frequencies and magnitudes and required an action to avoid a negative outcome. SDI did not learn to avoid negative outcomes to the same degree as controls. This difference was driven by the magnitude, not the frequency, of negative feedback. In contrast, approach behaviors in response to positive reinforcement were similar in both groups. Our findings are consistent with a specific deficit in negative reinforcement learning in SDI. SDI were relatively insensitive to the magnitude, not frequency, of loss. If this generalizes to drug-related stimuli, it suggests that repeated episodes of withdrawal may drive relapse more than the severity of a single episode. Thompson LL, Claus ED, Mikulich-Gilbertson SK, Banich MT, Crowley T, Krmpotich T, Miller D, Tanabe J. Negative reinforcement learning is affected in substance dependence [Internet]. Drug Alcohol Depend 2011 Nov. [Epub ahead of print].

Distribution of Vesicular Monoamine Transporter 2 Protein in Human Brain: Implications for Brain Imaging Studies The choice of reference region in positron emission tomography (PET) human brain imaging of the vesicular monoamine transporter 2 (VMAT2), a marker of striatal dopamine innervation, has been arbitrary, with cerebellar, whole cerebral, frontal, or occipital cortices used. To establish whether levels of VMAT2 are in fact low in these cortical areas, the authors measured VMAT2 protein distribution by quantitative immunoblotting in autopsied normal human brain (n=6). Four or five species of VMAT2 immunoreactivity (75, 55, 52, 45, 35 kDa) were detected, which were all markedly reduced in intensity in nigrostriatal regions of patients with parkinsonian conditions versus matched controls (n=9 to 10 each). Using

the intact VMAT2 immunoreactivity, cerebellar and cerebral neocortices had levels of the transporter >100-fold lower than the VMAT2-rich striatum and with no significant differences among the cortical regions. The authors conclude that human cerebellar and cerebral cortices contain negligible VMAT2 protein versus the striatum and, in this respect, all satisfy a criterion for a useful reference region for VMAT2 imaging. The slightly lower PET signal for VMAT2 binding in occipital (the currently preferred reference region) versus cerebellar cortex might not therefore be explained by differences in VMAT2 protein itself but possibly by other imaging variables, for example, partial volume effects. Tong J, Boileau I, Furukawa Y, Chang L-J, Wilson AA, Houle S, Kish SJ. Distribution of vesicular monoamine transporter 2 protein in human brain: implications for brain imaging studies. J. Cereb. Blood Flow Metab. 2011 Oct; 31(10): 2065-2075.

An Improved Method for Mapping Cerebrovascular Reserve Using Concurrent fMRI and Near-Infrared Spectroscopy with Regressor Interpolation at Progressive Time Delays (RIPTiDe) Cerebrovascular reserve (CVR) reflects the compensatory dilatory capacity of cerebral vasculature to a dilatory stimulus. Blood oxygen-level dependent (BOLD) fMRI has been proven to be an effective imaging technique to obtain CVR maps when subjects perform CO(2) inhalation or a breath-holding (BH) task. Here the authors propose a novel way to process the fMRI data obtained during a blocked BH task by using simultaneously collected near-infrared spectroscopy (NIRS) data as regressors to estimate the vascular contribution to the BOLD signal. Six healthy subjects underwent a 6min 30s resting state (RS) fMRI scan, followed by a scan of the same duration with a blocked BH task (5 breath holds with 20s durations separated by ~50s of regular breathing). NIRS data were recorded from a probe over the subjects' right prefrontal area. For each scan, the time course of changes in total hemoglobin (Δ[tHb]) was calculated from the NIRS data, time shifted by various amounts, and resampled to the fMRI acquisition rate. Each shifted time course was used as regressor in a general linear model analysis. The maximum parameter estimate across all time shifts was calculated at all voxels in both the BH and RS scans, and then converted into signal percentage changes. The ratio of these signal changes generates a CVR map of the BH response, normalized to the resting state. The NIRS regressor method makes no assumptions about the shape (or presence) of the BH response, and allows direct, quantitative comparison of the vascular BOLD response to BH to the baseline map obtained in the resting state. Tong Y, Bergethon PR, Frederick BD. An improved method for mapping cerebrovascular reserve using concurrent fMRI and near-infrared spectroscopy with Regressor Interpolation at Progressive Time Delays (RIPTiDe). Neuroimage 2011 Jun; 56(4): 2047-2057.

Cocaine-Related Attentional Bias Following Trauma Cue Exposure among Cocaine Dependent in-Patients with and without Post-Traumatic Stress Disorder Although the co-occurrence of post-traumatic stress disorder (PTSD) and cocaine dependence is associated with a wide range of negative clinical outcomes, little is known about the mechanisms that underlie this association. This study investigated one potential mechanism-attentional bias to cocaine imagery following trauma cue exposure. Male and female cocaine-dependent in-patients with and without PTSD were exposed to both a neutral and personalized trauma script on separate days, followed by a visual dot-probe task. A 2 (PTSD versus non-PTSD) × 2 (neutral versus trauma script) × 2 (male versus female) design was used to examine hypotheses. Participants were recruited from a residential substance use disorder (SUD) treatment center. Participants were 60 trauma-exposed cocaine dependent in-patients, 30 with current PTSD and 30 without a history of PTSD. Attentional bias was assessed using a visual dot-probe task depicting cocaine-related imagery

following both a neutral script and personalized trauma script. Following neutral script exposure, PTSD (versus non-PTSD) participants exhibited an attentional bias away from cocaine imagery. This effect was reversed following trauma script exposure, with PTSD participants exhibiting a greater attentional bias towards the location of cocaine imagery than non-PTSD participants. Severity of subjective distress following trauma script exposure predicted level of attentional bias among PTSD participants. Cocaine appears to serve an emotion-regulating function among post-traumatic stress disorder patients and may be a potential target for brief post-traumatic stress disorder-substance use disorder interventions that can facilitate residential substance use disorder treatment retention. Tull MT, McDermott MJ, Gratz KL, Coffey SF, Lejuez CW. Cocaine-related attentional bias following trauma cue exposure among cocaine dependent in-patients with and without post-traumatic stress disorder. Addiction 2011 Oct; 106(10): 1810-1818.

Amping up Effort: Effects of D-Amphetamine on Human Effort-Based Decision-Making Animal studies suggest the neurotransmitter dopamine (DA) plays an important role in decision-making. In rats, DA depletion decreases tolerance for effort and probability costs, while drugs enhancing DA increase tolerance for these costs. However, data regarding the effect of DA manipulations on effort and probability costs in humans remain scarce. The current study examined acute effects of d-amphetamine, an indirect DA agonist, on willingness of healthy human volunteers to exert effort for monetary rewards at varying levels of reward value and reward probability. Based on preclinical research, the authors predicted amphetamine would increase exertion of effort, particularly when reward probability was low. Over three sessions, 17 healthy normal adults received placebo, d-amphetamine 10 mg, and 20 mg under counterbalanced double-blind conditions and completed the Effort Expenditure for Rewards Task. Consistent with predictions, amphetamine enhanced willingness to exert effort, particularly when reward probability was lower. Amphetamine did not alter effects of reward magnitude on willingness to exert effort. Amphetamine sped task performance, but its psychomotor effects were not strongly related to its effects on decision-making. This is the first demonstration in humans that dopaminergic manipulations alter willingness to exert effort for rewards. These findings help elucidate neurochemical substrates of choice, with implications for neuropsychiatric diseases characterized by dopaminergic dysfunction and motivational deficits. Wardle MC, Treadway MT, Mayo LM, Zald DH, de Wit H. Amping up effort: effects of d-amphetamine on human effort-based decision-making. J. Neurosci. 2011 Nov; 31(46): 16597-16602.

Effects of Nicotine on Attention and Inhibitory Control in Healthy Nonsmokers Nicotine improves cognitive functioning in smokers and psychiatric populations, but its cognitive-enhancing effects in healthy nonsmokers are less well understood. Nicotine appears to enhance certain forms of cognition in nonsmokers, but its specificity to subtypes of cognition is not known. This study sought to replicate and extend previous findings on the effects of nicotine on cognitive performance in healthy nonsmokers. Healthy young adults (N = 40, 50% women) participated in a placebo-controlled, double-blind, repeated measures experiment examining the effects of 7 mg transdermal nicotine or placebo. Participants completed tests of attention (Attention Network Test), behavioral inhibition (stop signal task, Stroop test), reward responsiveness (signal detection task), and risk-taking behavior (Balloon Analogue Risk Task). Physiological (heart rate, blood pressure) and subjective (Profile of Mood States, Drug Effects Questionnaire) measures were also obtained. Nicotine significantly improved performance only on the Stroop test, but it impaired performance on one aspect of the Attention Network Test, the

orienting effect. Nicotine produced its expected effects on physiologic and subjective measures within the intended time course. The findings of this study contribute to a growing literature indicating that nicotine differentially affects specific subtypes of cognitive performance in healthy nonsmokers. Wignall ND, de Wit H. Effects of nicotine on attention and inhibitory control in healthy nonsmokers. Exp Clin Psychopharmacol 2011 Jun; 19(3): 183-191.

Neural Substrates of Time Perception and Impulsivity Several studies provide empirical evidence for the association between impulsivity and time perception. However, little is known about the neural substrates underlying this function. This investigation examined the influence of impulsivity on neural activation patterns during the encoding and reproduction of intervals with durations of 3, 9 and 18s using event-related functional magnetic resonance imaging (fMRI). Twenty-seven subjects participated in this study, including 15 high impulsive subjects that were classified based on their self-rating. FMRI activation during the duration reproduction task was correlated with measures of two self-report questionnaires related to the concept of impulsivity (Barratt Impulsiveness Scale, BIS; Zimbardo Time Perspective Inventory, ZTPI). Behaviorally, those individuals who under-reproduced temporal intervals also showed lower scores on the ZTPI future perspective subscale and higher scores on the BIS. FMRI activation revealed an accumulating pattern of neural activity peaking at the end of the 9- and 18-s intervals within right posterior insula. Activations of brain regions during the reproduction phase of the timing task, such as those related to motor execution as well as to the "core control network" - encompassing the inferior frontal and medial frontal cortices, the anterior insula as well as the inferior parietal cortex - were significantly correlated with reproduced duration, as well as with BIS and ZTPI subscales. In particular, the greater activation in these regions the shorter were the reproduced intervals, the more impulsive was an individual and the less pronounced the future perspective. Activation in the core control network, thus, may form a biological marker for cognitive time management and for impulsiveness. Wittmann M, Simmons AN, Flagan T, Lane SD, Wackermann J, Paulus MP. Neural substrates of time perception and impulsivity. Brain Res. 2011 Aug; 1406: 43-58.

BEHAVIORAL & INTEGRATIVE TREATMENT RESEARCH

Personality Disorders and Cigarette Smoking among Adults in the United States There is a paucity of empirical information pertaining to the association between personality disorders and cigarette smoking. The present study examined whether, and to what degree, personality disorders are associated with cigarette smoking; investigated the specificity of any observed smoking-personality disorder association; and the role of mood/anxiety disorders, substance use, and nicotine dependence in those relations. Data were drawn from the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC), a nationally representative sample of 43,083 adults in the United States. Results indicated a substantial percentage of those with personality disorders are nicotine dependent. Interestingly, the association between dependent, avoidant, histrionic, schizoid and paranoid personality disorders as well as former dependent smoking was partially explained by co-occurring mood/anxiety disorders, and adjusting for such clinical conditions appeared to generally attenuate the strength of many other associations. Finally, the association between personality disorders and smoking appears to differ by specific personality disorder, with some of the strongest relations being evident for antisocial personality disorder. These novel empirical findings are discussed in relation to the relevance of cigarette smoking among those with personality disorders. Zvolensky MJ, Jenkins EF, Johnson KA, Goodwin RD. Personality disorders and cigarette smoking among adults in the United States. J Psychiatr Res. 2011 Jun; 45(6): 835-841.

A Randomized Trial of a Multicomponent Cessation Strategy for Emergency Department Smokers The objective of this study was to determine the efficacy of an emergency department (ED)-based smoking cessation intervention. This study was a randomized trial conducted from January 2006 to September 2007 at an urban ED that treats 90,000 adults per year. Discharged adults who smoked at least 10 cigarettes per day were randomized to 1) usual care, receiving a smoking cessation brochure; or 2) enhanced care, receiving the brochure, a motivational interview (MI), nicotine patches, and a phone call at 3 days. Interventions were performed by a peer educator trained in tobacco treatment. Blinded follow-up was performed at 3 months. A total of 338 subjects were enrolled, mean (±SD) age was 40.2 (±12.0) years, 51.8% were female, and 56.5% were either self-pay or Medicaid. Demographic and clinical variables were comparable between groups. Enhanced and usual care arms showed similar cessation rates at 3 months (14.7% vs. 13.2%, respectively). The proportion of subjects making a quit attempt (69.2% vs. 66.5%) and decrease in daily cigarette use (five vs. one; all $p > 0.05$) were also similar. In logistic modeling, factors associated with quitting included any tobacco-related International Classification of Diseases, ninth revision (ICD-9), code for the ED visit (odds ratio [OR]= 3.42, 95% confidence interval [CI] = 1.61 to 7.26) or subject belief that the ED visit was tobacco-related (OR = 2.47, 95% CI = 1.17 to 5.21). Conversely, subjects who reported having a preexisting tobacco-related illness were less likely to quit (OR = 0.22, 95% CI = 0.10 to 0.50). The primary endpoint was negative, reflecting a higher-than-expected quit rate in the control group. Subjects whose ED visit was tobacco-related, based either on physician diagnosis or subject perception, were more than twice as likely to quit. These data suggest that even low-intensity screening and referral may prompt substantial numbers of ED smokers to quit or attempt to quit. Bernstein SL, Bijur P, Cooperman N, Jearld S, Arnsten JH, Moadel A, Gallagher EJ. A randomized trial of a multicomponent cessation strategy for emergency department smokers. Acad Emerg Med. 2011 Jun; 18(6): 575-583.

A Pilot Examination of Stress-related Changes in Impulsivity and Risk Taking as Related to Smoking Status and Cessation Outcome in Adolescents Psychosocial stress and impulsivity are each associated with smoking in adolescents. There is also evidence that stress can increase impulsive responding, and impulsive adolescent smokers attempting cessation are at greater risk of relapse. The authors performed a pilot investigation to examine stress-induced changes in response inhibition, inattention, and risk taking as related to smoking status and posttreatment smoking abstinence. Twelve adolescent smokers participating in a smoking cessation intervention and 15 adolescent nonsmokers completed a 2-session protocol assessing stress-related change in response inhibition and inattention (on the Conners' Continuous Performance Test-II), risk taking (on the Balloon Analogue Risk Task), nicotine withdrawal symptoms, and self-reported stress. The investigators found that at baseline, smokers had greater inattentive responding and risk taking when compared with nonsmokers. Stress exposure led to significant increases in stress, anger, and depression in all participants and also increased nicotine craving (on the Minnesota Nicotine Withdrawal Scale item) and impulsive responding in smokers. After covarying for baseline differences in impulsivity/risk taking, smokers who were not abstinent at the end of treatment experienced greater stress-induced risk taking when compared with those who were abstinent. In all, it appears that response inhibition and risk taking may be differentially altered by stress exposure in adolescent smokers and nonsmokers and that adolescent smoking cessation success may be associated with less risk taking in the face of stress. Schepis TS, McFetridge A, Chaplin TM, Sinha R, Krishnan-Sarin S. A pilot examination of stress-related changes in impulsivity and risk taking as related to smoking status and cessation outcome in adolescents. Nicotine Tob Res. 2011 Jul; 13(7): 611-615.

The Effect of Removing Cost as a Barrier to Treatment Initiation with Outpatient Tobacco Dependence Clinics among Emergency Department Patients The campaign against tobacco addiction and smoking continues to play an important role in public health. However, referrals to outpatient tobacco cessation programs by emergency physicians are rarely pursued by patients following discharge. This study explored cost as a barrier to follow-up. The study was performed at a large urban hospital emergency department (ED) in Camden, New Jersey. Enrollment included adults who reported tobacco use in the past 30 days. Study participants were informed about a "Stop Smoking Clinic" affiliated with the hospital and, depending on enrollment date, cost of treatment was advertised as $150 (standard fee), $20 (reduced fee), or $0 (no fee). Monitoring of patient inquiries and visits to the clinic was performed for 6 months following enrollment of the last study subject. The analyzed sample consisted of 577 tobacco users. There were no statistically significant demographic differences between treatment groups ($p > 0.05$). Two-hundred forty-seven (43%) participants reported "very much" interest in smoking cessation. However, there was no significant difference in initiating treatment with the Stop Smoking Clinic across experimental condition. Only a single subject, enrolled in the no-fee phase, initiated treatment with the clinic. Cost is unlikely to be the only barrier to pursing outpatient tobacco treatment after an ED visit. Further research is needed to determine the critical components of counseling and referral that maximize postdischarge treatment initiation. Ozhathil DK, Abar B, Baumann BM, Camargo CA Jr, Ziedonis D, Boudreaux ED. The effect of removing cost as a barrier to treatment initiation with outpatient tobacco dependence clinics among emergency department patients. Acad Emerg Med. 2011 Jun; 18(6): 662-664.

A Comprehensive Model for Mental Health Tobacco Recovery in New Jersey Despite the high prevalence of tobacco use, disproportionate tobacco consumption, and excess morbidity and mortality, smokers with mental illness have reduced access to tobacco dependence treatment across the health care spectrum. The authors have developed a comprehensive model for Mental Health Tobacco Recovery in New Jersey (MHTR-NJ) that has the overarching goal of improving tobacco cessation for smokers with serious mental illness. Important steps involve engaging patients, professionals and the community to increase understanding that addressing tobacco use is important. In addition to increasing demand for tobacco treatment services, mental health professionals must be educated in evidence-based treatments so that patients can seek help in their usual behavioral health care setting. Peer services that offer hope and support to smokers are essential. Each of the policy or cessation initiatives described address the two core goals of this model: to increase demand for tobacco cessation services for mentally ill smokers and to help more smokers with mental illness to quit. Each has been pilot tested for feasibility and/or effectiveness and revised with feedback from stakeholders. In this way this implementation model has brought together academics, clinicians, administrators and mental health consumers to develop tobacco programming and policy that has been tested in a real world environment and serves as a model for other states. Williams JM, Zimmermann MH, Steinberg ML, Gandhi KK, Delnevo C, Steinberg MB, Foulds J. A comprehensive model for mental health tobacco recovery in New Jersey. Adm Policy Ment Health. 2011 Sep; 38(5): 368-383.

Effects of Contingency Management and Bupropion on Cigarette Smoking in Smokers with Schizophrenia Individuals with schizophrenia have high smoking-related morbidity and mortality rates and need powerful and innovative smoking cessation interventions. This proof-of-concept study investigated the feasibility and initial efficacy of combining a contingency management intervention with bupropion to reduce smoking in people with schizophrenia. Using a double-blind, placebo-controlled, between-groups design, 57 non-treatment-seeking participants were randomized to receive 300 mg/day bupropion or placebo. One week later, participants were randomized to a contingency management (CM) intervention in which reductions in urinary cotinine levels were reinforced, or a non-contingent reinforcement (NR) condition in which session attendance was reinforced, regardless of cotinine level. Over the 22-day study period, participants visited the laboratory approximately three times per week to provide urine samples for analysis of cotinine levels, to give breath samples for analysis of carbon monoxide (CO) levels, and to report number of cigarettes smoked per day, nicotine withdrawal symptoms, cigarette craving, and psychiatric symptoms. Cotinine and CO levels significantly decreased during the study period in participants randomized to the CM condition, but not the NR condition. Bupropion did not reduce cotinine levels or increase the efficacy of CM. Cigarette craving and psychiatric symptom levels significantly decreased during the study in all groups. The results of this study indicate the efficacy and feasibility of this CM intervention for reducing smoking in individuals with schizophrenia. Tidey JW, Rohsenow DJ, Kaplan GB, Swift RM, Reid N. Effects of contingency management and bupropion on cigarette smoking in smokers with schizophrenia. Psychopharmacology (Berl). 2011 Sep; 217(2): 279-287.

Relationship between Weight Status and Delay Discounting in a Sample of Adolescent Cigarette Smokers Obesity and cigarette smoking are often cited separately as the top two preventable causes of death in the United States; however, little research has explored the factors associated with being both obese and a smoker. Delay discounting is a behavioral characteristic that may underlie both of these conditions/behaviors. Delay discounting describes the extent to

which an individual discounts the value of an outcome because of a delay in its occurrence. Higher rates of discounting are often considered as an index of impulsivity and have been linked with obesity and cigarette smoking. No research to date has explored delay discounting in a sample of obese smokers. For this study, adolescent smokers classified as obese (body mass index >95th percentile) and healthy weight (body mass index between the 5th and 85th percentiles) were compared on a laboratory assessment of delay discounting. Obese smokers discounted significantly more by delay than healthy weight smokers. This difference remained statistically significant even after controlling for demographic variables that differed across groups. These findings suggest that the relationships between delay discounting and obesity and cigarette smoking may be additive, such that extreme discounting might proportionally increase the risk of becoming an obese smoker. However, future prospective study is needed to fully determine the veracity of this hypothesis. Fields SA, Sabet M, Peal A, Reynolds B. Relationship between weight status and delay discounting in a sample of adolescent cigarette smokers. Behav Pharmacol. 2011 Jun; 22(3): 266-268.

Attrition and Adherence Rates of Sustained vs. Intermittent Exercise Interventions No conclusions have been drawn regarding the relative attrition and adherence rates associated with sustained vs. intermittent exercise programs. The study aims to systematically examine randomized controlled exercise intervention trials that report attrition and/or adherence rates to sustained vs. intermittent aerobic exercise programs. A comprehensive literature search was conducted, and references from qualifying articles were searched for additional papers. Fourteen articles met inclusion criteria, capturing 783 (76% female) enrolled and 599 (74% female) retained participants (mean age = 42.3 ± 6.6 years). Study durations ranged from 8 weeks to 18 months (mean duration = 22.7 ± 21.9 weeks). Although results varied, no consistent differences in attrition or adherence rates between sustained and intermittent exercise protocols were revealed. Linke SE, Gallo LC, Norman GJ. Attrition and adherence rates of sustained vs. intermittent exercise interventions. Ann Behav Med. 2011 Oct; 42(2): 197-209.

Nicotine Therapy Sampling to Induce Quit Attempts among Smokers Unmotivated to Quit: A Randomized Clinical Trial Rates of smoking cessation have not changed in a decade, accentuating the need for novel approaches to prompt quit attempts. Within a nationwide randomized clinical trial (N = 849) to induce further quit attempts and cessation, smokers currently unmotivated to quit were randomized to a practice quit attempt (PQA) alone or to nicotine replacement therapy (hereafter referred to as nicotine therapy), sampling within the context of a PQA. Following a 6-week intervention period, participants were followed up for 6 months to assess outcomes. The PQA intervention was designed to increase motivation, confidence, and coping skills. The combination of a PQA plus nicotine therapy sampling added samples of nicotine lozenges to enhance attitudes toward pharmacotherapy and to promote the use of additional cessation resources. Primary outcomes included the incidence of any ever occurring self-defined quit attempt and 24-hour quit attempt. Secondary measures included 7-day point prevalence abstinence at any time during the study (i.e., floating abstinence) and at the final follow-up assessment. Compared with PQA intervention, nicotine therapy sampling was associated with a significantly higher incidence of any quit attempt (49% vs 40%; relative risk [RR], 1.2; 95% CI, 1.1-1.4) and any 24-hour quit attempt (43% vs 34%; 1.3; 1.1-1.5). Nicotine therapy sampling was marginally more likely to promote floating abstinence (19% vs 15%; RR, 1.3; 95% CI, 1.0-1.7); 6-month point prevalence abstinence rates were no different between groups (16% vs 14%; 1.2; 0.9-1.6). Nicotine therapy sampling during a PQA represents a novel strategy to motivate smokers to make a quit attempt. Carpenter MJ, Hughes JR, Gray KM,

Wahlquist AE, Saladin ME, Alberg AJ. Nicotine therapy sampling to induce quit attempts among smokers unmotivated to quit: A randomized clinical trial. Arch Intern Med. 2011 Nov 28; 171(21): 1901-1907.

Exercise Preferences of Patients in Substance Abuse Treatment While emerging studies have demonstrated the benefit of exercise in early recovery from substance use disorders, recruitment and adherence to exercise interventions have been challenging. Tailoring interventions based on patient exercise preferences may address these concerns. Ninety-seven (N=97; age=41.6 years; 44% female) patients were recruited from an intensive substance abuse outpatient program and filled out questionnaires about their exercise preferences. Most (71%) patients were not currently engaged in an exercise program (i.e., exercising less than 20 minutes/day for 3 days/week over the last 6 months). The vast majority (95%) expressed an interest in engaging in an exercise program specifically designed for persons in substance use recovery and 89% reported wanting to initiate an exercise program within the first 3 months of sobriety. Specific exercise preferences regarding type of physical activity, exercise intervention components, and perceived benefits and barriers to exercise differed between males and females. These findings suggest low rates of regular exercise, high level of interest in engaging in exercise during early recovery, and point toward the need to tailor interventions to the unique preferences of individuals. Abrantes AM, Battle CL, Strong DR, Ing E, Dubreuil ME, Gordon A, Brown RA. Exercise preferences of patients in substance abuse treatment. Ment Health Phys Act. 2011 Dec; 4(2): 79-87.

Teen Marijuana Check-up: Engaging and Reducing Adolescent Cannabis Use through Motivational Enhancement Therapy Cannabis use adversely affects adolescents and interventions that are attractive to adolescents are needed. This trial compared the effects of a brief motivational intervention for cannabis use with a brief educational feedback control and a no-assessment control. Participants were randomized into one of three treatment conditions: Motivational Enhancement Therapy (MET), Educational Feedback Control (EFC), or Delayed Feedback Control (DFC). Those who were assigned to MET and EFC were administered a computerized baseline assessment immediately following randomization and completed assessments at the 3- and 12-month follow-up periods. Participants in the DFC condition were not assessed until the 3-month follow-up. Following the completion of treatment sessions, all participants were offered up to four optional individual treatment sessions aimed at cessation of cannabis use. The research was conducted in high schools in Seattle, Washington. The participants included 310 self-referred adolescents who smoked cannabis regularly. The main outcome measures included days of cannabis use, associated negative consequences, and engagement in additional treatment. At the 3-month follow-up, participants in both the MET and EFC conditions reported significantly fewer days of cannabis use and negative consequences compared to those in the DFC. The frequency of cannabis use was less in MET relative to EFC at 3 months, but it did not translate to differences in negative consequences. Reductions in use and problems were sustained at 12 months, but there were no differences between MET and EFC interventions. Engagement in additional treatment was minimal and did not differ by condition. Brief interventions can attract adolescent cannabis users and have positive impacts on them, but the mechanisms of the effects are yet to be identified. Walker DD, Stephens R, Roffman R, Demarce J, Lozano B, Towe S, Berg B. Randomized controlled trial of motivational enhancement therapy with nontreatment-seeking adolescent cannabis users: A further test of the teen marijuana check-up. Psychol Addict Behav. 2011 Sep; 25(3): 474-484.

Motives for Using Cannabis Linked to Dependence Symptoms The present investigation examined the relationships between motives for cannabis use and negative consequences associated with cannabis use following a brief intervention. The sample consisted of 205 adolescent cannabis users (66.3% male), who were recruited in high schools and randomly assigned to a brief two-session motivational enhancement therapy (MET) or an educational feedback control (EFC). Results supported the hypothesis that using cannabis to cope with negative affect would predict the number of problems and dependence symptoms related to cannabis use, after controlling for age, gender, years and frequency of cannabis use, and internalizing and externalizing behavior problems. Significant interactions between internalizing behavior problems and the coping motive showed that using to cope was associated with a higher number of cannabis dependence symptoms among adolescents reporting lower levels of internalizing behavior problems. Findings support the potential utility of conducting further research to explore the coping motive as an important indicator of problematic cannabis use. Fox CL, Towe SL, Stephens RS, Walker DD, Roffman RA. Motives for cannabis use in high-risk adolescent users. Psychol Addict Behav. 2011 Sep; 25(3): 492-500.

HIV Prevention Improves HIV Testing and Substance Use During Sex Among Juvenile Drug Court Offenders Juvenile drug court (JDC) offenders have benefited from evidence-based interventions addressing antisocial behavior, mental health, and substance use; however, interventions addressing HIV risk behavior are lacking. This study presents pilot findings and lessons learned from a group-based HIV prevention intervention delivered to JDC offenders. Participants were randomized to a five-session HIV prevention (n = 29) or health promotion (n = 28) condition and completed measures of sexual risk taking and substance use at baseline and 3 months postintervention. No between-group differences by time emerged on measures of sexual risk taking or other HIV-related behaviors and attitudes. Both groups improved their rates of HIV testing and decreased their substance use during sex over time. Delivering an HIV prevention intervention to drug court offenders is feasible; however, more intensive interventions that incorporate multiple systems and address co-occurring mental health difficulties may be needed to effect sexual behavioral change among these high-risk court-involved youth. Tolou-Shams M, Houck C, Conrad SM, Tarantino N, Stein LA, Brown LK. HIV prevention for juvenile drug court offenders: A randomized controlled trial focusing on affect management. J Correct Health Care. 2011 Jul; 17(3): 226-232.

Osmotic-Release Methylphenidate Versus Placebo for Improving ADHD/SUDs in Adolescents Receiving CBT This study evaluated the efficacy and safety of osmotic-release methylphenidate (OROS-MPH) compared with placebo for attention-deficit/hyperactivity disorder (ADHD), and the impact on substance treatment outcomes in adolescents concurrently receiving cognitive-behavioral therapy (CBT) for substance use disorders (SUD). This was a 16-week, randomized, controlled, multi-site trial of OROS-MPH + CBT versus placebo + CBT in 303 adolescents (aged 13 through 18 years) meeting DSM-IV diagnostic criteria for ADHD and SUD. Primary outcome measures included the following: for ADHD, clinician-administered ADHD Rating Scale (ADHD-RS), adolescent informant; for substance use, adolescent-reported days of use in the past 28 days. Secondary outcome measures included parent ADHD-RS and weekly urine drug screens (UDS). There were no group differences on reduction in ADHD-RS scores (OROS-MPH: -19.2, 95% confidence interval [CI], -17.1 to -21.2; placebo, -21.2, 95% CI, -19.1 to -23.2) or reduction in days of substance use (OROS-MPH: -5.7 days, 95% CI, 4.0-7.4; placebo: -5.2 days, 95% CI, 3.5-7.0). Some secondary outcomes favored OROS-MPH, including lower parent ADHD-RS scores at 8 (mean difference = 4.4, 95% CI, 0.8-7.9) and 16

weeks (mean difference =6.9; 95% CI, 2.9-10.9) and more negative UDS in OROS-MPH (mean = 3.8) compared with placebo (mean = 2.8; p = .04). OROS-MPH did not show greater efficacy than placebo for ADHD or on reduction in substance use in adolescents concurrently receiving individual CBT for co-occurring SUD. However, OROS-MPH was relatively well tolerated and was associated with modestly greater clinical improvement on some secondary ADHD and substance outcome measures. Riggs PD, Winhusen T, Davies RD, Leimberger JD, Mikulich-Gilbertson S, Klein C, Macdonald M, Lohman M, Bailey GL, Haynes L, Jaffee WB, Haminton N, Hodgkins C, Whitmore E, Trello-Rishel K, Tamm L, Acosta MC, Royer-Malvestuto C, Subramaniam G, Fishman M, Holmes BW, Kaye ME, Vargo MA, Woody GE, Nunes EV, Liu D. Randomized controlled trial of osmotic-release methylphenidate with cognitive-behavioral therapy in adolescents with attention-deficit/hyperactivity disorder and substance use disorders. J Am Acad Child Adolesc Psychiatry. 2011 Sep; 50(9): 903-914.

Acceptance of Drug Testing by Adolescents in Outpatient Substance Abuse Treatment Laboratory drug testing programs may be effective in reducing substance use by adolescents, but developmentally appropriate programs have not been described, and it is unknown if adolescents would be willing to participate in drug testing. This study describes a drug testing protocol for adolescents and report on acceptance rate by patients participating in an outpatient adolescent substance abuse program. Eligible adolescents participating in an outpatient substance abuse treatment program were offered a random laboratory drug testing program that is described in detail in this manuscript. The authors recorded whether they accepted and, if not, the reason for refusal. Of the first 114 eligible patients, 67 (59%) agreed to participate in a drug testing program (PDT). A majority of adolescents participating in an outpatient drug treatment program agreed to participate in a drug testing program that requires frequent urine specimens and reports results to parents. Future studies should determine how this program affects treatment outcomes and whether this program is feasible in primary care. Levy S, Knight JR, Moore T, Weinstein Z, Sherritt L, Weiss RD. Acceptability of drug testing in an outpatient substance abuse program for adolescents. J Adolesc Health. 2011 Mar; 48(3): 229-233.

Declines in Adolescents Substance Use over Ten-Year Period Greater Among Those Without History of Interpersonal Victimization and PTSD Epidemiological studies have identified recent declines in specific types of adolescent substance use. The current study examined whether these declines varied among youth with and without a history of interpersonal victimization or posttraumatic stress disorder (PTSD). Data for this study come from two distinct samples of youth (12–17 years of age) participating in the 1995 National Survey of Adolescents (N = 3,906) and the 2005 National Survey of Adolescents–Replication (N = 3,423). Results revealed significant declines in adolescents' use of cigarettes and alcohol between 1995 and 2005; use of marijuana and hard drugs remained stable. Of importance, declines in nonexperimental cigarette use were significantly greater among youth without versus with a history of victimization and declines in alcohol use were significantly greater among youth without versus with a history of PTSD. McCart MR, Zajac K, Danielson CK, Strachan M, Ruggiero KJ, Smith DW, Saunders BE, Kilpatrick DG. Interpersonal victimization, posttraumatic stress disorder, and change in adolescent substance use prevalence over a ten-year period. J Clin Child Adolesc Psychol. 2011; 40(1): 136-143.

Cultural Accommodation of Substance Abuse Treatment for Latino Adolescents
Collaboration with community stakeholders is an often suggested step when integrating cultural variables into psychological treatments for members of ethnic minority groups. However, there is a dearth of literature describing how to accomplish this process within the context of substance abuse treatment studies. This article describes a qualitative study conducted through a series of focus groups with stakeholders in the Latino community. Data from focus groups were used by the researchers to guide the integration of cultural variables into an empirically supported substance abuse treatment for Latino adolescents currently being evaluated for efficacy. A model for culturally accommodating empirically supported treatments for ethnic minority participants is also described. Burrow-Sanchez JJ, Martinez CR, Hops H, Wrona M. Cultural accommodation of substance abuse treatment for Latino adolescents. Ethn Subst Abuse. 2011; 10(3): 202-225.

Marijuana Use Expectancies and Refusal Self-Efficacy Mediate Associations Between Impulsivity and Frequency of Use, Related Problems, and Dependence This study tests the acquired preparedness model (APM) to explain associations among trait impulsivity, social learning principles, and marijuana use outcomes in a community sample of female marijuana users. The APM states that individuals with high-risk dispositions are more likely to acquire certain types of learning that, in turn, instigate problematic substance use behaviors. In this study, three domains of psychosocial learning were tested: Positive and negative marijuana use expectancies, and marijuana refusal self-efficacy. Participants were 332 community-recruited women aged 18–24 enrolled in a study of motivational interviewing for marijuana use reduction. The present analysis is based on participant self-reports of their impulsivity, marijuana use expectancies, marijuana refusal self-efficacy, marijuana use frequency, marijuana use-related problems, and marijuana dependence. In this sample, impulsivity was significantly associated with marijuana use frequency, marijuana-related problems, and marijuana dependence. Results also indicate that the effect of impulsivity on all three marijuana outcomes was fully mediated by the three principles of psychosocial learning tested in the model, namely, positive and negative marijuana expectancies, and marijuana refusal self-efficacy. These findings lend support to the APM as it relates to marijuana use. In particular, they extend the applicability of the theory to include marijuana refusal self-efficacy, suggesting that, among high-impulsives, those who lack appropriate strategies to resist the temptation to use marijuana are more likely to exhibit more frequent marijuana use and use-related negative consequences. Hayaki J, Herman DS, Hagerty CE, de Dios MA, Anderson BJ, Stein MD. Expectancies and self-efficacy mediate the effects of impulsivity on marijuana use outcomes: An application of the acquired preparedness model. Addict Behav. 2011 Apr; 36(4): 389-396.

The Impact of Fatherhood on Treatment Response for Men with Co-occurring Alcohol Dependence and Intimate Partner Violence The role of fathers in the lives of children has gained increasing attention over the last several decades, however, studies that specifically examine the parenting role among men who are alcohol dependent and have co-occurring intimate partner violence (IPV) have been limited. This brief report is intended to highlight the need to develop and focus interventions for men with co-occurring substance abuse and IPV with an emphasis on their roles as fathers. Sixty-nine men who participated in a randomized comparison study of a coordinated substance abuse and domestic violence treatment program (SADV) and Twelve Step Facilitation (TSF) provided information about whether they were fathers. Analysis of covariance was used to assess the impact of fatherhood on the outcomes of intimate partner violence and alcohol use during the 12 weeks of treatment. There was a significant interaction between type of treatment (SADV vs. TSF) and fatherhood. SADV

resulted in significantly less IPV and use of alcohol over the 12 weeks of treatment than TSF for men without children. There were no significant differences between SADV and TSF for men who were fathers. Results indicate a need to further explore the role of fatherhood for men with co-occurring substance abuse and IPV and development of specialized treatments that may improve treatment outcomes for fathers. Smith Stover C, McMahon TJ, Easton C. The impact of fatherhood on treatment response for men with co-occurring alcohol dependence and intimate partner violence. Am J Drug Alcohol Abuse. 2011 Jan; 37(1): 74-78.

Propensity to Work Among Chronically Unemployed Adult Drug Users Analyses were conducted to compare rates of employment before, during, and after employment at the therapeutic workplace, which is a novel employment-based treatment for drug misuse. Participants in two clinical trials attended the therapeutic workplace at higher rates than they worked before intake and six months after discharge. These data suggest that unemployed chronic drug misusers will attend work at higher rates at the therapeutic workplace than in the community when paid modest wages, and that the failure of chronic drug misusers to obtain employment in the community may not result from lack of interest in work. Sigurdsson SO, DeFulio A, Long L, Silverman K. Propensity to work among chronically unemployed adult drug users. Subst Use Misuse. 2011; 46(5): 599-607.

Characteristics of Rural Crack and Powder Cocaine Use: Gender and Other Correlates Little is known about the relationship of gender with cocaine use in rural areas. This study describes these relationships among stimulant users residing in rural areas of Arkansas, Kentucky, and Ohio. Understanding the characteristics of crack and powder cocaine users in rural areas may help inform prevention, education, and treatment efforts to address rural stimulant use. Participants were 690 stimulant users, including 274 (38.6%) females, residing in nine rural counties. Cocaine use was measured by self-report of cocaine use, frequency of use, age of first use, and cocaine abuse/dependence. Powder cocaine use was reported by 49% of this sample of stimulant users and 59% reported using crack cocaine. Differing use patterns emerged for female and male cocaine users in this rural sample; females began using alcohol, marijuana, and cocaine at later ages than males, but there were no gender differences in current powder cocaine use. Females reported more frequent use of crack cocaine and more cocaine abuse/ dependence than males, and in regression analyses, female crack cocaine users had 1.8 times greater odds of reporting frequent crack use than male crack users. These findings suggest differing profiles and patterns of cocaine use for male and female users in rural areas, supporting previous findings in urban areas of gender-based vulnerability to negative consequences of cocaine use. Further research on cocaine use in rural areas can provide insights into gender differences that can inform development and refinement of effective interventions in rural communities. Pope SK, Falck RS, Carlson RG, Leukefeld C, Booth BM. Characteristics of rural crack and powder cocaine use: Gender and other correlates. Am J Drug Alcohol Abuse. 2011 Nov; 37(6): 491-496.

Illicit Use of Buprenorphine in a Community Sample of Young Adult Non-Medical Users of Pharmaceutical Opioids There is growing evidence about illicit use of buprenorphine in the U.S. The study aims to: (1) identify prevalence and predictors of illicit buprenorphine use in a community sample of 396 young adult (18-23 years old) non-medical users of pharmaceutical opioids and (2) describe knowledge, attitudes and behaviors linked to illicit buprenorphine use as reported by a qualitative sub-sample (n=51). Participants were recruited using respondent-driven sampling. Qualitative interview participants were selected from the larger sample. The sample

(n=396) was 54% male and 50% white; 7.8% reported lifetime illicit use of buprenorphine. Logistic regression analysis results indicate that white ethnicity, intranasal inhalation of pharmaceutical opioids, symptoms of opioid dependence, and a greater number of pharmaceutical opioids used in lifetime were statistically significant predictors of illicit buprenorphine use. Qualitative interviews revealed that buprenorphine was more commonly used by more experienced users who were introduced to it by their "junkie friends." Those who used buprenorphine to self-medicate withdrawal referred to it as a "miracle pill." When used to get high, reported experiences ranged from "the best high ever" to "puking for days." Participants reported using buprenorphine/naloxone orally or by intranasal inhalation. Injection of buprenorphine without naloxone was also reported. Findings suggest that illicit buprenorphine use is gaining ground primarily among whites and those who are more advanced in their drug use careers. Continued monitoring is needed to better understand evolving patterns and trends of illicit buprenorphine use. Daniulaityte R, Falck R, Carlson RG. Illicit Use of Buprenorphine in a community sample of young adult non-medical users of pharmaceutical opioids. Drug Alcohol Depend. 2011 Oct 28. [Epub ahead of print].

Traumatic Event Re-exposure in Injecting Drug Users Drug users have very high rates of lifetime exposure to traumatic events, leading to significant psychiatric complications. In spite of the high rate of lifetime exposure, very little is known about the rate of ongoing re-exposure to new traumatic events in drug users. The authors investigated the rate of traumatic event re-exposure in male and female injecting drug users using syringe exchange services in Baltimore (N = 197). Participants were assessed monthly for traumatic event re-exposure for 16 months. Averaged over the entire follow-up period, 27% of participants were re-exposed to a traumatic event each month and 72% were re-exposed over the 16-month study period. Women were over twice as likely to report any traumatic event re-exposure as men (adjusted odds ratio [AOR] = 2.48; 95% CI = 1.54-3.99), with the specific events of life-threatening illness, death of a loved one, and injury or illness of a loved one being more common in women than men. Traumatic event re-exposure occurs far more often than previously reported, with women injecting drug users at the highest risk. Reassessment of traumatic events may help to identify people most in need and encourage entry into treatment. Peirce JM, Kolodner K, Brooner RK, Kidorf MS. Traumatic event re-exposure in injecting drug users. J Urban Health. 2011 Oct 12. [Epub ahead of print].

Drug Use in Rural China: A Preliminary Investigation in Hunan Province This study aimed to compare characteristics and illicit drug abuse patterns among drug abusers in rural and urban areas of Hunan Province, China. Data collected by public security bureau on newly registered drug abusers between 2005 and 2008 in 5 urban and 5 rural areas (N = 1639) were extracted anonymously and analyzed. Participants included all newly registered drug users in urban (n = 812) and rural (n = 827) areas of Hunan. The investigators found that drug users from the rural areas were younger (31 (6.6) vs. 34 (8.0) years, $p < 0.001$), with a higher proportion of males (86% vs. 82%, $p < 0.05$), or married (34% vs. 27%, $p < 0.01$). Rural drug users reported an earlier onset of drug use (27 (5.9) vs. 30 (7.9) years old, $p < 0.001$), were more likely to report heroin as their primary drug of abuse (53% vs. 47%, $p < 0.001$), and had a lower prevalence of criminal activities (19% vs. 31%, $p < 0.001$). Rural drug users were less likely to report needle sharing (1.8% vs. 4.3%, $p < 0.01$), less likely to report being HIV+ (0.8% vs. 2.6%, $p < 0.01$), and less likely to report prior drug treatment participation (2.8% vs. 6.8%, $p < 0.001$). The authors conclude that drug abuse is a substantial problem in both urban and rural areas in China. The very low proportion of newly registered drug users reporting any prior drug abuse treatment

points to the importance of expanding substance abuse treatments, especially in rural areas where treatment penetration is even lower than in urban areas. Deng Q, Tang Q, Schottenfeld RS, Hao W, Chawarski MC. Drug use in rural China: A preliminary investigation in Hunan Province. Addiction. 2011 Sep. [Epub ahead of print].

Contingency Management with Community Reinforcement Approach or Twelve-Step Facilitation 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 ($p<.01$), higher proportion of cocaine-negative urine tests ($p<0.01$), and higher proportion of documented abstinence across the 3-, 6-, 9- and 12-month assessments ($p<0.05$), compared to VC. The differences between CRA and TSF were not significant for any of these measures (all p values ≥ 0.75). PDC decreased significantly from baseline during treatment in all four groups ($p<0.001$) but did not differ significantly between CM and VC ($p=0.10$) or between TSF and CRA ($p=0.23$). 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.

Extended Telephone-Based Continuing Care for Alcohol Dependence: 24-month Outcomes and Subgroup Analyses This study examined the extent to which 18 months of telephone continuing care improves 24-month outcomes for patients with alcohol dependence. Subgroup analyses were performed to identify patients who would benefit most from continuing care. In a comparative effectiveness trial of continuing care consisting of monitoring and feedback only (TM) or monitoring and feedback plus counseling (TMC); patients were randomized to treatment as usual (TAU), TAU plus TM or TAU plus TMC, and followed quarterly for 24 months. A total of 252 alcohol-dependent patients (49% with current cocaine dependence) who completed 3 weeks of intensive out-patient programs (IOP) were recruited. In the intent-to-treat sample, group differences in alcohol outcomes to 18 months favored TMC over TAU but were no longer present in months 19-24. There also was a non-significant trend for TMC to perform better than usual care on the good clinical outcome measure (60% vs. 46% good clinical outcome in months 19-24). Overall significant effects favoring TMC and TM over TAU were seen for women; and TMC also was superior to TAU for participants with social support for drinking, low readiness to change and prior alcohol treatments. Most of these effects were obtained on at least two of three outcomes. However, no effects remained significant at 24 months. The benefits of an extended telephone-based continuing care program to treat alcohol dependence did not persist after the end of the intervention. A post-hoc analysis suggested that women and individuals with social support for drinking, low readiness to change or prior alcohol treatments may benefit from the

intervention. McKay JR, Van Horn D, Oslin DW, Ivey M, Drapkin ML, Coviello DM, Yu Q, Lynch KG. Extended telephone-based continuing care for alcohol dependence: 24-month outcomes and subgroup analyses. Addiction. 2011 Oct; 106(10): 1760-1769.

A Randomized Trial of Contingency Management Delivered in the Context of Group Counseling Contingency management (CM) is efficacious in reducing drug use. Typically, reinforcers are provided on an individual basis to patients for submitting drug-negative samples. However, most treatment is provided in a group context, and poor attendance is a substantial concern. This study evaluated whether adding CM to group-based outpatient treatment would increase attendance and drug abstinence relative to standard care. Substance abusing patients (N = 239) initiating outpatient treatment at 2 community-based clinics were randomized to standard care with frequent urine sample monitoring for 12 weeks (SC) or that same treatment with CM delivered in the context of group counseling sessions. In the CM condition, patients earned opportunities to put their names in a hat based on attendance and submission of drug-negative samples. At group counseling sessions, therapists selected names randomly from the hat, and individuals whose names were drawn won prizes ranging from $1 to $100. Patients assigned to CM earned a median of $160 in prizes, and they attended significantly more days of treatment (d = 0.25), remained in treatment for more continuous weeks (d = 0.40), and achieved longer durations of drug abstinence (d = 0.26) than patients randomized to SC. Group adherence and therapeutic alliance also improved with CM. In addition, HIV risk behaviors were significantly lower in CM relative to SC patients during early phases of treatment and at the 12-month follow-up. These data demonstrate that CM delivered in the context of outpatient group counseling can increase attendance and improve drug abstinence. Petry NM, Weinstock J, Alessi SM. A randomized trial of contingency management delivered in the context of group counseling. J Consult Clin Psychol. 2011 Oct; 79(5): 686-696.

Testing an Optimized Community-Based Human Immunodeficiency Virus (HIV) Risk Reduction and Antiretroviral Adherence Intervention for HIV-Infected Injection Drug Users The authors conducted a preliminary study of the 4-session Holistic Health for HIV (3H+), which was adapted from a 12-session evidence-based risk reduction and antiretroviral adherence intervention. Improvements were found in the behavioral skills required to properly adhere to HIV medication regimens. Enhancements were found in all measured aspects of sex-risk reduction outcomes, including HIV knowledge, motivation to reduce sex-risk behavior, behavioral skills related to engaging in reduced sexual risk, and reduced risk behavior. Improvements in drug use outcomes included enhancements in risk reduction skills as well as reduced heroin and cocaine use. Intervention effects also showed durability from post-intervention to the follow-up assessment point. Females responded particularly well in terms of improvements in risk reduction skills and risk behavior. This study suggests that an evidence-based behavioral intervention may be successfully adapted for use in community-based clinical settings where HIV-infected drug users can be more efficiently reached. Copenhaver MM, Lee IC, Margolin A, Bruce RD, Altice FL. Testing an optimized community-based human immunodeficiency virus (HIV) risk reduction and antiretroviral adherence intervention for HIV-infected injection drug users. Subst Abus. 2011 Jan; 32(1): 16-26.

A Mechanism for Reducing Delay Discounting by Altering Temporal Attention Rewards that are not immediately available are discounted compared to rewards that are immediately available. The more a person discounts a delayed reward, the more likely that person is to have a range of behavioral problems, including clinical disorders. This latter observation has motivated the search for interventions that reduce discounting. One surprisingly simple method to reduce discounting is an "explicit-zero" reframing that states default or null outcomes. Reframing a classical discounting choice as "something now but nothing later" versus "nothing now but more later" decreases discount rates. However, it is not clear how this "explicit-zero" framing intervention works. The present studies delineate and test two possible mechanisms to explain the phenomenon. One mechanism proposes that the explicit-zero framing creates the impression of an improving sequence, thereby enhancing the present value of the delayed reward. A second possible mechanism posits an increase in attention allocation to temporally distant reward representations. In four experiments, the authors distinguish between these two hypothesized mechanisms and conclude that the temporal attention hypothesis is superior for explaining our results. The authors propose a model of temporal attention whereby framing affects intertemporal preferences by modifying present bias. Radu PT, Yi R, Bickel WK, Gross JJ, McClure SM. A mechanism for reducing delay discounting by altering temporal attention. J Exp Anal Behav. 2011 Nov; 96(3): 363-385.

RESEARCH ON PHARMACOTHERAPIES FOR DRUG ABUSE

Mirtazapine to Reduce Methamphetamine Use: a Randomized Controlled Trial
Context No approved pharmacologic treatments for methamphetamine dependence exist. Methamphetamine use is associated with high morbidity and is a major cofactor in the human immunodeficiency virus epidemic among men who have sex with men (MSM). The objective of the study is to determine whether mirtazapine would reduce methamphetamine use among MSM who are actively using methamphetamine. A Double-blind, randomized, controlled, 12-week trial of mirtazapine vs placebo conducted from September 5, 2007, to March 4, 2010, San Francisco Department of Public Health. Participants were actively using, methamphetamine-dependent, sexually active MSM seen weekly for urine sample collection and substance use counseling and were randomly assigned to daily oral mirtazapine (30 mg) or placebo; both arms included 30-minute weekly substance use counseling. The primary study outcome was reduction in methamphetamine-positive urine test results. Secondary outcomes were study medication adherence (by self-report and medication event monitoring systems) and sexual risk behavior. Sixty MSM were randomized, 85% of follow-up visits were completed, and 56 participants (93%) completed the final visit. In the primary intent-to-treat analysis, participants assigned to the mirtazapine group had fewer methamphetamine-positive urine test results compared with participants assigned to the placebo group (relative risk, 0.57; 95% CI, 0.35-0.93, $P = .02$). Urine positivity decreased from 67% (20 of 30 participants) to 63% (17 of 27) in the placebo arm and from 73% (22 of 30) to 44% (12 of 27) in the mirtazapine arm. The number needed to treat to achieve a negative weekly urine test result was 3.1. Adherence was 48.5% by medication event monitoring systems and 74.7% by self-report; adherence measures were not significantly different between arms (medication event monitoring systems, $P = .82$; self-report, $P = .92$). Most sexual risk behaviors decreased significantly more among participants taking mirtazapine compared with those taking placebo (number of male partners with whom methamphetamine was used, $P = .009$; number of male partners, $P = .04$; episodes of anal sex with serodiscordant partners, $P = .003$; episodes of unprotected anal sex with serodiscordant partners, $P = .003$; episodes of insertive anal sex with serodiscordant partners, $P = .001$). There were no serious adverse events related to study drug or significant differences in adverse events by arm ($P \geq .99$). The addition of mirtazapine to substance use counseling decreased methamphetamine use among active users and was associated with decreases in sexual risk despite low to moderate medication adherence. Colfax GN, Santos GM, Das M, Santos DM, Matheson T, Gasper J, Shoptaw S, Vittinghoff E. Mirtazapine to reduce methamphetamine use: a randomized controlled trial. Arch Gen Psychiatry. 2011 Nov; 68(11): 1168-1175.

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. This was a randomized, double-blind, placebo-controlled, cross-over study conducted in an outpatient research unit at the New York State Psychiatric Institute. The 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). Amphetamines 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). No significant

differences between the drugs were found on the majority of measures. Under the $5 condition, both amphetamines dose-dependently increased self-administration, 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. 2011 Nov 2. [Epub ahead of print]

Results of an Initial Clinical Trial of Varenicline for the Treatment of Cocaine Dependence Cocaine use, abuse and dependence remains a pressing public health problem. Based on its mechanism of action, varenicline, an alpha4beta2 partial agonist seemed to be a likely candidate for treating cocaine dependence. Cocaine dependent participants (n=37) were enrolled in a 9-week double-blind placebo controlled clinical trial. Varenicline was titrated up to a target dose of 1mg BID during the first week of medication. Varenicline was associated with lower odds of cocaine use than placebo (OR=2.02, p=0.08), as measured by thrice-weekly urinalysis results. Compared to placebo-treated participants, varenicline treated participants had significantly decreased rates of cocaine reward, as measured by the Multiple Choice Procedure (MCP) (p=0.02). Varenicline appears to decrease cocaine use and reward, suggesting that further investigation of varenicline may be warranted. Plebani JG, Lynch KG, Yu Q, Pettinati HM, O'Brien CP, Kampman KM. Results of an intial clinical trial of varenicline for the treatment of cocaine dependence. Drug Alcohol Depend. 2011 Sep 16. [Epub ahead of print]

Further Evidence for Association of Polymorphisms in the CNR1 Gene with Cocaine Addiction: Confirmation in an Independent Sample and Meta-Analysis Genetic research on cocaine dependence (CD) may help to understand the disorder as well as provide insights for effective treatment. As endocannabinoid signaling and dopamine neurotransmission have been shown to be involved in drug reward, genes related to these systems are plausible candidates for susceptibility to CD. The cannabinoid receptor 1 protein regulates both the endocannabinoid and dopaminergic neurobiological systems, and polymorphisms in the cannabinoid receptor gene, CNR1, have been associated previously with substance dependence. This study, attempts to replicate findings associating CNR1 with CD in African Americans. Cocaine-addicted individuals (n=860) and unaffected controls (n=334) of African descent were genotyped for two single nucleotide polymorphisms (SNPs) in CNR1 (rs6454674, rs806368). The authors observed a significant difference in genotype frequencies between cases and controls for both SNPs ($P \leq 0.042$). A meta-analysis was also performed combining this data with that of Zuo et al. who also studied these polymorphisms in African American cocaine addicts (total n=1253 cases versus 543 controls). When these data were combined, rs6454674 increased in significance to P=0.027; however, rs806368 was no longer significant. This study confirms the association between rs6454674 and CD. However, because there is considerable co-morbidity of CD with other drugs of abuse, additional studies are necessary to determine whether polymorphisms in CNR1 induce a general susceptibility to substance dependence or are specific to cocaine addiction. Furthermore, as this population consists of American individuals of African descent, the possibility of population stratification should not be excluded. Clarke TK, Bloch PJ, Ambrose-Lanci LM, Ferraro TN, Berrettini WH, Kampman KM, Dackis CA, Pettinati HM, O'Brien CP, Oslin DW, Lohoff FW. Further evidence for association of polymorphisms in the

CNR1 gene with cocaine addiction: confirmation in an independent sample and meta-analysis. Addict Biol. 2011 July 25 [Epub ahead of print].

Sertraline Delays Relapse in Recently Abstinent Cocaine-Dependent Patients with Depressive Symptoms The authors investigated whether the selective serotonin re-uptake inhibitor sertraline at 200 mg/day delays relapse in recently abstinent cocaine-dependent individuals. The study involved a 12-week, double-blind, placebo-controlled clinical trial with 2-week residential stay followed by 10-week out-patient participation, Veterans Affairs residential unit and out-patient treatment research program. Cocaine-dependent volunteers (n=86) with depressive symptoms (Hamilton score > 15), but otherwise no major psychiatric or medical disorder or contraindication to sertraline. Participants were housed on a drug-free residential unit (weeks 1-2) and randomized to receive sertraline or placebo. Participants then participated on an out-patient basis during weeks 3-12 while continuing to receive study medication. Patients participated in a day substance abuse/day treatment program during weeks 1-3 and underwent weekly cognitive behavioral therapy during weeks 4-12. The primary outcome measure was thrice-weekly urine results and the secondary measure was Hamilton Depression scores. Pre-hoc analyses were performed on those who participated beyond week 2. Generally, no group differences in retention or baseline characteristics occurred. Sertraline patients showed a trend towards longer time before their first cocaine-positive urine ('lapse', $\chi(2)=3.67$, $P=0.056$), went significantly longer before having two consecutive urine samples positive for cocaine ('relapse', $\chi(2)=4.03$, $P=0.04$) and showed significantly more days to lapse (26.1±16.7 versus 13.2±10.5; $Z=2.89$, $P=0.004$) and relapse (21.3±10.8 versus 32.3±14.9; $Z=2.25$, $P=0.02$). Depression scores decreased over time ($F=43.43$, $P<0.0001$), but did not differ between groups ($F=0.09$, $P=0.77$). Sertraline delays time to relapse relative to placebo in cocaine-dependent patients who initially achieve at least 2 weeks of abstinence. Oliveto A, Poling J, Mancino MJ, Williams DK, Thostenson J, Pruzinsky R, Gonsai K, Sofuoglu M, Gonzalez G, Tripathi S, Kosten TR. Sertraline delays relapse in recently abstinent cocaine-dependent patients with depressive symptoms. Addiction. 2012 Jan; 107(1): 131-141.

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. Substance use after participaton in laboratory studies involving smoked cocaine self-administration. Drug Alcohol Depend. 2012 Jan 1; 120(1-3): 162-167.

Improvement in Psychopathology Among Opioid-dependent Adolescents During Behavioral-pharmacological Treatment This study examined changes in behavioral and emotional problems among opioid-dependent adolescents during a 4-week combined behavioral and pharmacological treatment. The authors examined scales of behavioral and emotional problems in youth using the Youth Self-Report measure at the time of substance abuse treatment intake and changes in scale scores during treatment participants were 36 adolescents (aged 13-18 years, eligible) who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for opioid dependence. Participants received a 28-day outpatient, medication-assisted withdrawal with either buprenorphine, or clonidine, as part of a double-blind, double dummy comparison of these medications. All participants received a common behavioral intervention, composed of 3 individual counseling sessions per week, and incentives contingent on opioid-negative urine samples (collected 3 times/week) attendance and completion of weekly assessments. Although a markedly greater number of youth who received buprenorphine remained in treatment relative to those who received clonidine, youth who remained in treatment showed significant reductions during treatment on 2 Youth Self-Report grouping scales (internalizing problems and total problems) and 4 of the empirically based syndrome scales (somatic, social, attention, and thought). On Youth Self-Report competence and adaptive scales, no significant changes were observed. There was no evidence that changes in any scales differed across medication condition. Youth who were retained demonstrated substantive improvements in a number of clinically meaningful behavioral and emotional problems, irrespective of pharma-cotherapy provided to them. Moore SK, Marsch LA, Badger GJ, Solhkhah R, Hofstein Y. Improvement in psychopathology among opioids-dependent adolescents during behavioral-pharmacological treatment. J. Addict Med. 2011 Dec; 5(4): 264-271.

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 aim 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 is the 2005 to 2008 National Survey on Drug Use and Health. The setting was Academic research, and 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 LT, Woody GE, Yang C, Pan JJ, Blazer DG. Racial/ethnic variations in substance-related disorders among adolescents in the United States. Arch Gen Psychiatry. 2011 Nov; (11): 1176-1185.

Compensation Effects on Clinical Trial Data Collection in Opioid-Dependent Young Adults

Attrition in studies of substance use disorder treatment is problematic, potentially introducing bias into data analysis. This study aimed to determine the effect of participant compensation amounts on rates of missing data and observed rates of drug use. The authors performed a secondary analysis of a clinical trial of buprenorphine/naloxone among 152 treatment-seeking opioid-dependent subjects aged 15-21 during participation in a randomized trial. Subjects were randomized to a 2-week detoxification with buprenorphine/naloxone (DETOX; N = 78) or 12 weeks buprenorphine/naloxone (BUP; N = 74). Participants were compensated $5 for weekly urine drug screens and self-reported drug use information and $75 for more extensive assessments at weeks 4, 8, and 12. Though BUP assignment decreased the likelihood of missing data, there were significantly less missing data at 4, 8, and 12 weeks than other weeks, and the effect of compensation on the probability of urine screens being positive was more pronounced in DETOX subjects. These findings suggest that variations in the amount of compensation for completing assessments can differentially affect outcome measurements, depending on treatment group assignment. Adequate financial compensation may minimize bias when treatment condition is associated with differential dropout and may be a cost-effective way to reduce attrition. Moreover, active users may be more likely than non-active users to drop out if compensation is inadequate, especially in control groups or in groups who are not receiving active treatment. Wilcox CE, Bogenschutz MP, Nakazawa M, Woody GE. Compensation Effects on Clinical Trial Data Collection in Opioid-Dependent Young Adults. Am J Drug Alcohol Abuse. 2011 Sep; [Epub ahead of print].

Treatment Use and Barriers Among Adolescents with Prescription Opioid Use Disorders

This study examined national trends, patterns, correlates, and barriers to substance abuse treatment use by adolescents aged 12-17 years who met at least one of the past-year criteria for prescription opioid abuse or dependence (N=1788). Data were from the 2005-2008 National Surveys of Drug Use and Health (NSDUH). Past-year substance use disorders, major depression, and treatment use were assessed by audio computer-assisted self-interviewing. About 17% of adolescents with opioid dependence (n=434) and 16% of those with opioid abuse (n=355) used any substance abuse treatment in the past year compared with 9% of subthreshold users, i.e., adolescents who reported 1-2 prescription opioid dependence criteria but no abuse criteria (n=999). Only 4.2% of adolescents with opioid dependence, 0.5% of those with abuse, and 0.6% of subthreshold users reported a perceived need for treatment of nonmedical opioid use. Self-help groups and outpatient rehabilitation were the most commonly used sources of treatment. Few black adolescents used treatment (medical settings, 3.3%; self-help groups, 1.7%) or reported a need for treatment (1.8%). Talking to parents/guardians about dangers of substance

use increased the odds of treatment use. Barriers to treatment use included "wasn't ready to stop substance use," "didn't want others to find out," and "could handle the problem without treatment."Adolescents with prescription opioid use disorders markedly underutilize treatment. Non-financial barriers are pervasive, including stigma and a lack of perceived treatment need. Wu LT, Blazer DG, Li TK, Woody GE. Treatment use and barriers among adolescents with prescription opioid use disorders. Addict Behav. 2011 Dec; (12): 1233-1239.

Substance Use Disorders and Comorbid Axis I and II Psychiatric Disorders Among Young Psychiatric Patients: Findings From a Large Electronic Health Records Database This study examined the prevalence of substance use disorders (SUDs) among psychiatric patients aged 2-17 years in an electronic health records database (N=11,457) and determined patterns of comorbid diagnoses among patients with a SUD to inform emerging comparative effectiveness research (CER) efforts. DSM-IV diagnoses of all inpatients and outpatients at a large university-based hospital and its associated psychiatric clinics were systematically captured between 2000 and 2010: SUD, anxiety (AD), mood (MD), conduct (CD), attention deficit/hyperactivity (ADHD), personality (PD), adjustment, eating, impulse-control, psychotic, learning, mental retardation, and relational disorders. The prevalence of SUD in the 2-12-year age group (n=6210) was 1.6% and increased to 25% in the 13-17-year age group (n=5247). Cannabis diagnosis was the most prevalent SUD, accounting for more than 80% of all SUD cases. Among patients with a SUD (n=1423), children aged 2-12 years (95%) and females (75-100%) showed high rates of comorbidities; blacks were more likely than whites to be diagnosed with CD, impulse-control, and psychotic diagnoses, while whites had elevated odds of having AD, ADHD, MD, PD, relational, and eating diagnoses. Patients with a SUD used more inpatient treatment than patients without a SUD (43% vs. 21%); children, females, and blacks had elevated odds of inpatient psychiatric treatment. Collectively, results add clinical evidence on treatment needs and diagnostic patterns for understudied diagnoses. Wu LT, Gersing K, Burchett B, Woody GE, Blazer DG. Substance use disorders and comorbid Axis I and II psychiatric disorders among young psychiatric patients: findings from a large electronic health records database. J Psychiatr Res. 2011 Nov; (11): 1453-1462.

Influence of Acute Bupropion Pretreatment on the Effects of Intranasal Cocaine The aim of this experiment was to determine the influence of acute bupropion pretreatment on subject-rated effects and choice of intranasal cocaine versus money. A randomized, within-subject, placebo-controlled, double-blind experiment. The setting was an outpatient research unit. Eight cocaine-using adults participated. Subjects completed 9 experimental sessions in which they were pretreated with 0, 100 or 200 mg oral immediate release bupropion. Ninety min later they sampled an intranasal cocaine dose (4 [placebo], 15 or 45 mg) and made 6 choices between that dose and an alternative reinforcer (US $0.25), available on independent, concurrent progressive ratio schedules. Subjects also completed a battery of subject-rated, performance and physiological measures following the sample doses of cocaine. After 0 mg bupropion, the high dose of cocaine (45 mg) was chosen 5 of 6 times on average compared to 2.25 of 6 choices for placebo cocaine (4 mg) ($p < 0.05$). Active bupropion reduced choice of 45 mg cocaine to 3.13 (100 mg) or 4.00 (200 mg) out of 6 drug choices on average. Bupropion also consistently enhanced positive subject-rated effects of cocaine (e.g. Good Effects; Willing to Take Again) while having no effects of its own. The atypical anti-depressant, bupropion, acutely appears to reduce preference for intranasal cocaine versus a small amount of money but to increase reported positive experiences of the drug. Stoops WW, Lile JA, Glaser PE, Hays LR, Rush CR. Influence

of acute bupropion pretreatment on the effects of intranasal cocaine. Addiction 2011 Dec; [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) 2011 Sep; [Epub ahead of print].

A Novel Recruitment Message to Increase Enrollment into a Smoking Cessation Treatment Program: Preliminary Results from a Randomized Trial Most smokers do not utilize approved interventions for nicotine dependence, reducing the probability of cessation. Smoking cessation programs typically use recruitment messages emphasizing the health threats of smoking. Augmenting this threat message by describing the genetic aspects of nicotine addiction may enhance enrollment into a cessation program. During telephone recruitment, 125 treatment-seeking smokers were randomized to receive by phone either a standard threat message or a threat plus genetic prime message and were offered open-label varenicline and counseling. There was a greater rate of enrollment into the cessation program for the threat plus genetic prime participants (51.7%) versus the threat-only participants (37.7%; $p = .03$). Smokers who self-identified from racial/ethnic minority groups were less likely to enroll in the cessation program ($p = .01$) versus smokers who self-identified as Caucasian. These preliminary data suggest that a simple, affordable, and transportable communication approach enhances enrollment of smokers into a smoking cessation program. A larger clinical trial to evaluate a genetic prime message for improving recruitment into smoking cessation programs is warranted. Schnoll RA, Cappella J, Lerman C, Pinto A, Patterson F, Wileyto EP, Bigman C, Leone F. A novel recruitment message to increase enrollment into a smoking cessation treatment program: preliminary results from a randomized trial. Health Commun. 2011 Dec; (8): 735-742.

Selective Serotonin 5-HT(2C) Receptor Activation Suppresses the Reinforcing Efficacy of Cocaine and Sucrose but Differentially Affects the Incentive-Salience Value of Cocaine- Vs. Sucrose-Associated Cues Serotonin (5-HT) controls affective and motivational aspects of palatable food and drug reward and the 5-HT(2C) receptor (5-HT(2C)R) has emerged as a key regulator in this regard. The authors have evaluated the efficacy of a selective 5-HT(2C)R

agonist, WAY 163909, in cocaine and sucrose self-administration and reinstatement assays employing parallel experimental designs in free-fed rats. WAY 163909 dose-dependently reduced the reinforcing efficacy of cocaine (ID(50) = 1.19 mg/kg) and sucrose (ID(50) = 0.7 mg/kg) as well as reinstatement (ID(50) = 0.5 mg/kg) elicited by exposure to cocaine-associated contextual cues, but not sucrose-associated contextual cues. The ID(50) of WAY 163909 predicted to decrease the reinforcing efficacy of cocaine or sucrose as well as reinstatement upon exposure to cocaine-associated cues was ~5-12-fold lower than that predicted to suppress horizontal ambulation (ID(50) = 5.89 mg/kg) and ~2-5-fold lower than that predicted to suppress vertical activity (ID(50) = 2.3 mg/kg). Thus, selective stimulation of the 5-HT(2C)R decreases the reinforcing efficacy of cocaine and sucrose in freely-fed rats, but differentially alters the incentive-salience value of cocaine- vs. sucrose-associated cues at doses that do not impair locomotor activity. Future research is needed to tease apart the precise contribution of 5-HT(2C)R neurocircuitry in reward and motivation and the learning and memory processes that carry the encoding for associations between environmental cues and consumption of rewarding stimuli. A more complete preclinical evaluation of these questions will ultimately allow educated proof-of-concept trials to test the efficacy of selective 5-HT(2C)R agonists as adjunctive therapy in chronic health maladies including obesity, eating disorders and drug addiction. Cunningham KA, Fox RG, Anastasio NC, Bubar MJ, Stutz SJ, Moeller FG, Gilbertson SR, Rosenzweig-Lipson S. Selective serotonin 5-HT(2C) receptor activation suppresses the reinforcing efficacy of cocaine and sucrose but differentially affects the incentive-salience value of cocaine- vs. sucrose-associated cues. Neuropharmacology. 2011 Sep; (3): 513-523.

The Dynamics of the Urge-to-Smoke Following Smoking Cessation Via Pharmacotherapy
The study examined person-specific urge-to-smoke trajectories during the first 7 days of abstinence and the relationship of trajectory parameters to continuous abstinence, demographics, medication and smoking history. Hierarchical linear modeling was used to model person-specific trajectories for urge-to-smoke in two university-based smoking cessation trials. Treatment-seeking smokers in a clinical trial of transdermal nicotine (n = 275) versus nicotine spray (n = 239) and of bupropion (n = 223) versus placebo (n = 198). Self-reported urge-to-smoke for 7 days after the planned quit date, and 7-day point prevalence and continuous abstinence at end of treatment (EOT) and 6 months. Urge-to-smoke trajectory parameters (average level, slope, curvature and volatility) varied substantially among individuals, had modest intercorrelations and predicted continuous and point prevalence abstinence at EOT and at 6 months. Higher trajectory level, slope and volatility were all significantly ($P \leq 0.001$) associated with a reduced likelihood of abstinence at EOT (odds ratios 0.44-0.75) and at 6-month follow-up (odds ratios from 0.63 to 0.78), controlling for demographic, medication and smoking use variables. Higher urge-to-smoke trajectory parameters of level, slope and volatility (measured over 7 days) predict continuous and 7-day point prevalence at EOT and 6 months. Although there were some associations of trajectory parameters with demographics and smoking history, the associations of trajectory parameters with relapse were relatively uninfluenced by demographics and smoking history. Javitz HS, Swan GE, Lerman C. The dynamics of the urge-to-smoke following smoking cessation via pharmacotherapy. Addiction. 2011 Oct; (10): 1835-1845.

Effects of Adrenal Sensitivity, Stress- and Cue-Induced Craving, and Anxiety on Subsequent Alcohol Relapse and Treatment Outcomes Alcoholism is a chronic, relapsing illness in which stress and alcohol cues contribute significantly to relapse risk. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, increased anxiety, and high alcohol craving have been documented during early alcohol recovery, but their influence on relapse risk has not been

well studied. To investigate these responses in treatment-engaged, 1-month-abstinent, recovering alcohol-dependent patients relative to matched controls (study 1) and to assess whether HPA axis function, anxiety, and craving responses are predictive of subsequent alcohol relapse and treatment outcome (study 2). Experimental exposure to stress, alcohol cues, and neutral, relaxing context to provoke alcohol craving, anxiety, and HPA axis responses (corticotropin and cortisol levels and cortisol to corticotropin ratio) and a prospective 90-day follow-up outcome design to assess alcohol relapse and aftercare treatment outcomes. Inpatient treatment in a community mental health center and hospital-based research unit. Treatment-engaged alcohol-dependent individuals and healthy controls. Time to alcohol relapse and to heavy drinking relapse. Significant HPA axis dysregulation, marked by higher basal corticotropin level and lack of stress- and cue-induced corticotropin and cortisol responses, higher anxiety, and greater stress- and cue-induced alcohol craving, was seen in the alcohol-dependent patients vs. the control group. Stress- and cue-induced anxiety and stress-induced alcohol craving were associated with fewer days in aftercare alcohol treatment. High provoked alcohol craving to both stress and to cues and greater neutral, relaxed-state cortisol to corticotropin ratio (adrenal sensitivity) were each predictive of shorter time to alcohol relapse. These results identify a significant effect of high adrenal sensitivity, anxiety, and increased stress- and cue-induced alcohol craving on subsequent alcohol relapse and treatment outcomes. Findings suggest that new treatments that decrease adrenal sensitivity, stress- and cue-induced alcohol craving, and anxiety could be beneficial in improving alcohol relapse outcomes. Sinha R, Fox HC, Hong KI, Hansen J, Tuit K, Kreek MJ. Effects of adrenal sensitivity, stress- and cue-induced craving, and anxiety on subsequent alcohol relapse and treatment outcomes. Arch Gen Psychiatry. 2011 Sep; (9): 942-952.

A Neurocognitive Comparison of Cognitive Flexibility and Response Inhibition in Gamblers with Varying Degrees of Clinical Severity As a behavioral addiction with clinical and phenomenological similarities to substance addiction, recreational and pathological gambling represent models for studying the neurobiology of addiction, without the confounding deleterious brain effects which may occur from chronic substance abuse. A community sample of individuals aged 18-65 years who gamble was solicited through newspaper advertising. Subjects were grouped a priori into three groups (no-risk, at-risk, and pathological gamblers) based on a diagnostic interview. All subjects underwent a psychiatric clinical interview and neurocognitive tests assessing motor impulsivity and cognitive flexibility. Subjects with a current axis I disorder, history of brain injury/trauma, or implementation or dose changes of psychoactive medication within 6 weeks of study enrollment were excluded. A total of 135 no-risk, 69 at-risk and 46 pathological gambling subjects were assessed. Pathological gamblers were significantly older, and exhibited significant deficiencies in motor impulse control (stop-signal reaction times), response speed (median 'go' trial response latency) and cognitive flexibility [total intra-dimensional/extra-dimensional (IDED) errors] versus controls. The finding of impaired impulse control and cognitive flexibility was robust in an age-matched subgroup analysis of pathological gamblers. The no-risk and at-risk gambling groups did not significantly differ from each other on task performance. Impaired response inhibition and cognitive flexibility exist in people with pathological gambling compared with no-risk and at-risk gamblers. The early identification of such illness in adolescence or young adulthood may aid in the prevention of addiction onset of such disabling disorders. Odlaug BL, Chamberlain SR, Kim SW, Schreiber R, Grant JE. A neurocognitive comparison of cognitive flexibility and response inhibition in gamblers with varying degrees of clinical severity. Psychol Med. 2011 Oct; (10): 2111-2119.

The Pharmacodynamic and Pharmacokinetic Profile of Intranasal Crushed Buprenorphine and Buprenorphine/Naloxone Tablets in Opioid Abusers Sublingual buprenorphine and buprenorphine/naloxone are efficacious opioid dependence pharmacotherapies, but there are reports of their diversion and misuse by the intranasal route. The study objectives were to characterize and compare their intranasal pharmacodynamic and pharmacokinetic profiles. A randomized, double-blind, placebo-controlled, cross-over study. An in-patient research unit at the University of Kentucky. Healthy adults (n = 10) abusing, but not physically dependent on, intranasal opioids participated in six sessions (72 hours apart) tested five intranasal doses [0/0, crushed buprenorphine (2, 8 mg), crushed buprenorphine/naloxone (2/0.5, 8/2 mg)] and one intravenous dose (0.8 mg buprenorphine/0.2 mg naloxone for bioavailability assessment). Plasma samples, physiological, subject- and observer-rated measures were collected before and for up to 72 hours after drug administration. Both formulations produced time- and dose-dependent increases on subjective and physiological mu-opioid agonist effects (e.g. 'liking', miosis). Subjects reported higher subjective ratings and street values for 8 mg compared to 8/2 mg, but these differences were not statistically significant. No significant formulation differences in peak plasma buprenorphine concentration or time-course were observed. Buprenorphine bioavailability was 38-44% and T(max) was 35-40 minutes after all intranasal doses. Naloxone bioavailability was 24% and 30% following 2/0.5 and 8/2 mg, respectively. It is difficult to determine if observed differences in abuse potential between intranasal buprenorphine and buprenorphine/naloxone are clinically relevant at the doses tested. Greater bioavailability and faster onset of pharmacodynamic effects compared to sublingual administration suggests a motivation for intranasal misuse in non-dependent opioid abusers. However, significant naloxone absorption from intranasal buprenorphine/naloxone administration may deter the likelihood of intranasal misuse of buprenorphine/naloxone, but not buprenorphine, in opioid-dependent individuals. Middleton LS, Nuzzo PA, Lofwall MR, Moody DE, Walsh SL. The pharmacodynamic and pharmacokinetic profile of intranasal crushed buprenorphine and buprenorphine/naloxone tablets in opioid abusers. Addiction. 2011 Aug; (8): 1460-1473.

Delayed Reward Discounting and Addictive Behavior: A Meta-Analysis Delayed reward discounting (DRD) is a behavioral economic index of impulsivity and numerous studies have examined DRD in relation to addictive behavior. To synthesize the findings across the literature, the current review is a meta-analysis of studies comparing DRD between criterion groups exhibiting addictive behavior and control groups. The meta-analysis sought to characterize the overall patterns of findings, systematic variability by sample and study type, and possible small study (publication) bias. Literature reviews identified 310 candidate articles from which 46 studies reporting 64 comparisons were identified (total N=56,013).From the total comparisons identified, a small magnitude effect was evident (d= .15; p< .00001) with very high heterogeneity of effect size. Based on systematic observed differences, large studies assessing DRD with a small number of self-report items were removed and an analysis of 57 comparisons (n=3,329) using equivalent methods and exhibiting acceptable heterogeneity revealed a medium magnitude effect (d= .58; p< .00001). Further analyses revealed significantly larger effect sizes for studies using clinical samples (d= .61) compared with studies using nonclinical samples (d=.45). Indices of small study bias among the various comparisons suggested varying levels of influence by unpublished findings, ranging from minimal to moderate. These results provide strong evidence of greater DRD in individuals exhibiting addictive behavior in general and particularly in individuals who meet criteria for an addictive disorder. Implications for the assessment of DRD and research priorities are discussed. MacKillop J, Amlung MT, Few LR,

Ray LA, Sweet LH, Munafò MR. Delayed reward discounting and addictive behavior: a meta-analysis. Psychopharmacology (Berl). 2011 Aug; (3): 305-321.

Cue Reactivity In Virtual Reality: The Role of Context Cigarette smokers in laboratory experiments readily respond to smoking stimuli with increased craving. An alternative to traditional cue-reactivity methods (e.g., exposure to cigarette photos), virtual reality (VR) has been shown to be a viable cue presentation method to elicit and assess cigarette craving within complex virtual environments. However, it remains poorly understood whether contextual cues from the environment contribute to craving increases in addition to specific cues, like cigarettes. This study examined the role of contextual cues in a VR environment to evoke craving. Smokers were exposed to a virtual convenience store devoid of any specific cigarette cues followed by exposure to the same convenience store with specific cigarette cues added. Smokers reported increased craving following exposure to the virtual convenience store without specific cues, and significantly greater craving following the convenience store with cigarette cues added. However, increased craving recorded after the second convenience store may have been due to the pre-exposure to the first convenience store. This study offers evidence that an environmental context where cigarette cues are normally present (but are not), elicits significant craving in the absence of specific cigarette cues. This finding suggests that VR may have stronger ecological validity over traditional cue reactivity exposure methods by exposing smokers to the full range of cigarette-related environmental stimuli, in addition to specific cigarette cues, that smokers typically experience in their daily lives. Paris MM, Carter BL, Traylor AC, Bordnick PS, Day SX, Armsworth MW, Cinciripini PM. Cue reactivity in virtual reality: the role of context. Addict Behav 2011 Jul; (7): 696-699.

Novel Cocaine Vaccine Linked to a Disrupted Adenovirus Gene Transfer Vector Blocks Cocaine Psychostimulant and Reinforcing Effects Immunotherapy is a promising treatment for drug addiction. However, insufficient immune responses to vaccines in most subjects pose a challenge. In this study, the authors tested the efficacy of a new cocaine vaccine (dAd5GNE) in antagonizing cocaine addiction-related behaviors in rats. This vaccine used a disrupted serotype 5 adenovirus (Ad) gene transfer vector coupled to a third-generation cocaine hapten, termed GNE (6-(2R,3S)-3-(benzoyloxy)-8-methyl-8-azabicyclo [3.2.1] octane-2-carboxamido-hexanoic acid). Three groups of rats were immunized with dAd5GNE. One group was injected with (3)H-cocaine, and radioactivity in the blood and brain was determined. A second group was tested for cocaine-induced locomotor sensitization. A third group was examined for cocaine self-administration, extinction, and reinstatement of responding for cocaine. Antibody titers were determined at various time-points. In each experiment, a control group was added that was immunized with dAd5 without a hapten. The vaccination with dAd5GNE produced long-lasting high titers (>10(5)) of anti-cocaine antibodies in all of the rats. The vaccination inhibited cocaine-induced hyperlocomotor activity and sensitization. Vaccinated rats acquired cocaine self-administration, but showed less motivation to self-administer cocaine under a progressive-ratio schedule than control rats. When cocaine was not available in a session, control rats exhibited 'extinction burst' responding, whereas vaccinated rats did not. Moreover, when primed with cocaine, vaccinated rats did not reinstate responding, suggesting a blockade of cocaine-seeking behavior. These data strongly suggest that dAd5GNE vector-based vaccine may be effective in treating cocaine abuse and addiction. Wee S, Hicks MJ, De BP, Rosenberg JB, Moreno AY, Kaminsky SM, Janda KD, Crystal RG, Koob GF. Novel Cocaine Vaccine Linked to a Disrupted Adenovirus Gene Transfer Vector Blocks Cocaine Psychostimulant and

Reinforcing Effects. Neuropsychopharmacology advance online publication, 14 September 2011; doi:10.1038/npp.2011.200.

A Vaccine Strategy That Induces Protective Immunity Against Heroin Heroin addiction is a wide-reaching problem with a spectrum of damaging social consequences. A vaccine capable of blocking heroin's effects could provide a long-lasting and sustainable adjunct to heroin addiction therapy. Heroin, however, presents a particularly challenging immunotherapeutic target, as it is metabolized to multiple psychoactive molecules. To reconcile this dilemma, the authors examined the idea of a singular vaccine with the potential to display multiple drug-like antigens; thus two haptens were synthesized, one heroin-like and another morphine-like in chemical structure. A key feature in this approach is that immunopresentation with the heroin-like hapten is thought to be immunochemically dynamic such that multiple haptens are simultaneously presented to the immune system. The authors demonstrate the significance of this approach through the extremely rapid generation of robust polyclonal antibody titers with remarkable specificity. Importantly, both the antinociceptive effects of heroin and acquisition of heroin self-administration were blocked in rats vaccinated using the heroin-like hapten. Stowe GN, Vendruscolo LF, Edwards S, Schlosburg JE, Misra KK, Schulteis G, Mayorov AV, Zakhari JS, Koob GF, Janda KD. A vaccine strategy that induces protective immunity against heroin. J Med Chem. 2011 Jul 28; 54(14): 5195-5204.

CJ-1639: A Potent and Highly Selective Dopamine D3 Receptor Full Agonist The authors have identified several ligands with high binding affinities to the dopamine D3 receptor and excellent selectivity over the D2 and D1 receptors. CJ-1639 (17) binds to the D3 receptor with a K(i) value of 0.50 nM and displays a selectivity of >5,000 times over D2 and D1 receptors in binding assays using dopamine receptors expressed in the native rat brain tissues. CJ-1639 binds to human D3 receptor with a K(i) value of 3.61 nM and displays over >1000-fold selectivity over human D1 and D2 receptors. CJ-1639 is active at 0.01 mg/kg at the dopamine D3 receptor in the rat and only starts to show a modest D2 activity at doses as high as 10 mg/kg. CJ-1639 is the most potent and selective D3 full agonist reported to date. Chen J, Collins GT, Levant B, Woods J, Deschamps JR, Wang S. CJ-1639: A Potent and Highly Selective Dopamine D3 Receptor Full Agonist. ACS Med Chem Lett. 2011 Aug 11; 2(8): 620-625.

(3-cyano-5-fluorophenyl)biaryl Negative Allosteric Modulators of mGlu(5): Discovery of a New Tool Compound with Activity in the OSS Mouse Model of Addiction Glutamate is the major excitatory transmitter in the mammalian CNS, exerting its effects through both ionotropic and metabotropic glutamate receptors. The metabotropic glutamate receptors (mGlus) belong to family C of the G-protein-coupled receptors (GPCRs). The eight mGlus identified to date are classified into three groups based on their structure, preferred signal transduction mechanisms, and pharmacology (Group I: mGlu(1) and mGlu(5); Group II: mGlu(2) and mGlu(3); Group III: mGlu(4), mGlu(6), mGlu(7), and mGlu(8)). Non-competitive antagonists, also known as negative allosteric modulators (NAMs), of mGlu(5) offer potential therapeutic applications in diseases such as pain, anxiety, gastroesophageal reflux disease (GERD), Parkinson's disease (PD), fragile X syndrome, and addiction. The development of SAR in a (3-cyano-5-fluorophenyl)biaryl series using the authors functional cell-based assay is described in this communication. Further characterization of a selected compound, 3-fluoro-5-(2-methylbenzo[d]thiazol-5-yl)benzonitrile, in additional cell based assays as well as in vitro assays designed to measure its metabolic stability and protein binding indicated its potential utility as an in vivo tool. Subsequent evaluation of the same compound in a pharmacokinetic study using

intraperitoneal dosing in mice showed good exposure in both plasma and brain samples. The compound was efficacious in a mouse marble burying model of anxiety, an assay known to be sensitive to mGlu(5) antagonists. A new operant model of addiction termed operant sensation seeking (OSS) was chosen as a second behavioral assay. The compound also proved efficacious in the OSS model and constitutes the first reported example of efficacy with a small molecule mGlu(5) NAM in this novel assay. Lindsley CW, Bates BS, Menon UN, Jadhav SB, Kane AS, Jones CK, Rodriguez AL, Conn PJ, Olsen CM, Winder DG, Emmitte KA. (3-cyano-5-fluorophenyl)biaryl Negative Allosteric Modulators of mGlu(5): Discovery of a New Tool Compound with Activity in the OSS Mouse Model of Addiction. ACS Chem Neurosci. 2011 Aug 17; 2(8): 471-482.

Recent Advances in the Design and Development of Novel Negative Allosteric Modulators of mGlu(5) Negative allosteric modulators (NAMs) of metabotropic glutamate receptor subtype 5 (mGlu(5)) have remained attractive to researchers as potential therapies for a number of central nervous system related diseases, including anxiety, pain, gastroesophageal reflux disease (GERD), addiction, Parkinson's disease (PD), and fragile X syndrome (FXS). In addition to the many publications with supportive preclinical data with key tool molecules, recent positive reports from the clinic have bolstered the confidence in this approach. During the two year time span from 2009 through 2010, a number of new mGlu(5) NAM chemotypes have been disclosed and discussed in the primary and patent literature. A summary of several efforts representing many diverse chemotypes are presented here, along with a discussion of representative structure activity relationships (SAR) and synthetic approaches to the templates where possible. Emmitte KA. Recent Advances in the Design And Development of Novel Negative Allosteric Modulators of mGlu(5). ACS Chem Neurosci. 2011 Aug 17; 2(8): 411-432.

Human Butyrylcholinesterase-Cocaine Binding Pathway and Free Energy Profiles by Molecular Dynamics and Potential of Mean Force Simulations In the present study, the authors have performed combined molecular dynamics and potential of mean force (PMF) simulations to determine the enzyme-substrate (ES) binding pathway and the corresponding free energy profiles for wild-type butyrylcholinesterase (BChE) binding with (-)/(+)-cocaine and for the A328W/Y332G mutant binding with (-)-cocaine. According to the PMF simulations, for each ES binding system, the substrate first binds with the enzyme at a peripheral anionic site around the entrance of the active-site gorge to form the first ES complex (ES1-like) during the binding process. Further evolution from the ES1-like complex to the nonprereactive ES complex is nearly barrierless, with a free energy barrier lower than 1.0 kcal/mol. So, the nonprereactive ES binding process should be very fast. The rate-determining step of the entire ES binding process is the subsequent evolution from the nonprereactive ES complex to the prereactive ES complex. Further accounting for the entire ES binding process, the PMF-based simulations qualitatively reproduced the relative order of the experimentally derived binding free energies ($\Delta G(bind)$), although the simulations systematically overestimated the magnitude of the binding affinity and systematically underestimated the differences between the $\Delta G(bind)$ values. The obtained structural and energetic insights into the entire ES binding process provide a valuable base for future rational design of high-activity mutants of BChE as candidates for an enzyme therapy for cocaine overdose and abuse. Huang X, Zheng F, Zhan CG. Human Butyrylcholinesterase-Cocaine Binding Pathway and Free Energy Profiles by Molecular Dynamics and Potential of Mean Force Simulations. J Phys Chem B. 2011 Sep 29; 115(38): 11254-11260.

New Aporphinoid 5-HT2A and A1a Antagonists via Structural Manipulations of Nantenine A series of C1, C2, C3 and N6 analogs of nantenine (2) was synthesized and evaluated in 5-HT(2A) and α(1A) receptor functional assays. Alkyl substitution of the C1 and N6 methyl groups of nantenine provided selective 5-HT(2A) and α(1A) antagonists, respectively. The C2 alkyloxy analogs studied were generally selective for α(1A) versus 5-HT(2A). The C3 bromo analog 15 is one of the most potent aporphinoid 5-HT(2A) antagonists known presently. Chaudhary S, Ponnala S, Legendre O, Gonzales JA, Navarro HA, Harding WW. New Aporphinoid 5-HT2A and A1a Antagonists via Structural Manipulations of Nantenine. Bioorg Med Chem. 2011 Oct 1; 19(19): 5861-5868.

Synthesis and Pharmacological Evaluation of Indole-Based Sigma Receptor Ligands A series of novel indole-based analogs were prepared and their affinities for sigma receptors were determined using in vitro radioligand binding assays. The results of this study identified several compounds with nanomolar sigma-2 affinity and significant selectivity over sigma-1 receptors. In particular, 2-(4-(3-(4-fluorophenyl)indol-1-yl)butyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9f) was found to display high affinity at sigma-2 receptors with good selectivity (σ-1/σ-2 = 395). The pharmacological binding profile for this compound was established with other relevant non-sigma sites. Mésangeau C, Amata E, Alsharif W, Seminerio MJ, Robson MJ, Matsumoto RR, Poupaert JH, McCurdy CR. Synthesis and Pharmacological Evaluation of Indole-Based Sigma Receptor Ligands. Eur J Med Chem. 2011 Oct; 46(10): 5154-5161.

Conformationally Constrained Analogs of BAY 59-3074 as Novel Cannabinoid Receptor Ligands In order to obtain information on the pharmacophoric requirements of the CB1/CB2 partial agonist BAY 59-3074, the authors have synthesized a series of new conformationally constrained dibenzofuran (4a-d) and dibenzopyran analogs (5). All constrained analogs exhibited reduced binding affinity at both cannabinoid receptor subtypes, suggesting that planar conformations of these ligands are less favored by both receptors. The have also found that 4c, 4d, and 5 exhibited 3- to 12-fold selectivity for hCB2 over rCB1 receptors and may serve as new chemotypes for the development of CB2-selective cannabinergics. Teng H, Thakur GA, Makriyannis A. Conformationally Constrained Analogs of BAY 59-3074 as Novel Cannabinoid Receptor Ligands Bioorg Med Chem Lett. 2011 Oct 1;21(19):5999-6002.

Augmented Cocaine Seeking in Response to Stress or CRF Delivered into the Ventral Tegmental Area Following Long-Access Self-Administration is Mediated by CRF Receptor Type 1 but not CRF Receptor Type 2 Stressful events are determinants of relapse in recovering cocaine addicts. Excessive cocaine use may increase susceptibility to stressor-induced relapse through alterations in brain corticotropin-releasing factor (CRF) regulation of neurocircuitry involved in drug seeking. The authors previously reported that the reinstatement of cocaine seeking by a stressor (footshock) is CRF dependent and is augmented in rats that self-administered cocaine under long-access (LgA; 6 h daily) conditions for 14 d when compared with rats provided shorter daily cocaine access [short access (ShA) rats; 2 h daily]. Further, the authors have demonstrated that reinstatement in response to intracerebroventricular CRF administration is heightened in LgA rats. This study examined the role of altered ventral tegmental area (VTA) responsiveness to CRF in intake-dependent increases in CRF- and stress-induced cocaine seeking. Bilateral intra-VTA administration of CRF (250 or 500 ng/side) produced reinstatement in LgA but not ShA rats. In LgA rats, intra-VTA CRF-induced reinstatement was blocked by administration of the CRF-receptor type 1 (CRF-R1) antagonist

antalarmin (500 ng/side) or CP-376395 (500 ng/side), but not the CRF-R2 antagonist astressin-2B (500 ng or 1 μg/side) or antisauvagine-30 (ASV-30; 500 ng/side) into the VTA. Likewise, intra-VTA antalarmin, but not astressin-2B, blocked footshock-induced reinstatement in LgA rats. By contrast, neither intra-VTA antalarmin nor CP-376395 altered food-reinforced lever pressing. Intra-VTA injection of the CRF-R1-selective agonist cortagine (100 ng/side) but not the CRF-R2-selective agonist rat urocortin II (rUCN II; 250 ng/side) produced reinstatement. These findings reveal that excessive cocaine use increases susceptibility to stressor-induced relapse in part by augmenting CRF-R1-dependent regulation of addiction-related neurocircuitry in the VTA. Blacktop JM, Seubert C, Baker DA, Ferda N, Lee G, Graf EN, Mantsch JR. Augmented cocaine seeking in response to stress or CRF delivered into the ventral tegmental area following long-access self-administration is mediated by CRF receptor type 1 but not CRF receptor type 2. J Neurosci. 2011 Aug 3; 31(31): 11396-11403.

CM156, a High Affinity Sigma Ligand, Attenuates the Stimulant and Neurotoxic Effects of Methamphetamine in Mice Methamphetamine (METH) is a highly addictive psychostimulant drug of abuse. Low and high dose administration of METH leads to locomotor stimulation, and dopaminergic and serotonergic neurotoxicity, respectively. The behavioral stimulant and neurotoxic effects of METH can contribute to addiction and other neuropsychiatric disorders, thus necessitating the identification of potential pharmacotherapeutics against these effects produced by METH. METH binds to σ receptors at physiologically relevant concentrations. Also, σ receptors are present on and can modulate dopaminergic and serotonergic neurons. Therefore, σ receptors provide a viable target for the development of pharmacotherapeutics against the adverse effects of METH. In the present study, CM156, a σ receptor ligand with high affinity and selectivity for σ receptors over 80 other non-σ binding sites, was evaluated against METH-induced stimulant, hyperthermic, and neurotoxic effects. Pretreatment of male, Swiss Webster mice with CM156 dose dependently attenuated the locomotor stimulation, hyperthermia, striatal dopamine and serotonin depletions, and striatal dopamine and serotonin transporter reductions produced by METH, without significant effects of CM156 on its own. These results demonstrate the ability of a highly selective σ ligand to mitigate the effects of METH. Kaushal N, Seminerio MJ, Shaikh J, Medina MA, Mesangeau C, Wilson LL, McCurdy CR, Matsumoto RR. CM156, a high affinity sigma ligand, attenuates the stimulant and neurotoxic effects of methamphetamine in mice. Neuropharmacology. 2011 Oct-Nov;61(5-6): 992-1000.

Effects of Selective Dopaminergic Compounds on A Delay-Discounting Task Impulsivity is widely regarded as a multidimensional trait that encompasses two or more distinct patterns of behavior, and dopaminergic systems are implicated in the expression of impulsive behavior in both humans and animal subjects. Impulsive choice, or the tendency to choose rewards associated with relatively little or no delay, has been extensively studied in humans and animal subjects using delay-discounting tasks. Here, delay-discounting procedures were used to assess the effects of receptor-selective dopaminergic agonists, antagonists, and dopamine transporter ligands on choices of immediate versus delayed sucrose pellets. The effects of d-amphetamine, GBR 12909, apomorphine, SKF 81297, sumanirole, pramipexole, ABT-724, SCH 23390, L-741,626, PG01037, and L-745,870 were assessed in 24 Sprague-Dawley rats. The only drugs to affect impulsive choice selectively without altering undelayed choice were the D1-like antagonist, SCH 23390 (0.01 mg/kg), and the D4 partial agonist, ABT-724 (3.2 mg/kg), which both increased impulsive choice. The shared effects of these compounds may be explained by their localization within the prefrontal cortex on different groups of neurons. None of the

selective agonists and antagonists tested reduced impulsive choice, so further research is needed to determine if direct dopaminergic agonists or antagonists may be therapeutically useful in the treatment of impulse-control disorders. Koffarnus MN, Newman AH, Grundt P, Rice KC, Woods JH. Effects of Selective Dopaminergic Compounds on A Delay-Discounting Task. Behav Pharmacol. 2011 Aug; 22(4): 300-311.

Synthesis of Mercapto-(+)-Methamphetamine Haptens and Their Use for Obtaining Improved Epitope Density on (+)-Methamphetamine Conjugate Vaccines This study reports the synthesis of the mercapto-hapten (S)-N-(2-(mercaptoethyl)-6-(3-(2-(methylamino) propyl)phenoxy)hexanamide [3, (+)-METH HSMO9] and its use to prepare METH-conjugated vaccines (MCV) from maleimide-activated proteins. MALDI-TOF mass spectrometry analysis of the MCV synthesized using 3 showed there was a high and controllable epitope density on two different carrier proteins. In addition, the MCV produced a substantially greater immunological response in mice than previous METH haptens, and a monoclonal antibody generated from this MCV in mice showed a very high affinity for (+)-METH (K(D) = 6.8 nM). The efficient covalent coupling of (+)-METH HSMO9 to the activated carrier proteins suggests that this approach could be cost-effective for large-scale production of MCV. In addition, the general methods described for the synthesis of (+)-METH HSMO9 (3) and its use to synthesize MCV will be applicable for conjugated vaccines of small molecules and other substances of abuse such as morphine, nicotine, and cocaine. Carroll FI, Blough BE, Pidaparthi RR, Abraham P, Gong PK, Deng L, Huang X, Gunnell M, Lay JO Jr, Peterson EC, Owens SM. Synthesis of mercapto-(+)-methamphetamine haptens and their use for obtaining improved epitope density on (+)-methamphetamine conjugate vaccines J Med Chem. 2011 Jul 28; 54(14): 5221-5228.

Synthesis and Pharmacological Evaluation of 6-Acetyl-3-(4-(4-(4-Fluorophenyl)Piperazin-1-Yl)Butyl)Benzo[D]Oxazol-2(3H)-One (SN79), a Cocaine Antagonist, in Rodents Cocaine interacts with monoamine transporters and sigma (σ) receptors, providing logical targets for medication development. In the present study, in vitro and in vivo pharmacological studies were conducted to characterize SN79, a novel compound which was evaluated for cocaine antagonist actions. Radioligand binding studies showed that SN79 had a nanomolar affinity for σ receptors and a notable affinity for 5-HT(2) receptors, and monoamine transporters. It did not inhibit major cytochrome P450 enzymes, including CYP1A2, CYP2A6, CYP2C19, CYP2C9*1, CYP2D6, and CYP3A4, suggesting a low propensity for potential drug-drug interactions. Oral administration of SN79 reached peak in vivo concentrations after 1.5 h and exhibited a half-life of just over 7.5 h in male, Sprague-Dawley rats. Behavioral studies conducted in male, Swiss Webster mice, intraperitoneal or oral dosing with SN79 prior to a convulsive or locomotor stimulant dose of cocaine led to a significant attenuation of cocaine-induced convulsions and locomotor activity. However, SN79 produced sedation and motor incoordination on its own at higher doses, to which animals became tolerant with repeated administration. SN79 also significantly attenuated the development and expression of the sensitized response to repeated cocaine exposures. The ability of SN79 to significantly attenuate the acute and subchronic effects of cocaine provides a promising compound lead to the development of an effective pharmacotherapy against cocaine. Kaushal N, Robson MJ, Vinnakota H, Narayanan S, Avery BA, McCurdy CR, Matsumoto RR. Synthesis and Pharmacological Evaluation of 6-Acetyl-3-(4-(4-(4-Fluorophenyl)Piperazin-1-Yl)Butyl) Benzo[D]Oxazol-2(3H)-One (SN79), a Cocaine Antagonist, in Rodents. AAPS J. 2011 Sep; 13(3): 336-346.

Effects of the Selective Sigma Receptor Ligand, 1-(2-Phenethyl)Piperidine Oxalate (AC927), on the Behavioral and Toxic Effects of Cocaine Sigma receptors represent a unique structural class of proteins and they have become increasingly studied as viable medication development targets for neurological and psychiatric disorders, including drug abuse. Earlier studies have shown that cocaine and many other abused substances interact with sigma receptors and that antagonism of these proteins can mitigate their actions. In the present study, AC927 (1-(2-phenethyl) piperidine oxalate), a selective sigma receptor ligand, was tested against the behavioral and toxic effects of cocaine in laboratory animals. Acute administration of AC927 in male, Swiss Webster mice significantly attenuated cocaine-induced convulsions, lethality, and locomotor activity, at doses that alone had no significant effects on behavior. Subchronic administration of AC927 also attenuated cocaine-induced conditioned place preference in mice, at doses that alone had no effects on place conditioning. In drug discrimination studies in male, Sprague-Dawley rats, AC927 partially substituted for the discriminative stimulus effects of cocaine. When it was administered with cocaine, AC927 shifted the cocaine dose-response curve to the left, suggesting an enhancement of the discriminative stimulus effects of cocaine. In non-human primates, AC927 was self-administered, maintaining responding that was intermediate between contingent saline and a maintenance dose of cocaine. The ability of AC927 to elicit some cocaine-like appetitive properties and to also reduce many cocaine-induced behaviors suggests that it is a promising lead for the development of a medication to treat cocaine abuse. Matsumoto RR, Li SM, Katz JL, Fantegrossi WE, Coop A. Effects of the Selective Sigma Receptor Ligand, 1-(2-Phenethyl)Piperidine Oxalate (AC927), on the Behavioral and Toxic Effects of Cocaine. Drug Alcohol Depend. 2011 Oct 1; 118(1): 40-47.

The Use-Dependent, Nicotinic Antagonist BTMPS Reduces the Adverse Consequences of Morphine Self-Administration In Rats In An Abstinence Model of Drug Seeking
In this study, the use-dependent, nicotinic receptor antagonist bis (2,2,6,6-tetramethyl-4-piperidinyl) sebacate (BTMPS) was evaluated for its ability to attenuate the adverse consequences associated with morphine in rats in all three phases of an abstinence model of drug seeking: self-administration, acute withdrawal, and delayed test of drug seeking. Rats were allowed to self-administer morphine (FR1 schedule) with an active response lever, on a 24 h basis inside operant chambers, for 14 days. Each rat was subsequently evaluated for stereotypical behaviors associated with spontaneous morphine withdrawal. Rats were then placed in standard housing cages for a six week period of protracted abstinence from morphine. After this period, each rat was placed back into its respective operant chamber for a 14 day assessment of unrewarded drug seeking responses. BTMPS was administered to the animals in all three clinically relevant phases in three separate sets of experiments. BTMPS treatment during the self-administration phase resulted in up to a 34% reduction of lever responses to morphine when compared to vehicle treated control animals, as well as a 32% reduction in the dose of morphine self-administered. When given during self-administration and acute withdrawal, BTMPS treatment decreased acute withdrawal symptoms (up to 64%) of morphine use and reduced (up to 45%) drug seeking responses after six weeks of protracted withdrawal compared to control animals. BTMPS treatment after six weeks of abstinence from morphine had no effect. These results offer insight into the role of central cholinergic receptors in the onset and maintenance of drug addiction. Hall BJ, Pearson LS, Terry AV Jr, Buccafusco JJ. The use-dependent, nicotinic antagonist BTMPS reduces the adverse consequences of morphine self-administration in rats in an abstinence model of drug seeking. Neuropharmacology. 2011 Sep;61(4):798-806. Epub 2011 May 30.

CPP-115, a Potent Γ-Aminobutyric Acid Aminotransferase Inactivator for the Treatment of Cocaine Addiction Vigabatrin, a GABA aminotransferase (GABA-AT) inactivator, is used to treat infantile spasms and refractory complex partial seizures and is in clinical trials to treat addiction. The authors evaluated a novel GABA-AT inactivator (CPP-115) and observed that it does not exhibit other GABAergic or off-target activities and is rapidly and completely orally absorbed and eliminated. Using in vivo microdialysis techniques in freely moving rats and micro-PET imaging techniques, CPP-115 produced similar inhibition of cocaine-induced increases in extracellular dopamine and in synaptic dopamine in the nucleus accumbe141ns at 1/300-1/600th the dose of vigabatrin. It also blocks expression of cocaine-induced conditioned place preference at a dose 1/300th that of vigabatrin. Electroretinographic (ERG) responses in rats treated with CPP-115, at doses 20-40 times higher than those needed to treat addiction in rats, exhibited reductions in ERG responses, which were less than the reductions observed in rats treated with vigabatrin at the same dose needed to treat addiction in rats. In conclusion, CPP-115 can be administered at significantly lower doses than vigabatrin, which suggests a potential new treatment for addiction with a significantly reduced risk of visual field defects. Pan Y, Gerasimov MR, Kvist T, Wellendorph P, Madsen KK, Pera E, Lee H, Schousboe A, Chebib M, Bräuner-Osborne H, Craft CM, Brodie JD, Schiffer WK, Dewey SL, Miller SR, Silverman RB. CPP-115, a Potent Γ-Aminobutyric Acid Aminotransferase Inactivator for the Treatment of Cocaine Addiction. J Med Chem. 2011 Nov; [Epub ahead of print].

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; (8): 824-836.

Jwh-018 and Jwh-073: {Delta}9-Tetrahydrocannabinol-Like Discriminative Stimulus Effects in Monkeys Products containing naphthalen-1-yl-(1-pentylindol-3-yl) methanone (JWH-018) and naphthalen-1-yl-(1-butylindol-3-yl) methanone (JWH-073) are emerging drugs of abuse. Here, the behavioral effects of JWH-018 and JWH-073 were examined in one behavioral assay selective for cannabinoid agonism, rhesus monkeys (n = 4) discriminating Δ(9)-tetrahydrocannabinol (Δ(9)-THC; 0.1 mg/kg i.v.), and another assay sensitive to cannabinoid withdrawal, i.e., monkeys (n = 3) discriminating the cannabinoid antagonist rimonabant (1 mg/kg i.v.) during chronic Δ(9)-THC (1 mg/kg s.c. 12 h) treatment. Δ(9)-THC, JWH-018, and JWH-073 increased drug-lever responding in monkeys discriminating Δ(9)-THC; the ED(50) values were 0.044, 0.013, and 0.058 mg/kg, respectively and the duration of action was 4, 2, and 1 h, respectively. Rimonabant (0.32-3.2 mg/kg) produced surmountable antagonism of Δ(9)-THC, JWH-018, and JWH-073. Schild analyses and single-dose apparent affinity estimates yielded apparent pA(2)/pK(B) values of 6.65, 6.68, and 6.79 in the presence of Δ(9)-THC, JWH-018, and JWH-073, respectively. In Δ(9)-THC-treated monkeys discriminating rimonabant, the training drug increased responding on the rimonabant lever; the ED(50) value of rimonabant was 0.20 mg/kg. Δ(9)-THC (1-10 mg/kg), JWH-018 (0.32-3.2 mg/kg), and JWH-073 (3.2-32 mg/kg) dose-dependently attenuated the rimonabant-discriminative stimulus (i.e., withdrawal). These results suggest that Δ(9)-THC, JWH-018, and JWH-073 act through the same receptors to produce Δ(9)-THC-like subjective effects and attenuate Δ(9)-THC withdrawal. The relatively short duration of action of JWH-018 and JWH-073 might lead to more frequent use, which could strengthen habitual use by increasing the frequency of stimulus-outcome pairings. This coupled with the possible greater efficacy of JWH-018 at cannabinoid 1 receptors could be associated with greater dependence liability than Δ(9)-THC. Ginsburg BC, Schulze DR, Hruba L, McMahon LR. JWH-018 and JWH-073: {Delta}9-Tetrahydrocannabinol-like discriminative stimulus effects in monkeys. J Pharmacol Exp Ther. 2012 Jan; (1): 37-45.

Delivery of Nicotine in an Extract of a Smokeless Tobacco Product Reduces its Reinforcement-Attenuating and Discriminative Stimulus Effects in Rats Animal models of tobacco addiction rely on administration of nicotine alone or nicotine combined with isolated constituents. Models using tobacco extracts derived from tobacco products and containing a range of tobacco constituents might more accurately simulate tobacco exposure in humans. The study compared the effects of nicotine alone and an aqueous smokeless tobacco extract in several addiction-related animal behavioral models. Nicotine alone and nicotine dose-equivalent concentrations of extract were compared in terms of their acute effects on intracranial self-stimulation (ICSS) thresholds, discriminative stimulus effects, and effects on locomotor activity. Similar levels of nicotine and minor alkaloids were achieved using either artificial saliva or saline for extraction, supporting the clinical relevance of the saline extracts used in these studies. Extract produced reinforcement-enhancing (ICSS threshold-decreasing) effects similar to those of nicotine alone at low to moderate nicotine doses, but reduced reinforcement-attenuating (ICSS threshold-increasing) effects at a high nicotine dose. In rats trained to discriminate nicotine alone from saline, intermediate extract doses did not substitute for the training dose as well as nicotine alone. Locomotor stimulant effects and nicotine distribution to brain were similar following administration of extract or nicotine alone. The reinforcement-attenuating and discriminative stimulus effects of nicotine delivered in an extract of a commercial smokeless tobacco product differed from those of nicotine alone. Extracts of tobacco products may be useful for evaluating the abuse liability of those products and understanding the role of non-nicotine constituents in tobacco addiction. Harris AC, Stepanov I, Pentel PR, Lesage MG. Delivery of nicotine in an

extract of a smokeless tobacco product reduces its reinforcement-attenuating and discriminative stimulus effects in rats. Psychopharmacology (Berl). 2011 Sep; [Epub ahead of print].

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; (2): 209-214.

Effects of Varenicline on the Reinforcing and Discriminative Stimulus Effects of Cocaine in Rhesus Monkeys Varenicline is a low-efficacy, α4β2* subtype-selective nicotinic acetylcholine receptor (nAChR) agonist that has shown success in smoking cessation and promise in preclinical assessments relating to other drugs of abuse. The primary goal of the present study was to examine the effects of varenicline on cocaine self-administration and cocaine discrimination and compare these effects with those of the nAChR agonist nicotine and antagonist mecamylamine. One limitation of agonist treatments is the potential for abuse. Thus, a second goal was to examine the abuse potential of varenicline in rhesus monkeys. In the first experiment, rhesus monkeys (n = 3) were trained to self-administer cocaine (saline, 0.01-0.56 mg/kg) under a progressive-ratio schedule of reinforcement; monkeys also earned all of their food by responding on another lever under a fixed-ratio 50 schedule of reinforcement. Chronic administration of varenicline (0.01-0.56 mg/kg p.o., salt) potentiated the reinforcing effects of cocaine, whereas mecamylamine (0.3-1.7 mg/kg p.o, i.m., i.v., salt) had no significant effects on cocaine self-administration up to doses that disrupted food-maintained responding. Neither varenicline (0.01-0.17 mg/kg, salt) nor nicotine (0.01-0.1 mg/kg, base) functioned as reinforcers when substituted for cocaine. Finally, in monkeys trained to discriminate self-administered 0.3 mg/kg cocaine, varenicline (0.1-0.3 mg/kg i.v.) did not substitute for cocaine but, along with mecamylamine (0.3-1.7 mg/kg i.v.) and nicotine (0.03-0.1 mg/kg i.v.), potentiated the discriminative stimulus effects of cocaine. These results suggest that varenicline has low abuse liability in monkey models of cocaine abuse, but would not be an effective medication for cocaine addiction. Gould RW, Czoty PW, Nader SH, Nader MA. Effects of varenicline on the reinforcing and discriminative stimulus effects of cocaine in rhesus monkeys. J Pharmacol Exp Ther. 2011 Nov; (2): 678-686.

5-Ht(2C) Receptors Localize To Dopamine and GABA Neurons In The Rat Mesoaccumbens Pathway The serotonin 5-HT(2C) receptor (5-HT(2C)R) is localized to the limbic-corticostriatal circuit, which plays an integral role in mediating attention, motivation, cognition, and reward processes. The 5-HT(2C)R is linked to modulation of mesoaccumbens dopamine neurotransmission via an activation of γ-aminobutyric acid (GABA) neurons in the ventral tegmental area (VTA). However, the authors recently demonstrated the expression of the

5-HT(2C)R within dopamine VTA neurons suggesting the possibility of a direct influence of the 5-HT(2C)R upon mesoaccumbens dopamine output. Here, they employed double-label fluorescence immunochemistry with the synthetic enzymes for dopamine (tyrosine hydroxylase; TH) and GABA (glutamic acid decarboxylase isoform 67; GAD-67) and retrograde tract tracing with FluoroGold (FG) to uncover whether dopamine and GABA VTA neurons that possess 5-HT(2C)R innervate the nucleus accumbens (NAc). The highest numbers of FG-labeled cells were detected in the middle versus rostral and caudal levels of the VTA, and included a subset of TH- and GAD-67 immunoreactive cells, of which >50% also contained 5-HT(2C)R immunoreactivity. Thus, they demonstrate for the first time that the 5-HT(2C)R colocalizes in DA and GABA VTA neurons which project to the NAc, describe in detail the distribution of NAc-projecting GABA VTA neurons, and identify the colocalization of TH and GAD-67 in the same NAc-projecting VTA neurons. These data suggest that the 5-HT(2C)R may exert direct influence upon both dopamine and GABA VTA output to the NAc. Further, the indication that a proportion of NAc-projecting VTA neurons synthesize and potentially release both dopamine and GABA adds intriguing complexity to the framework of the VTA and its postulated neuroanatomical roles. Bubar MJ, Stutz SJ, Cunningham KA. 5-HT(2C) receptors localize to dopamine and GABA neurons in the rat mesoaccumbens pathway. PLoS One. 2011; (6): e20508.

The Fatty Acid Amide Hydrolase Inhibitor URB 597: Interactions with Anandamide in Rhesus Monkeys The fatty acid amide hydrolase inhibitor URB 597 increases brain anandamide levels, suggesting that URB 597 could enhance the behavioural effects of anandamide. The goal of the current study was to examine and characterize the in vivo pharmacology of URB 597 alone and in combination with anandamide and Δ^9-tetrahydrocannabinol (Δ^9 -THC) in two drug discrimination assays in rhesus monkeys. The effects of URB 597 alone and in combination with anandamide were investigated in one group of monkeys (n= 4) that discriminated Δ^9-THC (0.1 mg·kg^{-1} i.v.) from vehicle, and in another group (n= 5) receiving chronic Δ^9-THC (1 mg·kg^{-1} 12 h^{-1} s.c.) that discriminated the cannabinoid antagonist rimonabant (1 mg·kg^{-1} i.v.).Intravenous anandamide fully substituted for, and had infra-additive effects with, Δ^9-THC. URB 597 (up to 3.2 mg·kg^{-1} i.v.) did not substitute for or modify the effects of Δ^9-THC but markedly increased the potency (32-fold) and duration of action of anandamide. The rimonabant discriminative stimulus in Δ^9-THC-treated monkeys (i.e. Δ^9-THC withdrawal) was attenuated by both Δ^9-THC (at doses larger than 1 mg·kg^{-1} per 12 h) and anandamide but not by URB 597 (3.2 mg·kg^{-1}). URB 597 did not increase the potency of anandamide to attenuate the rimonabant-discriminative stimulus.URB 597 enhanced the behavioural effects of anandamide but not other CB_1 agonists. However, URB 597 did not significantly enhance the attenuation of Δ^9-THC withdrawal induced by anandamide. Collectively, these data suggest that endogenous anandamide in primate brain does not readily mimic the behavioural effects of exogenously administered anandamide. Stewart JL, McMahon LR. The fatty acid amide hydrolase inhibitor URB 597: interactions with anandamide in rhesus monkeys. Br J Pharmacol. 2011 Sep; (2b): 655-666.

Discovery of Novel Selective Serotonin Reuptake Inhibitors through Development of a Protein-Based Pharmacophore The serotonin transporter (SERT), a member of the neurotransmitter sodium symporter (NSS) family, is responsible for the reuptake of serotonin from the synaptic cleft to maintain neurotransmitter homeostasis. SERT is established as an important target in the treatment of anxiety and depression. Because a high-resolution crystal

structure is not available, a computational model of SERT was built based upon the X-ray coordinates of the leucine transporter LeuT, a bacterial NSS homologue. The model was used to develop the first SERT structure-based pharmacophore. Virtual screening (VS) of a small molecule structural library using the generated SERT computational model yielded candidate ligands of diverse scaffolds. Pharmacological analysis of the VS hits identified two SERT-selective compounds, potential lead compounds for further SERT-related medication development. Manepalli S, Geffert LM, Surratt CK, Madura JD. Discovery of novel selective serotonin reuptake inhibitors through development of a protein-based pharmacophore. J Chem Inf Model. 2011 Sep 26; 5(9): 2417-2426.

The Effect of a Novel VMAT2 Inhibitor, GZ-793A, on Methamphetamine Reward in Rats Previous research suggests that the vesicular monoamine transporter-2 (VMAT2) is a novel target for the treatment of methamphetamine (METH) abuse. The effects GZ-793A, a novel, selective, and potent lobelane analog, on the rewarding effects of METH, cocaine, and palatable food in rats were determined. GZ-793A (3-30 mg/kg, s.c.) was administered 20 min prior to each session in which the groups of rats pressed a lever for infusions of METH (0.03 mg/kg/infusion), cocaine (0.3 mg/kg/infusion), or food pellets. Tolerance to repeated GZ-793A (15 mg/kg, s.c. for 7 days) on METH self-administration and food-maintained responding was determined. The ability of increasing doses of METH (0.001-0.56 mg/kg, i.v.) to surmount inhibition produced by GZ-793A (15 mg/kg, s.c.) was determined. Self-administration of GZ-793A (0.01-0.3 mg/kg/infusion, i.v.) was tested as a substitute for METH infusion. GZ-793A (15 mg/kg, s.c.) was administered 20 min prior to METH or saline conditioning in a place preference test. GZ-793A specifically decreased METH self-administration, without the development of tolerance. Increasing the unit dose of METH did not surmount the inhibition produced by GZ-793A on METH self-administration. GZ-793A did not serve as a substitute for self-administered METH. GZ-793A blocked METH-induced conditioned place preference (CPP) and did not induce CPP alone. These results indicate that VMAT2 is a viable target for pharmacological inhibition of METH reward and that GZ-793A represents a new lead in the discovery of a treatment for METH abuse. Beckmann JS, Denehy ED, Zheng G, Crooks PA, Dwoskin LP, Bardo MT. Psychopharmacology (Berl). 2011 Sep 21. [Epub ahead of print]

Discriminative Stimulus Effects of NMDA, AMPA, and mGluR5 Glutamate Receptor Ligands in Methamphetamine-trained Rats Glutamate contributes to the reinforcing and stimulant effects of methamphetamine, yet its potential role in the interoceptive stimulus properties of methamphetamine is unknown. In this study, adult male Sprague-Dawley rats were trained to discriminate methamphetamine [1.0 mg/kg, intraperitoneally] from saline in a standard operant discrimination task. The effects of methamphetamine (0.1-1.0 mg/kg, intraperitoneally); N-methyl-D-aspartate (NMDA) receptor channel blockers, MK-801 (0.03-0.3 mg/kg, intraperitoneally) and ketamine (1.0-10.0 mg/kg, intraperitoneally); polyamine site NMDA receptor antagonist, ifenprodil (1-10 mg/kg); α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor antagonist, 6-cyano-7-nitroquinoxaline-2,3-dione (1-10 mg/kg, intraperitoneally); and metabotropic 5 glutamate receptor antagonist, 6-methyl-2-(phenylethynyl)pyridine (1-10 mg/kg), given alone were determined in substitution tests. The effects of MK-801 (0.03 and 0.1 mg/kg), ketamine (1.0 and 3.0 mg/kg), ifenprodil (5.6 mg/kg), 6-cyano-7-nitroquinoxaline-2,3-dione (5.6 mg/kg), and 6-methyl-2-(phenylethynyl)pyridine (5.6 mg/kg) were also tested in combination with methamphetamine to assess for alterations in the methamphetamine cue. In substitution tests, none of the test drugs generalized to the methamphetamine cue. However, ketamine and ifenprodil produced significant leftward shifts in

the methamphetamine dose-response curve. In addition, the potention by MK-801 nearly attained significance. These results suggest that blockade of the NMDA receptor augments the interoceptive stimulus properties of methamphetamine. Wooters TE, Dwoskin LP, Bardo MT. Behav Pharmacol. 2011 Sep; 22(5-6): 516-524.

Tetrabenazine Inhibition of Monoamine Uptake and Methamphetamine Behavioral Effects: Locomotor Activity, Drug Discrimination and Self-Administration

Tetrabenazine (TBZ), a benzoquinolizine derivative, binds with high affinity to the vesicular monoamine transporter-2 (VMAT2), inhibiting uptake of cytosolic monoamines. The current study aimed to provide preclinical evidence supporting the potential use of TBZ as a treatment for methamphetamine abuse. Effects of TBZ on function of the dopamine transporter (DAT) and serotonin transporter (SERT) in striatal and hippocampal synaptosomes, respectively, and on VMAT2 function in isolated striatal synaptic vesicles were determined. Effect of TBZ (acute, 0.1-3.0 mg/kg, s.c.; repeated, 1.0 mg/kg for 7 days) on locomotor activity in methamphetamine-sensitized rats was assessed. Ability of TBZ (0.1-3.0 mg/kg; s.c.) or vehicle to decrease the discriminative effect of methamphetamine also was determined. Ability of TBZ (acute, 0.1-1.0 mg/kg, s.c.; repeated, 0.1 or 1.0 mg/kg for 7 days) to specifically decrease methamphetamine self-administration was determined; for comparison, a separate group of rats was assessed for effects of TBZ on food-maintained responding. Results show that TBZ was 11-fold more potent inhibiting DAT than SERT, and 2.5-fold more potent inhibiting VMAT2 than DAT. Results from behavioral studies showed that the lowest dose of TBZ transiently increased methamphetamine self-administration, whereas higher TBZ doses decreased methamphetamine self-administration. Also, TBZ at high doses decreased methamphetamine locomotor sensitization and discriminative stimulus effects, as well as food-maintained responding. Thus, despite acting as a potent VMAT2 inhibitor, these preclinical results indicate that TBZ lacks behavioral specificity as an inhibitor of methamphetamine-induced reinforcement, diminishing its viability as a suitable treatment for methamphetamine abuse. Meyer AC, Horton DB, Neugebauer NM, Wooters TE, Nickell JR, Dwoskin LP, Bardo MT. Neuropharmacology. 2011 Sep; 61(4): 849-856.

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

Controlled HIV Viral Replication, not Liver Disease Severity Associated with Low Bone Mineral Density in HIV/HCV Co-infection This study evaluated 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 ≤-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. ≥400 copies/ml) was associated with lower Z-scores (mean ± standard error) at the total hip (-0.44 ± 0.17, p = 0.01), femoral neck (-0.59 ± 0.18, p = 0.001), and the spine (-0.98 ± 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 Oct; 55(4): 770-776. Epub 2011 Feb 19.

Strategies to Improve Access to and Utilization of Health Care Services and Adherence to Antiretroviral Therapy Among HIV-infected Drug Users The authors review five innovative strategies to improve access, utilization, and adherence for HIV-infected drug users and suggest areas that need further attention. In addition, they highlight two innovative programs. The first increases access and utilization through integrated HIV and opioid addiction treatment with buprenorphine in a community health center, and the second incorporates adherence counseling for antiretroviral therapy in methadone programs. Preliminary evaluations demonstrated that these strategies may improve both HIV and opioid addiction outcomes and may be appropriate for wider dissemination. Further refinement and expansion of strategies to improve outcomes of HIV-infected drug users is warranted. Cunningham CO, Sohler NL, Cooperman NA, Berg KM, Litwin AH, Arnsten JH. Strategies to improve access to and utilization of health care services and adherence to antiretroviral therapy among HIV-infected drug users. Subst Use Misuse. 2011; 46(2-3): 218-232.

Development of the Perceived Risk of HIV Scale Past studies have used various methods to assess perceived risk of HIV infection; however, few have included multiple items covering different dimensions of risk perception or have examined the characteristics of individual items. This study describes the use of Item Response Theory (IRT) to develop a short measure of perceived risk of HIV infection scale (PRHS). An item pool was administered by trained interviewers to 771 participants. Participants also completed the risk behavior assessment (RBA) which includes items measuring risky sexual behaviors, and 652 participants completed HIV testing. The final measure consisted of 8 items, including items assessing likelihood estimates,

intuitive judgments and salience of risk. Higher scores on the PRHS were positively associated with a greater number of sex partners, episodes of unprotected sex and having sex while high. Participants who tested positive for HIV reported higher perceived risk. The PRHS demonstrated good reliability and concurrent criterion-related validity. Compared to single item measures of risk perception, the PRHS is more robust by examining multiple dimensions of perceived risk. Possible uses of the measure and directions for future research are discussed. Napper LE, Fisher DG, Reynolds GL. Development of the Perceived Risk of HIV Scale. AIDS Behav. 2011 Jul 22. [Epub ahead of print].

Malnutrition in a Population of HIV-positive and HIV-negative Drug Users Living in Chennai, South India Malnutrition is a strong predictor of poor outcomes in people living with HIV (PLHIV). Drug users are at increased risk of malnutrition regardless of whether or not they are infected with HIV. Little data exists on the nutritional status of drug users (with or without HIV infection) in India. The authors describe and compare the nutrition and metabolic status of 107 HIV-positive and 193 HIV-negative male clients of a community-based drop-in center for injection drug users in Chennai, India. Measures of nutrition and metabolic status include body composition, dietary intake, food insecurity, and serum lipid levels. The authors found poor overall nutritional status in both the HIV-positive and HIV-negative clients, with HIV-positive men faring worse on some parameters. Both groups had extremely low percent body fat, but levels in HIV-positive participants were significantly lower (6.5% versus 7.9%, p=.01). HIV-positive men also had significantly lower total caloric and fat intakes compared to HIV-negative men. A considerable proportion (70%) of both HIV-positive and HIV-negative drug users were food insecure. HDL cholesterol levels were significantly lower and below normal range in the HIV-positive compared to HIV-negative men. The high levels of food insecurity and poor nutritional status in this population, regardless of HIV status, indicates critical need for intervention. Improving nutritional status in those who are infected with HIV prior to initiation of antiretroviral treatment may help patients to reap the full benefits of therapy. Tang AM, Bhatnagar T, Ramachandran R, Dong K, Skinner S, Kumar MS, Wanke CA. Drug Alcohol Depend. 2011 Oct 1; 118(1): 73-77. Epub 2011 Mar 21.

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. HIV-related research in correctional populations: now is the time. Curr HIV/AIDS Rep. 2011 Dec; 8(4): 288-296.

Regulation of the Production of Infectious Genotype 1a Hepatitis C Virus by NS5A Domain III Although hepatitis C virus (HCV) assembly remains incompletely understood, recent studies with the genotype 2a JFH-1 strain suggest that it is dependent upon the phosphorylation of Ser residues near the C terminus of NS5A, a multifunctional nonstructural protein. Since genotype 1 viruses account for most HCV disease yet differ substantially in sequence from that of JFH-1, the authors studied the role of NS5A in the production of the H77S virus. While less efficient than JFH-1, genotype 1a H77S RNA produces infectious virus when transfected into permissive Huh-7 cells. The exchange of complete NS5A sequences between these viruses was highly detrimental to replication, while exchanges of the C-terminal domain III sequence (46% amino acid sequence identity) were well tolerated, with little effect on RNA synthesis. Surprisingly, the placement of the H77S domain III sequence into JFH-1 resulted in increased virus yields; conversely, H77S yields were reduced by the introduction of domain III from JFH-1. These changes in infectious virus yield correlated well with changes in the abundance of NS5A in RNA-transfected cells but not with RNA replication or core protein expression levels. Alanine replacement mutagenesis of selected Ser and Thr residues in the C-terminal domain III sequence revealed no single residue to be essential for infectious H77S virus production. However, virus production was eliminated by Ala substitutions at multiple residues and could be restored by phosphomimetic Asp substitutions at these sites. Thus, despite low overall sequence homology, the production of infectious virus is regulated similarly in JFH-1 and H77S viruses by a conserved function associated with a C-terminal Ser/Thr cluster in domain III of NS5A. Kim S, Welsch C, Yi M, Lemon SM. Regulation of the production of infectious genotype 1a hepatitis C virus by NS5A domain III. J Virol. 2011 Jul; 85(13): 6645-6656. Epub 2011 Apr 27.

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 PT, Hahn J, Delwart E, Edlin B, Martin J, Lum P, Evans J, Kral A, Deeks S, Busch M, and Page K. Temporal changes in HCV genotype distribution in three different high risk populations in San Francisco, California. BMC Infect Dis. 2011; 11: 208.

Induction of CXCR3- and CCR5-associated Chemokines During Acute Hepatitis C Virus Infection Characterization of inflammatory mediators, such as chemokines, during acute hepatitis C virus (HCV) infection might shed some light on viral clearance mechanisms. Plasma levels of CXCR3 (CXCL9-11)- and CCR5 (CCL3-4)-associated chemokines, ALT, and HCV RNA were measured in nine injection drug users (median 26 samples/patient) before and during 10 acute (eight primary and two secondary) HCV infections. Using functional data analysis, the authors estimated smooth long-term trends in chemokine expression levels to obtain the magnitude and timing of overall changes. Residuals were analyzed to characterize short-term fluctuations. CXCL9-11 induction began 38-53days and peaked 72-83days after virus acquisition. Increases in ALT levels followed a similar pattern. Substantial negative auto-correlations of chemokine levels at 1 week lags suggested substantial week-to-week oscillations. Significant correlations were observed between CXCL10 and HCV RNA as well as ALT and CXCR3-associated chemokines measured in the preceding week, CCL3-4 expression levels did not change appreciably during acute HCV infection. Elevation of CXCR3-associated chemokines late during acute HCV infection suggests a role for cellular immune responses in chemokine induction. Week-to-week oscillations of HCV RNA, chemokines, and ALT suggest frequent, repeated cycles of gain and loss of immune control during acute hepatitis C. Zeremski M, Hooker G, Shu MA, Winkelstein E, Brown Q, Des Jarlais DC, Tobler LH, Rehermann B, Busch MP, Edlin BR, Talal AH. Induction of CXCR3- and CCR5-associated chemokines during acute hepatitis C virus infection. J Hepatol. 2011 Sep; 55(3): 545-553. Epub 2011 Jan 21.

High Plasma Interleukin-18 Levels Mark the Acute Phase of Hepatitis C Virus Infection Proinflammatory cytokines play a critical role in antiviral immune responses. Large-scale genome studies have found correlations between single-nucleotide polymorphisms (SNPs) in the interleukin (IL) 18 promoter and spontaneous control of hepatitis C virus (HCV), suggesting a role in clearance. Plasma IL-18, IL-1β, IL-6, IL-8, IL-12, interferon-γ, tumor necrosis factor–α, alanine aminotransferase (ALT), and HCV RNA levels were assessed longitudinally in subjects with known dates of HCV acquisition and analyzed according to IL-18 SNPs and outcome, either spontaneous clearance (SC) (n = 13) or persistent infection (PI) (n = 25). No significant change in plasma proinflammatory cytokine expression was observed with the exception of IL-18, which increased in every subject with initial detection of HCV RNA. In every SC subject, IL-18 returned to the preinfection baseline concomitant with HCV control. In PI subjects, IL-18 declined following the acute phase of infection but remained above the preinfection baseline throughout chronic infection and did not correlate with HCV RNA or ALT levels. Plasma IL-18 was an early and the most reliably detected host response to HCV infection measured in blood. Reduced IL-18 production with transition to chronic infection without correlation with HCV RNA or ALT levels suggests modulation of the innate response with persistent infection. Chattergoon MA, Levine JS, Latanich R, Osburn WO, Thomas DL, Cox AL**.** High Plasma Interleukin-18 Levels Mark the Acute Phase of Hepatitis C Virus Infection. J Infect Dis. 2011 Dec; 204(11): 1730-1740. Epub 2011 Oct 7.

Genetic Polymorphism in IL28B is Associated with Spontaneous Clearance of Hepatitis C virus Genotype 4 Infection in an Egyptian Cohort Single-nucleotide polymorphisms (SNPs) around IL28B are associated with spontaneous hepatitis C virus (HCV) clearance of genotypes 1 and 3 in white and African-American populations. This study investigated whether the IL28B SNP (rs12979860) is associated with spontaneous clearance of HCV, principally genotype 4, in 162 Egyptians (80 with clearance). The protective C allele was more common in those with spontaneous clearance (76.3% vs 57.9%; P = .0006). Individuals with clearance were 3.4 (95%

confidence interval, 1.8-6.5) times more likely to have C/C genotype. Thus, IL28B plays a role in spontaneous clearance of HCV genotype 4 in North Africa. Kurbanov F, Abdel-Hamid M, Latanich R, Astemborski J, Mohamed M, Mikhail NM, El-Daly M, El-Kafrawy S, Thomas DL, Thio CL. Genetic polymorphism in IL28B is associated with spontaneous clearance of hepatitis C virus genotype 4 infection in an Egyptian cohort. J Infect Dis. 2011 Nov; 204(9): 1391-1394. Epub 2011 Sep 20.

Adherence to Treatment for Recently Acquired Hepatitis C Virus (HCV) Infection Among Injecting Drug Users Adherence to HCV therapy impacts sustained virological response (SVR) but there are limited data on adherence, particularly among injecting drug users (IDUs). The authors assessed 80/80 adherence (≥80% of PEG-IFN doses, ≥80% treatment), on-treatment adherence, and treatment completion in a study of treatment of recent HCV infection (ATAHC). Participants with HCV received pegylated interferon (PEG-IFN) alfa-2a (180µg/week, n=74) and those with HCV/HIV received PEG-IFN alfa-2a with ribavirin (n=35), for a planned 24 weeks. Logistic regression analyses were used to identify predictors of PEG-IFN 80/80 adherence. A total of 109 out of 163 patients received treatment (HCV, n=74; HCV/HIV, n=35), with 75% ever reporting IDU. The proportion with 80/80 PEG-IFN adherence was 82% (n=89). During treatment, 14% missed ≥1 dose (on-treatment adherence=99%). Completion of 0-4, 5-19, 20-23, and all 24 weeks of PEG-IFN therapy occurred in 10% (n=11), 14% (n=15), 6% (n=7) and 70% (n=76) of cases, respectively. Participants with no tertiary education were less likely to have 80/80 PEG-IFN adherence (AOR 0.29, p=0.045). IDU prior to or during treatment did not impact 80/80 PEG-IFN adherence. SVR was higher among those patients with ≥80/80 PEG-IFN adherence (67% vs. 35%, p=0.007), but similar among those with and without missed doses during therapy (73% vs. 60%, p=0.309). SVR in those patients discontinuing therapy between 0-4, 5-19, 20-23, and 24 weeks was 9%, 33%, 43%, and 76%, respectively (p<0.001). High adherence to treatment for recent HCV was observed, irrespective of IDU prior to, or during, therapy. Sub-optimal PEG-IFN exposure was mainly driven by early treatment discontinuation rather than missed doses during therapy. Grebely J, Matthews GV, Hellard M, Shaw D, van Beek I, Petoumenos K, Alavi M, Yeung B, Haber PS, Lloyd AR, Kaldor JM, Dore GJ; ATAHC Study Group. Adherence to treatment for recently acquired hepatitis C virus (HCV) infection among injecting drug users. J Hepatol. 2011 Jul; 55(1): 76-85. Epub 2010 Nov 23.

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, they 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. International Journal of Drug Policy, January 2012; 23(1): 54-61.

Tuberculosis Among Participants in an Academic Global Health Medical Exchange Program Although individuals from low tuberculosis (TB) burden countries experience an increased risk of TB infection when traveling to high burden countries for medical training or service, the degree of risk has not been well quantified. Improved knowledge will aid development of guidelines for TB screening, pre/post-travel education, and risk reduction. A retrospective survey including questions on demographic characteristics, pre-travel TB counseling, in-country activities, and post-travel TB testing was conducted. Six hundred eight individuals who traveled to Eldoret, Kenya with the Academic Model Providing Access to Healthcare (AMPATH) medical exchange program between July 2004 and June 2009 were invited to complete an online survey in January 2010 were assessed. The percentage of participants with a tuberculin skin test (TST) conversion and percentage reporting pre-travel and post-travel counseling and testing for TB were examined. Four hundred thirteen out of 608 (68%) responded with sufficient information to be included in the analysis. Two hundred thirty-nine individuals (58%) reported that TB prevention was discussed in pre-travel preparations. One hundred thirteen (27%) of the survey participants reported "ideal" care [definition: pre-travel TST (within 1 year of travel), pre-travel counseling, and a post-travel TST specifically related to their travel]. Out of 267 participants at risk for TST conversion, 11 (4.1%; 95% CI: 2.2-7.3) had a conversion. TST conversion was not associated with longer duration of stay or participation in direct medical care. Travelers to TB-endemic areas with international medical exchange programs are at risk for TB infection, regardless of their length of stay or whether or not they participate in direct medical care. Many receive inadequate pre- and post-travel TB counseling and testing. Efforts should be made to improve TB education for program participants. Gardner A, Cohen T, Carter EJ. Tuberculosis among participants in an academic global health medical exchange program. J Gen Intern Med. 2011 Aug; 26(8): 841-845. Epub 2011 Feb 26.

Rifampin, but not Rifabutin, May Produce Opiate Withdrawal in Buprenorphine-maintained Patients This series of studies examines the pharmacokinetic/ pharmacodynamic interactions between buprenorphine, an opioid partial agonist increasingly used in treatment of opioid dependence, and rifampin, a medication used as a first line treatment for tuberculosis; or rifabutin, an alternative antituberculosis medication. Opioid-dependent individuals on stable doses of buprenorphine/naloxone underwent two, 24-h blood sampling studies: (1) for buprenorphine pharmacokinetics and (2) following 15 days of rifampin 600 mg daily or rifabutin 300 mg daily for buprenorphine and rifampin or rifabutin pharmacokinetics. Rifampin administration produced significant reduction in plasma buprenorphine concentrations (70% reduction in mean area under the curve (AUC); p=<0.001) and onset of opiate withdrawal symptoms in 50% of participants (p=0.02). While rifabutin administration to buprenorphine-

maintained subjects resulted in a significant decrease in buprenorphine plasma concentrations (35% decrease in AUC; $p<0.001$) no opiate withdrawal was seen. Compared with historical control data, buprenorphine had no significant effect on rifampin pharmacokinetics, but was associated with 22% lower rifabutin mean AUC ($p=0.009$), although rifabutin and its active metabolite concentrations remained in the therapeutic range. Rifampin is a more potent inducer of buprenorphine metabolism than rifabutin with pharmacokinetic and pharmacodynamic adverse consequences. Those patients requiring rifampin treatment for tuberculosis and receiving buprenorphine therapy are likely to require an increase in buprenorphine dose to prevent withdrawal symptoms. Rifabutin administration was associated with decreases in buprenorphine plasma concentrations, but no clinically significant adverse events were observed. McCance-Katz EF, Moody DE, Prathikanti S, Friedland G, Rainey PM. Rifampin, but not rifabutin, may produce opiate withdrawal in buprenorphine-maintained patients. Drug Alcohol Depend. 2011 Nov 1; 118(2-3): 326-334. Epub 2011 May 19.

Gender Differences in Pharmacokinetics of Maintenance Dosed Buprenorphine Gender differences are known to occur in the pharmacokinetics of many drugs. Mechanisms may include differences in body composition, body weight, cardiac output, hormonal status, and use of different co-medications. Recently subtle gender-dependent differences in cytochrome P450 (CYP) 3A-dependent metabolism have been demonstrated. Buprenorphine N-dealkylation to norbuprenorphine is primarily performed by CYP3A. The authors therefore asked whether gender-dependent differences occur in the pharmacokinetics of buprenorphine. A retrospective examination was made of control (buprenorphine/naloxone-only) sessions from a number of drug interaction studies between buprenorphine and antiretroviral drugs. Twenty males and eleven females were identified who had a negative cocaine urine test prior to participation in the control session and were all on the same maintenance dose (16/4 mg) of sublingual buprenorphine/naloxone. Pharmacokinetic data from their control sessions (buprenorphine/ naloxone only) were sorted by gender and compared using the two-sample t-test. Females had significantly higher area under the plasma concentration curve (AUC) and maximum plasma concentrations for buprenorphine, norbuprenorphine and norbuprenorphine-3-glucuronide. AUCs relative to dose per body weight and surface area were significantly higher for only norbuprenorphine. AUCs relative to lean body mass were, however, not significantly different. Gender-related differences exist in the pharmacokinetics of buprenorphine; differences in body composition appear to have a major impact; differences in CYPA-dependent metabolism may also contribute. Moody DE, Fang WB, Morrison J, McCance-Katz E. Gender differences in pharmacokinetics of maintenance dosed buprenorphine. Drug Alcohol Depend. 2011 Nov 1; 118(2-3): 479-483. Epub 2011 Apr 23.

Effects of Alcohol on Histone Deacetylase 2 (HDAC2) and the Neuroprotective Role of Trichostatin A (TSA) Previous studies have implicated histone deacetylases (HDACs) and HDAC inhibitors (HDIs) such as trichostatin A (TSA) in the regulation of gene expression during drug addiction. Furthermore, an increase in HDAC activity has been linked to neurodegeneration. Alcohol has also been shown to promote abundant generation of reactive oxygen species (ROS) resulting in oxidative stress. TSA inhibits HDACs and has been shown to be neuroprotective in other neurodegenerative disease models. Although HDACs and HDIs have been associated with drug addiction, there is no evidence of the neurodegenerative role of HDAC2 and neuroprotective role of TSA in alcohol addiction. Therefore, the authors hypothesize that alcohol modulates HDAC2 through mechanisms involving oxidative stress. To test their hypothesis, the human neuronal cell line, SK-N-MC, was treated with different

concentrations of ethanol (EtOH); HDAC2 gene and protein expression were assessed at different time points. Pharmacological inhibition of HDAC2 with TSA was evaluated at the gene level using qRT-PCR and at the protein level using Western blot and flow cytometry. ROS production was measured with a fluorescence microplate reader and fluorescence microscopy. The results showed a dose-dependent increase in HDAC2 expression with EtOH treatment. Additionally, alcohol significantly induced ROS, and pharmacological inhibition of HDAC2 with TSA was shown to be neuroprotective by significantly inhibiting HDAC2 and ROS. These results suggest that EtOH can upregulate HDAC2 through mechanisms involving oxidative stress and HDACs may play an important role in alcohol use disorders (AUDs). Moreover, the use of HDIs may be of therapeutic significance for the treatment of neurodegenerative disorders including AUDs. Agudelo M, Gandhi N, Saiyed Z, Pichili V, Thangavel S, Khatavkar P, Yndart-Arias A, Nair M. Effects of alcohol on histone deacetylase 2 (HDAC2) and the neuroprotective role of trichostatin A (TSA). Alcohol Clin Exp Res. 2011 Aug; 35(8): 1550-1556.

Risk Factors for Illicit Anabolic-Androgenic Steroid Use in Male Weightlifters: A Cross-Sectional Cohort Study Illicit anabolic-androgenic steroid (AAS) abuse, though an important public health problem, remains inadequately studied. Almost all AAS abusers are male and lift weights, but the risk factors for AAS use among male weightlifters remain poorly understood. 233 experienced male weightlifters were recruited, of whom 102 (44%) reported lifetime AAS use, and assessed their childhood and adolescent attributes retrospectively, using structured clinical interviews and computerized questionnaires. This cross-sectional cohort approach-a design that they have formally presented in the recent methodological literature-utilizes a study cohort, not selected for outcomes of interest, and assesses exposures and outcomes retrospectively. The authors hypothesized that conduct disorder and body-image concerns would be major risk factors for subsequent AAS use among male weightlifters. Within this study population, many attributes showed little association with AAS use, but conduct disorder and body-image concerns showed strong associations. For individuals with prior conduct disorder versus those without, the hazard ratio (95% confidence interval) for subsequent AAS use was 2.2 (1.5, 3.4). For individuals in the middle versus lowest tertile of scores on a retrospective adolescent muscle-dysmorphia scale, the hazard ratio was 1.5 (.84, 2.6); for the highest versus lowest tertile, the hazard ratio was 3.3 (2.0, 5.3); and for the linear trend of hazard ratios, $p < .001$. Conduct disorder and body-image concerns represent important risk factors for AAS use among male weightlifters. Thus, assessment of these attributes may help to identify individuals most likely to require interventions to discourage this form of substance abuse. Pope HG Jr, Kanayama G, Hudson JI. Risk Factors for Illicit Anabolic-Androgenic Steroid Use in Male Weightlifters: A Cross-Sectional Cohort Study. Biol Psychiatry. 2011 Aug 10. [Epub ahead of print].

SERVICES RESEARCH

Delivery of Smoking Cessation Counseling in Substance Abuse Treatment Research on the uptake of smoking cessation counseling within substance abuse treatment organizations is limited. This study examines associations among counselors' delivery of therapy sessions dedicated to smoking cessation, organizational factors, and counselor-level variables. A two-level hierarchical linear model including organization- and counselor-level variables was estimated using survey data collected from 1,794 counselors working in 359 treatment organizations. Overall provision of smoking cessation counseling was low. In the final model, service delivery was positively associated with counselors' knowledge of the Public Health Service's clinical practice guideline, perceived managerial support, and belief that smoking cessation had a positive impact on recovery. Private versus public funding and presence of a formal smoking cessation program were organization-level variables which interacted with these counselor-level effects. These results highlight the importance of organizational contexts as well as counselors' knowledge and attitudes for meaningful adoption of smoking cessation counseling in substance abuse treatment organizations. Knudsen HK, Studts CR, Studts JL. The implementation of smoking cessation counseling in substance abuse treatment. J Behav Health Serv Res. 2011, (epub ahead of print.

Continuing Care and Long-Term Substance Use Outcomes In Managed Care: Early Evidence For A Primary Care-Based Model How best to provide ongoing services to patients with substance use disorders to sustain long-term recovery is a significant clinical and policy question that has not been adequately addressed. Analyzing nine years of prospective data for 991 adults who entered substance abuse treatment in a private, nonprofit managed care health plan, this study aimed to examine the components of a continuing care model (primary care, specialty substance abuse treatment, and psychiatric services) and their combined effect on outcomes over nine years after treatment entry. In a longitudinal observational study, follow-up measures included self-reported alcohol and drug use, Addiction Severity Index scores, and service utilization data extracted from the health plan databases. Remission, defined as abstinence or nonproblematic use, was the outcome measure. A mixed-effects logistic random intercept model controlling for time and other covariates found that yearly primary care, and specialty care based on need as measured at the prior time point, were positively associated with remission over time. Persons receiving continuing care (defined as having yearly primary care and specialty substance abuse treatment and psychiatric services when needed) had twice the odds of achieving remission at follow-ups ($p<.001$) as those without. Continuing care that included both primary care and specialty care management to support ongoing monitoring, self-care, and treatment as needed was important for long-term recovery of patients with substance use disorders. (Psychiatric Services 62:1194-1200, 2011). Chi F, Parthasarathy S, Mertens J, Weisner C. Continuing care and long-term substance use outcomes in managed care: early evidence for a primary care-based model. Psychiatr Serv. 2011; 62 (10): 1194-1200.

Clinical Correlates Of Health-Related Quality Of Life Among Opioid-Dependent Patients Previous work suggests that opioid users have lower health-related quality of life (HRQOL) than patients with more prevalent chronic illnesses such as hypertension or diabetes. Although comparisons with population norms are informative, studies of the correlates of HRQOL for opioid users are needed to plan clinical services. The authors tested a conceptual model of the pathways between physiologic factors and symptoms in relation to HRQOL among 344 opioid users in a clinical trial. Physical and mental HRQOL were measured by the Short-Form (SF)-36;

withdrawal signs, symptoms, and functioning were also measured with validated instruments. Using structural equation modeling, they tested hypotheses that medical history directly predicts withdrawal signs and symptoms, and that medical history, withdrawal signs and symptoms, and functioning predict the physical and mental HRQOL latent variables of the SF-36. Most hypothesized relationships were significant, and model fit was good. The model explained 36% of the variance in mental HRQOL and 34% of the variance in physical HRQOL. The conceptual framework appears valid for explaining variation in the physical and mental HRQOL of opioid users undergoing medically managed withdrawal. Analysis of longitudinal data would help to evaluate more rigorously the adequacy of the model for explaining HRQOL in opioid withdrawal. Heslin K, Stein J, Heinzerling K, Pan D, Magladry C, Hays R. Clinical correlates of health-related quality of life among opioid-dependent patients. Qual Life Res. 2011; 20 (8): 1205-1213.

Basic Subsistence Needs and Overall Health Among Human Immunodeficiency Virus-Infected Homeless and Unstably Housed Women Some gender differences in the progression of human immunodeficiency virus (HIV) infection have been attributed to delayed treatment among women and the social context of poverty. Recent economic difficulties have led to multiple service cuts, highlighting the need to identify factors with the most influence on health in order to prioritize scarce resources. The aim of this study was to empirically rank factors that longitudinally impact the health status of HIV-infected homeless and unstably housed women. Study participants were recruited between 2002 and 2008 from community-based venues in San Francisco, California, and followed over time; marginal structural models and targeted variable importance were used to rank factors by their influence. In adjusted analysis, the factor with the strongest effect on overall mental health was unmet subsistence needs (i.e., food, hygiene, and shelter needs), followed by poor adherence to antiretroviral therapy, not having a close friend, and the use of crack cocaine. Factors with the strongest effects on physical health and gynecologic symptoms followed similar patterns. Within this population, an inability to meet basic subsistence needs has at least as much of an effect on overall health as adherence to antiretroviral therapy, suggesting that advances in HIV medicine will not fully benefit indigent women until their subsistence needs are met. Riley E, Moore K, Sorensen J, Tulsky J, Bangsberg D, Neilands T. Basic subsistence needs and overall health among human immunodeficiency virus-infected homeless and unstably housed women. Am J Epidemiol. 2011; 174 (5): 515-522.

Opioid Overdose Prevention and Naloxone Distribution In Rhode Island Opioid overdose is a major public health concern that affects a diverse group of individuals across all categories of race, class, and geography. Overdose is the leading cause of adult accidental death in Rhode Island, making this state one of only 16 where overdose mortality exceeds that of motor vehicle accidents. Drug-related deaths, of which overdose is the largest component, claimed the lives of 193 Rhode Islanders in 2008. Opioid overdose (OD) occurs when opioids bind receptors in the brain stem, diminishing sensitivity to carbon dioxide and ultimately resulting in respiratory failure. Naloxone Hydrochloride (brand name Narcan®) is an opioid antagonist capable of reversing overdose due to opioids, such as heroin or prescription opioids. Naloxone has no potential for abuse; its only major contraindication, allergic reaction to prior administration, is rare. For more than three decades, emergency medical personnel have administered naloxone as a standard pre-hospital treatment for opioid overdose. Naloxone has been available, by prescription, to at-risk drug users and their family/friends since 1999 through select programs across the country. A common argument against the provision of naloxone to at-risk injection drug users (IDUs) is that the availability of naloxone will increase their risk behavior. To the

contrary, Seal *et al.* observed a decline in heroin use in participants enrolled in their naloxone (and resuscitation) intervention in San Francisco, with a simultaneous increase in overdose prevention knowledge. In two different studies of drug users in Rhode Island, the majority expressed a willingness to administer naloxone to a peer in the event of an overdose. Evaluations of naloxone interventions in major US cities, including San Francisco, Baltimore, Chicago, and New York, have found a notable increase in overdose knowledge among drug users trained in opioid OD recognition and response, dissemination of this knowledge through peer networks, and successful usage of naloxone by study participants Massachusetts instituted a statewide pilot OD prevention program in late 2007, which is operated by the Department of Public Health (DPH). The DPH purchases naloxone and distributes it to training centers, monitors the program, and tracks participant enrollment and naloxone use. The medical director has issued a standing order that allows non-medical personnel to distribute naloxone to trained lay responders in the community without a prescription. In Wilkes County, North Carolina, Project Lazarus began distributing naloxone through physicians in 2010, in collaboration with the state Medical Board. Naloxone is prescribed and distributed by physicians when patients with documented risk factors for overdose are prescribed opioid medications. Yokell M, Green T, Bowman S, McKenzie M, Rich J. Opioid overdose prevention and naloxone distribution in rhode island. Med Health R I. 2011; 94 (8): 240-242.

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. Springer S, Spaulding A, Meyer J, Altice F. Public health implications for adequate transitional care for hiv-infected prisoners: five essential components. Clin Infect Dis. 2011; 53 (5): 469-479.

Mental Health Of Victims Of Intimate Partner Violence: Results From A National Epidemiologic Survey This study assessed the national incidence and mental health correlates of recent intimate partner violence among adults interviewed by the wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. Data were collected about minor and severe forms of intimate partner violence among adults who reported being married, recently married, or in a romantic relationship in the past 12 months (N=25,626). A total of 1,608 individuals reported being victims of intimate partner violence, including 5.8% of men and 5.6% of women. New onset of axis I disorders was significantly more common among victims of intimate partner violence than among nonvictims (22.5% and 9.7%, respectively; OR=2.6) and was related to frequency of violent acts. Intimate partner violence is common, and victimization, especially if recurrent, markedly increases the risk for developing several psychiatric disorders.

Okuda M, Olfson M, Hasin D, Grant B, Lin K, Blanco C. Mental health of victims of intimate partner violence: results from a national epidemiologic survey. Psychiatr Serv. 2011; 62 (8): 959-962.

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. Weimer M, Korthuis P, Behonick G, Wunsch M. The source of methadone in overdose deaths in western virginia in 2004. J Addict Med. 2011; 5 (3): 188-202.

HIV Rapid Testing In Substance Abuse Treatment: Implementation Following A Clinical Trial The Substance Abuse Mental Health Services Administration has promoted HIV testing and counseling as an evidence-based practice. Nevertheless, adoption of HIV testing in substance abuse treatment programs has been slow. This article describes the experience of a substance abuse treatment agency where, following participation in a clinical trial, the agency implemented an HIV testing and counseling program. During the trial, a post-trial pilot, and early implementation the agency identified challenges and developed strategies to overcome barriers to adoption of the intervention. Their experience may be instructive for other treatment providers seeking to implement an HIV testing program. Lessons learned encompassed the observed acceptability of testing and counseling to clients, the importance of a "champion" and staff buy-in, the necessity of multiple levels of community and agency support and collaboration, the ability to streamline staff training, the need for a clear chain of command, the need to develop program specific strategies, and the requirement for sufficient funding. An examination of costs indicated that some staff time may not be adequately reimbursed by funding sources for activities such as adapting the intervention, start-up training, ongoing supervision and quality assurance, and overhead costs. Haynes L, Korte J, Holmes B, Gooden L, Matheson T, Feaster D, Leff J, Wilson L, Metsch L, Schackman B. HIV rapid testing in substance abuse treatment: implementation following a clinical trial. Eval Program Plann. 2011; 34 (4): 399-406.

Acculturation Among Mexican-Heritage Preadolescents: A Latent Class Analysis This study applies advanced conceptualization and measurement to an analysis of acculturation among 1,632 Mexican-heritage preadolescents. The authors assessed whether - and how - multiple measures combine to form a latent acculturation construct that groups individuals into classes; and determine how many and what classes (or types) of acculturation are experienced by this sample of 5(th) graders. Measures included attitudinal, behavioral, and linguistic

acculturation, generation status, time in the U.S., ethnic identification, and contact with the culture of origin. The analysis identified five classes of acculturation, differing in size and characterized by specific measures of acculturation: less acculturated, moderately bicultural, strongly bicultural, highly acculturated, and marginalized. Although most youths fell into the first four classes, consonant with their exposure to American society, a small minority of youths fell into the last class. Despite substantial exposure to U.S. culture and recent exposure to Mexican culture, these youth showed little affinity for either culture. Nieri T, Lee C, Kulis S, Marsiglia F. Acculturation among mexican-heritage preadolescents: a latent class analysis. Soc Sci Res. 2011; 40 (4): 1236-1248.

Epidemiology Of Chronic and Nonchronic Major Depressive Disorder: Results From The National Epidemiologic Survey On Alcohol And Related Conditions Burden related to major depressive disorder (MDD) derives mostly from long-term occurrence of symptoms. This study aims to examine the prevalence, sociodemographic correlates, patterns of 12-month and lifetime psychiatric comorbidity, lifetime risk factors, psychosocial functioning, and mental health service utilization of chronic major depressive disorder (CMDD) compared to nonchronic major depressive disorder. Face-to-face interviews were conducted in the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (n = 43,093). The 12-month and lifetime prevalence of CMDD within the population meeting criteria for MDD was 26.5% and 24.0%, respectively. Individuals reporting a chronic course of MDD were socioeconomically and educationally disadvantaged, tended to be older, report loss of spouse or history of divorce, live in rural areas, have public assistance, low self-esteem, worse overall health and more likely to report comorbidities, most importantly dysthymia, generalized anxiety disorder, avoidant, and dependant personality disorder. Individuals with chronic MDD were more likely to report familial but not childhood onset risk factors for MDD. Those suffering CMDD were more likely to seek and receive mental health care than other forms of MDD, even though it took longer to start treatment. Chronic course of MDD is related to still worse socioeconomic conditions, educational achievement, more comorbidities, and family risk factors, although other courses of MDD carried greater risk of unmet treatment. Rubio J, Markowitz J, Alegría A, Pérez-Fuentes G, Liu S, Lin K, Blanco C. Epidemiology of chronic and nonchronic major depressive disorder: results from the National Epidemiologic Survey On Alcohol And Related Conditions. Depress Anxiety. 2011; 28 (8): 622-631.

Estimating Risk For Suicide Attempt: Are We Asking The Right Questions? Passive Suicidal Ideation As A Marker For Suicidal Behavior Desire for death is not generally considered a harbinger of more severe suicidal behavior and is not routinely included in suicide research and assessment interviews. The authors aimed to compare desire for death and suicidal ideation as clinical markers for suicide attempts. Using data from two nationally representative surveys (n=42,862 and n=43,093 respectively), they examined whether desire for death predicts suicide attempts. They compared the odds ratio (OR) and "Number Needed to be Exposed for one additional person to be Harmed" [NNEH] for lifetime suicide attempts among those with desire for death but no suicidal ideation; those with suicidal ideation but no desire for death, and those with both desire for death and suicidal ideation, compared to those with neither desire for death nor suicidal ideation. The risk for lifetime suicide attempt was similar among those with lifetime desire for death with no suicidal ideation and those with lifetime suicidal ideation with no desire for death. Respondents with both lifetime desire for death and suicidal ideation had the highest risk for lifetime suicide attempts. Limitations: Cross-sectional design and self-reported suicidal ideation/attempts are viewed as limitations of this study. Querying individuals on desire

for death has the same value as assessing suicidal ideation to examine risk for suicide attempt. A combination of desire for death and suicidal ideation is the best predictor for suicide attempts. This is of high clinical relevance since we suggest that desire for death should be included as a potential clinical marker of suicidality in clinical assessments. Baca-Garcia E, Perez-Rodriguez M, Oquendo M, Keyes K, Hasin D, Grant B, Blanco C. Estimating risk for suicide attempt: are we asking the right questions? passive suicidal ideation as a marker for suicidal behavior. J Affect Disord. 2011; 134 (1-3): 327-332.

Organizational Characteristics That Foster Early Adoption Of Cultural And Linguistic Competence In Outpatient Substance Abuse Treatment In The United States 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 E. 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 (1): 9-15.

Profiles of Systems Involvement in a Sample of High-Risk Urban Adolescents with Unmet Treatment Needs This study examined profiles of involvement in four systems (education, child welfare, legal, and treatment) in a sample of 253 high-risk urban adolescents with unmet behavioral health needs. Self-report data were collected on multiple dimensions of involvement within each system, demographics, and DSM-IV diagnoses. Latent class analysis revealed four profiles: Education System: Academic and Disciplinary, Education System: Academic Only, Legal/Juvenile Justice Involved, and Multiple Systems/Child Welfare. Profiles differed based on gender and psychiatric diagnoses. Boys were overrepresented in Education System: Academic and Disciplinary and Legal/Juvenile Justice Involved, and girls were overrepresented in Multiple Systems/Child Welfare. The two education system focused classes were characterized by depressive disorders and ADHD. Youth in Legal/Juvenile Justice Involved and Multiple Systems/Child Welfare were characterized by conduct disorder and substance abuse. Implications for assessment and treatment planning for high-risk youth and for the organization of community-based behavioral health services are discussed. Dauber S, Hogue A. Profiles of systems involvement in a sample of high-risk urban adolescents with unmet treatment needs. Child Youth Serv Rev. 2011; 33 (10): 2018-2026.

The Influence of Rural and Urban Substance Abuse Treatment Counselor Characteristics on Client Outcomes Focus group data was collected from 28 substance abuse treatment counselors employed in rural and urban areas to examine their perceptions of factors influencing treatment outcomes. The influence of the counselor characteristics (i.e., education, experience, and recovery status) on client outcomes and geographic differences are explored. Focus group data was analyzed by three raters using line-by-line coding, focused coding, and memoing. This

analytic approach revealed geographic differences in the counselors' perceptions of the effect of counselor education, experience, and recovery status on client outcomes. Recommendations for treatment planning and future research are provided. Oser C, Biebel E, Pullen E, Harp K. The Influence of rural and urban substance abuse treatment counselor characteristics on client outcomes. J Soc Serv Res. 2011; 37 (4): 390-402.

Alcohol Use and Popularity: Social Payoffs from Conforming to Peers' Behavior Although many economic analyses of adolescents have examined the costs of risky behaviors, few have investigated the gains that young people derive from such actions, particularly in terms of social payoffs for complying with peer behavior. This paper studies the relationship between adolescents' use of alcohol (relative to that of their peers) and popularity at school. The authors use data from the National Longitudinal Study of Adolescent Health, a rich and nationally-representative survey with detailed information on social networks. Their findings suggest that adolescents are socially rewarded for conforming to their peers' alcohol use and penalized (to a lesser degree) for increasing their consumption above that of their peers. Male adolescents are rewarded for keeping up with their peers' drinking and for getting drunk. Female adolescents are rewarded for drinking per se, but not necessarily for keeping up with their peers. The results offer new information on peer influence and have implications for substance abuse interventions at school and in the community. Balsa A, Homer J, French M, Norton E. Alcohol use and popularity: social payoffs from conforming to peers' behavior. J Res Adolesc. 2011; 21 (3): 559-568.

Generalized Full-Information Item Bifactor Analysis Full-information item bifactor analysis is an important statistical method in psychological and educational measurement. Current methods are limited to single-group analysis and inflexible in the types of item response models supported. The authors propose a flexible multiple-group item bifactor analysis framework that supports a variety of multidimensional item response theory models for an arbitrary mixing of dichotomous, ordinal, and nominal items. The extended item bifactor model also enables the estimation of latent variable means and variances when data from more than 1 group are present. Generalized user-defined parameter restrictions are permitted within or across groups. The authors derive an efficient full-information maximum marginal likelihood estimator. Their estimation method achieves substantial computational savings by extending Gibbons and Hedeker's (1992) bifactor dimension reduction method so that the optimization of the marginal log-likelihood requires only 2-dimensional integration regardless of the dimensionality of the latent variables. The authors use simulation studies to demonstrate the flexibility and accuracy of the proposed methods. They apply the model to study cross-country differences, including differential item functioning, using data from a large international education survey on mathematics literacy. Cai L, Yang J, Hansen M. Generalized full-information item bifactor analysis. Psychol Methods. 2011; 16 (3): 221-248.

Parental Monitoring During Early Adolescence Deters Adolescent Sexual Initiation: Discrete-Time Survival Mixture Analysis The authors used discrete-time survival mixture modeling to examine 5,305 adolescents from the 1997 National Longitudinal Survey of Youth regarding the impact of parental monitoring during early adolescence (ages 14-16) on initiation of sexual intercourse and problem behavior engagement (ages 14-23). Four distinctive parental-monitoring groups were identified and labeled as "High," "Increasing," "Decreasing," and "Low". About 68% of adolescents received a high level of parental monitoring from ages 14 to 16 (High), 6 and 9% respectively exhibited an accelerated (Increasing) and a decelerated

trajectory (Decreasing), and 17% had consistently low parental monitoring (Low). Relative to participants in the Low group, adolescents in the High group delayed sexual initiation by 1.5 years. Males, relative to females, were more likely to have had a low trajectory of parental monitoring, and were more likely to initiate sexual intercourse before age 14. In contrast to White Adolescents, Hispanics and Blacks were less likely to receive High parental monitoring, and had a higher rate of early sexual initiation before age 14. The study demonstrates the temporal relationship of parental monitoring with adolescent sexual initiation from a longitudinal perspective. An increase of parental monitoring across ages is accompanied with a decrease of sexual risk. The continual high level of parental monitoring from ages 14 to 16 also mitigated the risk of engagement in substance use and delinquent behaviors from ages 14 to 23. Huang D, Murphy D, Hser Y. Parental Monitoring During early adolescence deters adolescent sexual initiation: discrete-time survival mixture analysis. J Child Fam Stud. 2011; 20 (4): 511-520.

Employment Trajectories: Exploring Gender Differences and Impacts of Drug Use This study investigated the impact of drug use on employment over 20 years among men and women, utilizing data on 7,661 participants in the National Longitudinal Survey of Youth. Growth mixture modeling was applied, and five distinct employment trajectory groups were identified for both men and women. The identified patterns were largely similar for men and women except that a U-shape employment trajectory was uniquely identified for women. Early-initiation drug users, users of "hard" drugs, and frequent drug users were more likely to demonstrate consistently low levels of employment, and the negative relationship between drug use and employment was more apparent among men than women. Also, positive associations between employment and marriage became more salient for men over time, as did negative associations between employment and childrearing among women. Processes are dynamic and complex, suggesting that throughout the life course, protective factors that reduce the risk of employment problems emerge and change, as do critical periods for maximizing the impact of drug prevention and intervention efforts. Huang D, Evans E, Hara M, Weiss R, Hser Y. Employment trajectories: exploring gender differences and impacts of drug use. J Vocat Behav. 2011; 79 (1): 277-289.

A Longitudinal Investigation Of The Predictability Of The Three-Factor Model Of The Important People Inventory Because of psychometric limitations and varied adaptations of the Important People Inventory (IP; a measure of alcohol social support), Groh et al. performed factor analyses and created a three-factor model (i.e., Support for Drinking from Network Members, Drinking Behaviors of Network Members, and General Social Support). The present study examined the ability of the three-factor model to predict alcohol use. This study consisted of 293 women and 604 men who were US residents of a network of self-run recovery homes known as Oxford House (OH). Logistic regression models were run. The first model examined which of the three IP factors was the best predictor of alcohol use over a 4-month period; next, models compared Drinking Behaviors of Network Members (the three-factor model) and Network Support for Drinking from Network Members (the original two-factor model) as predictors of 4-month alcohol use. Of the three factors measuring general support, network drinking behaviors, and support for drinking, Drinking Behaviors of Network Members was the only significant predictor of alcohol use over a 4-month period. Additionally, this component was a better predictor of drinking than the Support for Drinking from Network Members summary score from the original model. Compared to the original model, this new three-factor model of the IP is shorter, has stronger internal reliability, and is a better predictor of alcohol use over time. It is strongly recommended that researchers continue to explore the utility of this new

model. Groh D, Jason L, Ferrari J, Halpert J. A longitudinal investigation of the predictability of the three-factor model of the important people inventory. Am J Drug Alcohol Abuse. 2011; 37 (4): 259-263.

Assessing Jail Inmates' Proneness to Shame and Guilt: Feeling Bad About the Behavior or the Self? This study of 550 jail inmates (379 male and 171 female) held on felony charges examines the reliability and validity of the Test of Self Conscious Affect -Socially Deviant Version (TOSCA-SD; Hanson & Tangney, 1996) as a measure of offenders' proneness to shame and proneness to guilt. Discriminant validity (e.g., vis-à-vis self-esteem, negative affect, social desirability/impression management) and convergent validity (e.g., vis-à-vis correlations with empathy, externalization of blame, anger, psychological symptoms, and substance use problems) was supported, paralleling results from community samples. Further, proneness to shame and guilt were differentially related to widely used risk measures from the field of criminal justice (e.g., criminal history, psychopathy, violence risk, antisocial personality). Guilt-proneness appears to be a protective factor, whereas there was no evidence that shame-proneness serves an inhibitory function. Subsequent analyses indicate these findings generalize quite well across gender and race. Implications for intervention and sentencing practices are discussed. Tangney J, Stuewig J, Mashek D, Hastings M. Assessing jail inmates' proneness to shame and guilt: feeling bad about the behavior or the self?. Crim Justice Behav. 2011; 38 (7): 710-734.

Substance Use Disorder Among People With First-Episode Psychosis: A Systematic Review Of Course And Treatment People experiencing a first episode of psychosis frequently have co-occurring substance use disorders, usually involving alcohol and cannabis, which put them at risk for prolonged psychosis, psychotic relapse, and other adverse outcomes. Yet few studies of first-episode psychosis have addressed the course of substance use disorders and the response to specialized substance abuse treatments. The authors searched MEDLINE, PsycINFO, and other medical databases for English-language articles published between 1990 and 2009. Included studies addressed two research questions. First, do some clients become abstinent after a first episode of psychosis without specialized substance abuse treatments? Second, for clients who continue to use substances after a first episode of psychosis, does the addition of specialized substance abuse treatment enhance outcomes? Nine studies without specialized substance abuse treatment and five with specialized substance abuse treatment assessed the course of substance use (primarily cannabis and alcohol) after a first episode of psychosis. Many clients (approximately half) became abstinent or significantly reduced their alcohol and drug use after a first episode of psychosis. The few available studies of specialized substance abuse treatments did not find better rates of abstinence or reduction. Experience, education, treatment, or other factors led many clients to curtail their substance use disorders after a first episode of psychosis. Specialized interventions for others need to be developed and tested. Wisdom J, Manuel J, Drake R. Substance use disorder among people with first-episode psychosis: a systematic review of course and treatment. Psychiatr Serv. 2011; 62 (9): 1007-1012.

Public Managed Care and Service Access In Outpatient Substance Abuse Treatment Units The continued growth of public managed behavioral health care has raised concerns about possible effects on services provided. This study uses a national sample of outpatient substance abuse treatment units surveyed in 2005 to examine associations between public managed care and service access, measured as both the types of services provided and the amount of treatment received by clients. The percentage of clients funded through public managed care versus other types of public funding was positively associated with treatment units' odds of providing some

types of resource-intensive services and with the odds of providing transportation to clients, but was negatively associated with the average number of individual therapy sessions clients received over the course of treatment. In general, public managed care does not appear to restrict access to outpatient substance abuse treatment, although states should monitor these contracts to ensure clients receive adequate courses of individual treatment. Chuang E, Wells R, Alexander J. Public managed care and service access in outpatient substance abuse treatment units. J Behav Health Serv Res. 2011; 38 (4): 444-463.

Heterogeneity In The Composition Of Marijuana Seized In California Marijuana contains multiple cannabinoids. Most attention is given to delta-9-tetrahydrocannabinol (THC) which produces euphoria and in some cases anxiety and panic reactions. Research suggests that another cannabinoid, cannabidiol (CBD), may offset some of these effects. Thus, there is growing interest in the health consequences of the THC to CBD ratio for marijuana. Using data from over 5,000 marijuana samples in California from 1996 to 2008, the authors examine changes in the median THC-level, median CBD-level, and median THC:CBD-ratio. The median THC-level and median THC: CBD-ratio have dramatically increased for seizures in California, particularly north of the Mexican border. Research on the consequences of the THC: CBD ratio should continue, especially as more attention is devoted to thinking about how to regulate marijuana for medical and recreational use. Researchers should also consider the lack of uniformity in the chemical composition of marijuana when evaluating its health effects. Burgdorf J, Kilmer B, Pacula R. Heterogeneity in the composition of marijuana seized in california. Drug Alcohol Depend. 2011; 117 (1): 59-61.

Patterns Of Alcohol and Drug Use Among Depressed Older Adults Seeking Outpatient Psychiatric Services: Alcohol and drug use and related problems may compromise depression treatment, and older adults may be especially at risk for poor outcomes. However, alcohol and drug use among older adults have not been studied in settings in which depression treatment is provided. This study examined the prevalence and clinical and demographic correlates of alcohol and drug use and misuse of prescription drugs among adults with depression seeking outpatient psychiatric care (excluding chemical dependency treatment). The sample included 154 older adults (age 60 years and older who scored e10 on the Beck Depression Inventory-II [BDI-II] at intake). Participants also completed alcohol and drug use questions and the Short Michigan Alcohol Screening Test. Recent alcohol and drug use, heavy episodic drinking, and history of alcohol-related problems were common. Alcohol use in the prior 30 days was reported by 53% of men and 50% of women. Cannabis use in the prior 30 days was reported by 12% of men and 4% of women; and misuse of sedatives in the prior 30 days was reported by 16% of men and 9% of women. In exact logistic regression, higher BDI-II score was associated with cannabis use (odds ratio = 15.8, 95% confidence interval = 2.0-734.0, exactp = 0.003). Older adults with depression are likely to present for treatment with a range of concurrent alcohol and drug use patterns, including cannabis use and misuse of prescription medication. Clinicians should evaluate depressed patients for substance use and related problems and consider appropriate interventions. Satre D, Sterling S, Mackin R, Weisner C. Patterns of alcohol and drug use among depressed older adults seeking outpatient psychiatric services. Am J Geriatr Psychiatry. 2011; 19 (8): 695-703.

Organizational Correlates Of Service Availability In Outpatient Substance Abuse Treatment Programs In pursuit of quality care for drug abuse treatment programs, researchers continue to monitor program characteristics related to service provision. The current study examines 115 outpatient drug-free programs in four U.S. regions and documents typical methods of offering an array of services and the relationship between program characteristics and services offered onsite and by referral. Core services (e.g., comprehensive assessments) are offered primarily onsite, whereas delivery methods of wraparound services are mixed with transitional services offered generally onsite and medical services traditionally offered offsite. Accredited programs offered more core services onsite, while those providing case management offered more core and wraparound services onsite. Programs with a higher proportion of dually diagnosed clients offered more core services onsite and fewer wraparound services by referral. Programs with a higher concentration of criminal justice-referred clients offered fewer core services onsite. These findings suggest ways of improving access to services. Edwards J, Knight D, Flynn P. Organizational correlates of service availability in outpatient substance abuse treatment programs. J Behav Health Serv Res. 2011; 38 (4): 432-443.

Characteristics and Correlates Of Men and Women With Prescription Opioid Dependence Despite the fact that important gender differences in drug and alcohol use have been previously reported, little research to date has focused on gender differences with regard to nonmedical prescription opioid use. This study preliminarily examined the presenting characteristics and correlates (e.g., age of onset, route of administration, motives for using, and method of introduction) of men and women with prescription opioid dependence. Participants were 24 (12 men and 12 women) non-treatment seeking individuals at least 18 years of age with current (i.e., past 12 months) prescription opioid dependence who participated in an in-depth interview. The average age of onset of prescription opioid use was 22.2 years (SD=8.5). In comparison to men, women were approximately six years older when they initiated prescription opioid use, but were only three years older when they began to use prescription opioids regularly (i.e., weekly), suggesting an accelerated course of disease progression among women. Over half of the sample (61.5%) endorsed chewing and almost half (45.8%) endorsed crushing and snorting prescription opioids. Men were significantly more likely than women to crush and snort prescription opioids (75.0% vs. 16.7%; p=0.01). Women were significantly more likely than men to be motivated to use prescription opioids in order to cope with interpersonal stress, and to use them first thing in the morning (ps=0.04). Concomitant alcohol and other drug use were common among both men and women. The findings highlight clinically relevant gender differences and may help enhance the design of gender-sensitive screening and treatment interventions for prescription opioids. Back S, Lawson K, Singleton L, Brady K. Characteristics and correlates of men and women with prescription opioid dependence. Addict Behav. 2011; 36 (8): 829-834.

CTN-RELATED RESEARCH

Attention-Deficit/Hyperactivity Disorder Subtypes in Adolescents with Comorbid Substance-Use Disorder Little is known about the relationship between attention-deficit/hyperactivity disorder (ADHD) subtypes and substance-use disorder (SUD). As there is literature suggesting different subtype phenotypes, there may be subtype differences in regard to the risk for developing SUD and substance treatment response. The objectives of this study were to characterize the sample in a Clinical Trials Network (CTN) study according to ADHD subtypes and baseline psychosocial and substance-use characteristics and to compare subtypes on response to treatment. Secondary analyses were performed on data collected from adolescents (n = 276) diagnosed with ADHD and SUD (non-nicotine) and treated with stimulant medication or placebo and cognitive behavioral therapy (CBT) for substance use. Participants were characterized as inattentive or combined ADHD subtype and compared on baseline characteristics and treatment outcome. The combined subtype presented with more severe SUDs and higher rates of conduct disorder. There were a greater proportion of boys with inattentive subtype. The inattentive subtype appeared less ready for treatment (greater University of Rhode Island Change Assessment precontemplation scores) with poorer coping skills (poorer problem-solving and abstinence focused coping) at baseline. However, the two subtypes responded equally to treatment even after controlling for baseline differences. Findings from this large community sample indicate that there were no subtype differences in treatment response, although there were differences in terms of substance use, antisocial behavior, readiness for treatment, and gender prior to treatment. This study is the first to report on subtype differences for treatment response for non-nicotine SUD in a comorbid ADHD-SUD population. Despite some baseline differences, both subtypes responded equally to treatment, suggesting limited relevance for subtype designation on treatment planning. Tamm L, Adinoff B, Nakonezny PA, Winhusen T, Riggs P. Attention-deficit/hyperactivity disorder subtypes in adolescents with comorbid substance-use disorder. Am J Drug Alcohol Abuse. 2011 Aug 11. [Epub ahead of print].

Randomized Controlled Trial of Osmotic-Release Methylphenidate with Cognitive-Behavioral Therapy in Adolescents with Attention-Deficit/Hyperactivity Disorder and Substance Use Disorders The objectives of this study were to evaluate the efficacy and safety of osmotic-release methylphenidate (OROS-MPH) compared with placebo for attention-deficit/hyperactivity disorder (ADHD), and the impact on substance treatment outcomes in adolescents concurrently receiving cognitive-behavioral therapy (CBT) for substance use disorders (SUD). This was a 16-week, randomized, controlled, multi-site trial of OROS-MPH + CBT versus placebo + CBT in 303 adolescents (aged 13 through 18 years) meeting DSM-IV diagnostic criteria for ADHD and SUD. Primary outcome measures included the following: for ADHD, clinician-administered ADHD Rating Scale (ADHD-RS), adolescent informant; for substance use, adolescent-reported days of use in the past 28 days. Secondary outcome measures included parent ADHD-RS and weekly urine drug screens (UDS). There were no group differences on reduction in ADHD-RS scores (OROS-MPH: -19.2, 95% confidence interval [CI], -17.1 to -21.2; placebo, -21.2, 95% CI, -19.1 to -23.2) or reduction in days of substance use (OROS-MPH: -5.7 days, 95% CI, 4.0-7.4; placebo: -5.2 days, 95% CI, 3.5-7.0). Some secondary outcomes favored OROS-MPH, including lower parent ADHD-RS scores at 8 (mean difference = 4.4, 95% CI, 0.8-7.9) and 16 weeks (mean difference =6.9; 95% CI, 2.9-10.9) and more negative UDS in OROS-MPH (mean = 3.8) compared with placebo (mean = 2.8; p = .04). OROS-MPH did not show greater efficacy than placebo for ADHD or on reduction in substance

use in adolescents concurrently receiving individual CBT for co-occurring SUD. However, OROS-MPH was relatively well tolerated and was associated with modestly greater clinical improvement on some secondary ADHD and substance outcome measures. Riggs PD, Winhusen T, Davies RD, Leimberger JD, Mikulich-Gilbertson S, Klein C, Macdonald M, Lohman M, Bailey GL, Haynes L, Jaffee WB, Haminton N, Hodgkins C, Whitmore E, Trello-Rishel K, Tamm L, Acosta MC, Royer-Malvestuto C, Subramaniam G, Fishman M, Holmes BW, Kaye ME, Vargo MA, Woody GE, Nunes EV, Liu D. Randomized controlled trial of osmotic-release methylphenidate with cognitive-behavioral therapy in adolescents with attention-deficit/hyperactivity disorder and substance use disorders. J Am Acad Child Adolesc Psychiatry. 2011 Sep; 50(9): 903-914. Epub 2011 Aug 4.

Stimulant Reduction Intervention using Dosed Exercise (STRIDE) - CTN 0037: Study Protocol for a Randomized Controlled Trial There is a need for novel approaches to the treatment of stimulant abuse and dependence. Clinical data examining the use of exercise as a treatment for the abuse of nicotine, alcohol, and other substances suggest that exercise may be a beneficial treatment for stimulant abuse, with direct effects on decreased use and craving. In addition, exercise has the potential to improve other health domains that may be adversely affected by stimulant use or its treatment, such as sleep disturbance, cognitive function, mood, weight gain, quality of life, and anhedonia, since it has been shown to improve many of these domains in a number of other clinical disorders. Furthermore, neurobiological evidence provides plausible mechanisms by which exercise could positively affect treatment outcomes. The current manuscript presents the rationale, design considerations, and study design of the National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN) CTN-0037 Stimulant Reduction Intervention using Dosed Exercise (STRIDE) study. STRIDE is a multisite randomized clinical trial that compares exercise to health education as potential treatments for stimulant abuse or dependence. This study evaluated individuals diagnosed with stimulant abuse or dependence who are receiving treatment in a residential setting. Three hundred and thirty eligible and interested participants who provide informed consent were randomized to one of two treatment arms: Vigorous Intensity High Dose Exercise Augmentation (DEI) or Health Education Intervention Augmentation (HEI). Both groups will receive TAU (i.e., usual care). The treatment arms are structured such that the quantity of visits is similar to allow for equivalent contact between groups. In both arms, participants will begin with supervised sessions 3 times per week during the 12-week acute phase of the study. Supervised sessions will be conducted as one-on-one (i.e., individual) sessions, although other participants may be exercising at the same time. Following the 12-week acute phase, participants will begin a 6-month continuation phase during which time they will attend one weekly supervised DEI or HEI session. Trivedi MH, Greer TL, Grannemann BD, Church TS, Somoza E, Blair SN, Szapocznik J, Stoutenberg M, Rethorst C, Warden D, Ring KM, Walker R, Morris DW, Kosinski AS, Kyle T, Marcus B, Crowell B, Oden N, Nunes E. Stimulant Reduction Intervention using Dosed Exercise (STRIDE) - CTN 0037: study protocol for a randomized controlled trial. Trials. 2011 Sep 19; 12(1): 206.

Female Condom Skill and Attitude: Results from a NIDA Clinical Trials Network HIV Risk Reduction Study with Women in Substance Abuse Treatment The female condom is effective in reducing unprotected sexual acts; however, it remains underutilized in the United States. This study examined whether a five-session HIV prevention intervention (Safer Sex Skills Building [SSB]), including presentation, discussion, and practice with female condoms, improved female condom skills and attitude among women in outpatient substance abuse treatment. Mixed-effects modeling was used to test the effect of SSB on skills and attitude over

3- and 6-month posttreatment among 515 randomized women. SSB was significantly associated with increases in skills and attitude, and the female condom demonstration session was primarily responsible for skills improvement. Attitude was a partial mediator of the intervention effect in reducing unprotected sex. Findings emphasize the utility of integrating female condom messages targeting proximal behavioral outcomes into HIV prevention. The study supports the use of female condom skill instruction via brief, hands-on exercises, as well as further research to enhance attitudinal change to reduce sexual risk. Campbell, ANC, Tross S, Hu, MC, Pavlicova M, Kenney J; Nunes EV. Female condom skill and attitude: results from a NIDA Clinical Trials Network HIV risk reduction study with women in substance abuse treatment. AIDS Education and Prevention 2011; 23(4): 328-339.

Rationale and Methods for Site Selection for a Trial Using a Novel Intervention to Treat Stimulant Abuse Although the selection of appropriate clinical sites has a significant impact on the successful conduct of clinical trials, no generally accepted model is available for site selection. Use of an appropriate site selection process is even more pertinent when conducting large scale, practical clinical trials in practice settings. This report provides a rationale for selecting sites by identifying both a set of basic site selection criteria important to most trials as well as criteria specific to the features of a particular study's design. In this two-tier system, although all these criteria must be met, some criteria are firm and viewed as essential for a site to conduct the trial. Other criteria, such as those that support study recruitment or participant retention, are flexible. These flexible criteria may be addressed through several alternative solutions that meet the original intent of the criterion. The authors illustrate how the study specific features and requirements of Stimulant Reduction Intervention using Dosed Exercise (STRIDE), a multisite clinical trial evaluating the efficacy of exercise or health education, added to treatment as usual for stimulant abuse are linked to firm and flexible site selection criteria. The authors also present an iterative, multi-step approach to site selection including building awareness about the study and screening and evaluating sites using these criteria. This simple model could maximize the chance that selected sites will implement a study successfully and achieve trial aims. It may be helpful to researchers who are developing criteria and methods for site selection for specific clinical trials. Warden D, Trivedi MH, Greer TL, Nunes E, Grannemann BD, Horigian VE, Somoza E, Ring K, Kyle T, Szapocznik J. Rationale and methods for site selection for a trial using a novel intervention to treat stimulant abuse. Contemp Clin Trials. 2011 Sep 17. [Epub ahead of print].

Compensation Effects on Clinical Trial Data Collection in Opioid-dependent Young Adults Attrition in studies of substance use disorder treatment is problematic, potentially introducing bias into data analysis. This study aimed to determine the effect of participant compensation amounts on rates of missing data and observed rates of drug use. The authors performed a secondary analysis of a clinical trial of buprenorphine/naloxone among 152 treatment-seeking opioid-dependent subjects aged 15-21 during participation in a randomized trial. Subjects were randomized to a 2-week detoxification with buprenorphine/naloxone (DETOX; N = 78) or 12 weeks buprenorphine/naloxone (BUP; N = 74). Participants were compensated $5 for weekly urine drug screens and self-reported drug use information and $75 for more extensive assessments at weeks 4, 8, and 12. Though BUP assignment decreased the likelihood of missing data, there were significantly less missing data at 4, 8, and 12 weeks than other weeks, and the effect of compensation on the probability of urine screens being positive was more pronounced in DETOX subjects. These findings suggest that variations in the amount of compensation for completing assessments can differentially affect outcome measurements, depending on treatment

group assignment. Adequate financial compensation may minimize bias when treatment condition is associated with differential dropout and may be a cost-effective way to reduce attrition. Moreover, active users may be more likely than non-active users to drop out if compensation is inadequate, especially in control groups or in groups who are not receiving active treatment. Wilcox CE, Bogenschutz MP, Nakazawa M, Woody GE. Compensation effects on clinical trial data collection in opioid-dependent young adults. Am J Drug Alcohol Abuse. 2011 Sep 22. [Epub ahead of print].

The Substance Abuse Counseling Workforce: Education, Preparation, and Certification

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. Rieckmann T, Farentinos C, Tillotson CJ, Kocarnik J, McCarty D. The substance abuse counseling workforce: education, preparation, and certification. Subst Abus. 2011 Oct; 32(4): 180-190.

Subjective Effects, Misuse, and Adverse Effects of Osmotic-Release Methylphenidate Treatment in Adolescent Substance Abusers with Attention-Deficit/Hyperactivity Disorder

Psychostimulants are effective treatments for attention-deficit/hyperactivity disorder (ADHD) but may be associated with euphoric effects, misuse/diversion, and adverse effects. These risks are perceived by some clinicians to be greater in substance-abusing adolescents relative to non-substance-abusing adults. The present study evaluates the subjective effects, misuse/diversion, and adverse effects associated with the use of osmotic-release oral system methylphenidate (OROS-MPH), relative to placebo, for treating ADHD in adolescents with a substance use disorder (SUD) as a function of substance use severity and compared these risks with those associated with the treatment of ADHD in adults without a non-nicotine SUD. Datasets from two randomized placebo-controlled trials of OROS-MPH for treating ADHD, one conducted with 303 adolescents (13-18) with at least one non-nicotine SUD and one with 255 adult smokers (18-55), were analyzed. Outcome measures included the Massachusetts General Hospital Liking Scale, self-reported medication compliance, pill counts, and adverse events (AEs). Euphoric effects and misuse/diversion of OROS-MPH were not significantly affected by substance use severity. The euphoric effects of OROS-MPH did not significantly differ between the adolescent and adult samples. Adults rated OROS-MPH as more effective in treating ADHD, whereas adolescents reported feeling more depressed when taking OROS-MPH. The adolescents lost more pills relative to the adults regardless of treatment condition, which suggests the importance of careful medication monitoring. Higher baseline use of alcohol and cannabis was associated with an increased risk of experiencing a treatment-related AE in OROS-MPH, but baseline use did not increase the risk of serious AEs or of any particular category of AE and the adolescents did not experience more treatment-related AEs relative to the adults. Conclusions: With good monitoring, and in the context of substance abuse treatment, OROS-MPH can be safely used in adolescents with an SUD despite non-abstinence. Winhusen TM, Lewis DF, Riggs PD, Davies RD, Adler LA, Sonne S, Somoza EC. Subjective effects, misuse, and adverse effects of osmotic-

release methylphenidate treatment in adolescent substance abusers with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2011 Oct; 21(5): 455-463.

Design Considerations for a Study to Evaluate the Impact of Smoking Cessation Treatment on Stimulant Use Outcomes in Stimulant-dependent Individuals Cigarette smoking is prevalent in cocaine/methamphetamine-dependent patients and associated with significant morbidity and mortality, yet, the provision of smoking cessation treatment in conjunction with substance use disorder (SUD) treatment is not standard practice. This is due, in part, to clinician concern that combining smoking cessation treatment with SUD treatment could lead to poorer SUD outcomes. The NIDA Clinical Trials Network is conducting a 10-week, two-group, randomized trial to evaluate the impact of providing smoking cessation treatment (SCT) with SUD treatment as usual (TAU), compared to TAU alone, in smokers who are in outpatient treatment for cocaine or methamphetamine dependence. Approximately 528 participants, recruited from 12 community treatment programs, will be randomized into the trial. The present paper describes key design decisions made during protocol development. The trial is designed to evaluate the relationship between cigarette smoking and stimulant use, which prior research suggests is linked, and should contribute to our understanding of how best to address the co-occurring problems of nicotine dependence and cocaine/methamphetamine-dependence. Unique aspects of the trial include the primary question of interest, which concerns the impact of providing SCT on SUD outcomes rather than on smoking outcomes, and the intensity of the SCT chosen, which includes bupropion, nicotine replacement, and two psychosocial interventions. Winhusen T, Stitzer M, Woody G, Brigham G, Kropp F, Ghitza U, Lindblad R, Adinoff B, Green C, Sharma G, Somoza E. Design considerations for a study to evaluate the impact of smoking cessation treatment on stimulant use outcomes in stimulant-dependent individuals. Contemp Clin Trials. 2011 Oct 8. [Epub ahead of print].

Increasing Ethnic Minority Participation in Substance Abuse Clinical Trials: Lessons Learned in the National Institute on Drug Abuse's Clinical Trials Network
Underrepresentation in clinical trials limits the extent to which ethnic minorities benefit from advances in substance abuse treatment. The objective of this article is to share the knowledge gained within the Clinical Trials Network (CTN) of the National Institute on Drug Abuse and other research on recruiting and retaining ethnic minorities into substance abuse clinical trials. The article includes a discussion of two broad areas for improving inclusion-community involvement and cultural adaptation. CTN case studies are included to illustrate three promising strategies for improving ethnic minority inclusion: respondent-driven sampling, community-based participatory research, and the cultural adaptation of the recruitment and retention procedures. The article concludes with two sections describing a number of methodological concerns in the current research base and our proposed research agenda for improving ethnic minority inclusion that builds on the CTN experience. Burlew K, Larios S, Suarez-Morales L, Holmes B, Venner K, Chavez R. Increasing ethnic minority participation in substance abuse clinical trials: lessons learned in the National Institute on Drug Abuse's Clinical Trials Network. Cultur Divers Ethnic Minor Psychol. 2011 Oct; 17(4): 345-356.

Motivational Enhancement Therapy for African American Substance Users: A Randomized Clinical Trial Limited empirical evidence concerning the efficacy of substance abuse treatments among African Americans reduces opportunities to evaluate and improve program efficacy. The current study, conducted as a secondary analysis of a randomized clinical trial conducted by the Clinical Trials Network of the National Institute of Drug Abuse, addressed

this knowledge gap by examining the efficacy of motivational enhancement therapy (MET) compared with counseling as usual (CAU) among 194 African American adults seeking outpatient substance abuse treatment at 5 participating sites. The findings revealed higher retention rates among women in MET than in CAU during the initial 12 weeks of the 16-week study. Men in MET and CAU did not differ in retention. However, MET participants self-reported more drug-using days per week than participants in CAU. Implications for future substance abuse treatment research with African Americans are discussed. Montgomery L, Burlew AK, Kosinski AS, Forcehimes AA. Motivational enhancement therapy for African American substance users: A randomized clinical trial. Cultur Divers Ethnic Minor Psychol. 2011 Oct; 17(4): 357-365.

American Indian Methamphetamine and Other Drug Use in the Southwestern United States To investigate the extent of methamphetamine and other drug use among American Indians (AIs) in the Four Corners region, the authors developed collaborations with Southwestern tribal entities and treatment programs in and around New Mexico. They held nine focus groups, mostly with Southwestern AI participants (N = 81) from three diverse New Mexico communities to understand community members, treatment providers, and clients/relatives views on methamphetamine. They conducted a telephone survey of staff (N = 100) from agencies across New Mexico to assess perceptions of methamphetamine use among people working with AI populations. They collected and analyzed self-reported drug use data from 300 AI clients/relatives who completed the Addiction Severity Index (ASI) in the context of treatment at three diverse addiction treatment programs. Each focus group offered a unique perspective about the effect of drugs and alcohol on each respective community. Though data from the phone surveys and ASIs suggested concerning rates of methamphetamine use, with women more adversely affected by substance use in general, alcohol was identified as the biggest substance use problem for AI populations in the Southwest. There appears to be agreement that methamphetamine use is a significant problem in these communities, but that alcohol is much more prevalent and problematic. There was less agreement about what should be done to prevent and treat methamphetamine use. Future research should attend to regional and tribal differences due to variability in drug use patterns, and should focus on identifying and improving dissemination of effective substance use interventions. Forcehimes AA, Venner KL, Bogenschutz MP, Foley K, Davis MP, Houck JM, Willie EL, Begaye P. American Indian methamphetamine and other drug use in the Southwestern United States. Cultur Divers Ethnic Minor Psychol. 2011 Oct; 17(4): 366-376.

Hepatitis B virus and Hepatitis C Virus Services Offered by Substance Abuse Treatment Programs in the United States Although substance abuse treatment programs are important contact points for providing health services for hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, availability of services in these programs has not been well characterized. This study evaluated the spectrum of HBV and HCV services offered by substance abuse treatment programs within the National Drug Abuse Treatment Clinical Trials Network. The authors' survey of substance abuse treatment program administrators covered availability of testing for HBV and HCV; hepatitis A virus (HAV) and HBV immunization; and HCV medical and nonmedical services. There were also questions covering clarity of guidelines for HBV and HCV testing and HAV and HBV immunization. Differences between methadone and nonmethadone programs were examined. Despite the importance of substance abuse in sustaining the hepatitis epidemics, few programs offer comprehensive HBV and HCV testing or HCV health care services. Interventions to improve access to hepatitis services for substance-abusing patients are

needed. Bini EJ, Kritz S, Brown LS Jr, Robinson J, Calsyn D, Alderson D, Tracy K, McAuliffe P, Smith C, Rotrosen J. Hepatitis B virus and hepatitis C virus services offered by substance abuse treatment programs in the United States. J Subst Abuse Treat. 2011 Oct 27. [Epub ahead of print].

Is Exposure to an Effective Contingency Management Intervention Associated with More Positive Provider Beliefs? This study empirically examined opinions of treatment providers regarding contingency management (CM) programs while controlling for experience with a specific efficacious CM program. In addition to empirically describing provider opinions, the authors examined whether the opinions of providers at the sites that implemented the CM program were more positive than those of matched providers at sites that did not implement it. Participants from 7 CM treatment sites (n = 76) and 7 matched nonparticipating sites (n = 69) within the same nodes of the National Institute of Drug Abuse Clinical Trials Network completed the Provider Survey of Incentives (PSI), which assesses positive and negative beliefs about incentive programs. An intent-to-treat analysis found no differences in the PSI summary scores of providers in CM program versus matched sites, but correcting for experience with tangible incentives showed significant differences, with providers from CM sites reporting more positive opinions than those from matched sites. Some differences were found in opinions regarding costs of incentives, and these generally indicated that participants from CM sites were more likely to see the costs as worthwhile. The results from the study suggest that exposing community treatment providers to incentive programs may itself be an effective strategy in prompting the dissemination of CM interventions. Kirby KC, Carpenedo CM, Stitzer ML, Dugosh KL, Petry NM, Roll JM, Saladin ME, Cohen AJ, Hamilton J, Reese K, Sillo GR, Stabile PQ, Sterling RC. Is exposure to an effective contingency management intervention associated with more positive provider beliefs? J Subst Abuse Treat. 2011 Nov 22. [Epub ahead of print].

Addiction Treatment Trials: How Gender, Race/Ethnicity, and Age Relate To *Ongoing* Participation And Retention In Clinical Trials Historically, racial and ethnic minority populations have been underrepresented in clinical research, and the recruitment and retention of women and ethnic minorities in clinical trials has been a significant challenge for investigators. The National Drug Abuse Treatment Clinical Trials Network (CTN) conducts clinical trials in real-life settings and regularly monitors a number of variables critical to clinical trial implementation, including the retention and demographics of participants. The purpose of this study was the examination of gender, race/ethnicity, and age group differences with respect to retention characteristics in CTN trials. Reports for 24 completed trials that recruited over 11,000 participants were reviewed, and associations of gender, race/ethnicity, and age group characteristics were examined along with the rate of treatment exposure, the proportion of follow-up assessments obtained, and the availability of primary outcome measure(s). Analysis of the CTN data did not indicate statistical differences in retention across gender or race/ethnicity groups; however, retention rates increased for older participants. These results are based on a large sample of patients with substance use disorders recruited from a treatment-seeking population. The findings demonstrate that younger participants are less likely than older adults to be retained in clinical trials. Korte JE, Rosa CL, Wakim PG, Perl HI. Addiction treatment trials: how gender, race/ethnicity, and age relate to *ongoing* participation and retention in clinical trials. Substance Abuse and Rehabilitation 2011; 2(1): 205-218.

Design and Methodological Considerations of an Effectiveness Trial of a Computer-assisted Intervention: An Example from the NIDA Clinical Trials Network Computer-assisted interventions hold the promise of minimizing two problems that are ubiquitous in substance abuse treatment: the lack of ready access to treatment and the challenges to providing empirically-supported treatments. Reviews of research on computer-assisted treatments for mental health and substance abuse report promising findings, but study quality and methodological limitations remain an issue. In addition, relatively few computer-assisted treatments have been tested among illicit substance users. This manuscript describes the methodological considerations of a multi-site effectiveness trial conducted within the National Institute on Drug Abuse's (NIDA's) National Drug Abuse Treatment Clinical Trials Network (CTN). The study is evaluating a web-based version of the Community Reinforcement Approach, in addition to prize-based contingency management, among 500 participants enrolled in 10 outpatient substance abuse treatment programs. Several potential effectiveness trial designs were considered and the rationale for the choice of design in this study is described. The study uses a randomized controlled design (with independent treatment arm allocation), intention-to-treat primary outcome analysis, biological markers for the primary outcome of abstinence, long-term follow-up assessments, precise measurement of intervention dose, and a cost-effectiveness analysis. Input from community providers during protocol development highlighted potential concerns and helped to address issues of practicality and feasibility. Collaboration between providers and investigators supports the utility of infrastructures that enhance research partnerships to facilitate effectiveness trials and dissemination of promising, technologically innovative treatments. Outcomes from this study will further the empirical knowledge base on the effectiveness and cost-effectiveness of computer-assisted treatment in clinical treatment settings. Campbell AN, Nunes EV, Miele GM, Matthews A, Polsky D, Ghitza UE, Turrigiano E, Bailey GL, Vanveldhuisen P, Chapdelaine R, Froias A, Stitzer ML, Carroll KM, Winhusen T, Clingerman S, Perez L, McClure E, Goldman B, Crowell AR. Design and methodological considerations of an effectiveness trial of a computer-assisted intervention: An example from the NIDA Clinical Trials Network. Contemp Clin Trials. 2011 Nov 9. [Epub ahead of print].

Depressive Symptoms, Substance Use, and HIV-related High-risk Behaviors Among Opioid-dependent Individuals: Results from the Clinical Trials Network The sample included 343 opioid-dependent adults enrolled in two national multisite studies of the National Drug Abuse Treatment Clinical Trials Network (CTN001-002). Opioid-dependent individuals were recruited from 12 sites across the United States from January 2001 to July 2002. The authors examined associations between depressive symptoms, co-occurring substance use (i.e., the use of substances other than opioids), and HIV-related sexual and injection risk behaviors. Data were collected using the Addiction Severity Index and the HIV Risk Behavior Scale, and analyzed using linear regression. Depressive symptoms were associated with an increased level of injection risk behaviors but were not associated with risky sexual behaviors. The co-occurring use of amphetamines also increased the likelihood of risky sexual behaviors. The study limitations and clinical implications are noted. Pilowsky DJ, Wu LT, Burchett B, Blazer DG, Ling W. Depressive symptoms, substance use, and HIV-related high-risk behaviors among opioid-dependent individuals: results from the Clinical Trials Network. Subst Use Misuse. 2011; 46(14): 1716-1725. Epub 2011 Oct 5.

Predictors of Abstinence: National Institute of Drug Abuse Multisite Buprenorphine/ Naloxone Treatment Trial in Opioid-dependent Youth The objective of this study was to examine predictors of opioid abstinence in buprenorphine/naloxone (Bup/Nal)-assisted psychosocial treatment for opioid-dependent youth. Secondary analyses were performed of data from 152 youth (15-21 years old) randomly assigned to 12 weeks of extended Bup/Nal therapy or up to 2 weeks of Bup/Nal detoxification with weekly individual and group drug counseling. Logistic regression models were constructed to identify baseline and during-treatment predictors of opioid-positive urine (OPU) at week 12. Predictors were selected based on significance or trend toward significance (i.e., $p < .1$), and backward stepwise selection was used, controlling for treatment group, to produce final independent predictors at $p \leq .05$. Youth presenting to treatment with previous 30-day injection drug use and more active medical/psychiatric problems were less likely to have a week-12 OPU. Those with early treatment opioid abstinence (i.e., weeks 1 and 2) and those who received additional nonstudy treatments during the study were less likely to have a week-12 OPU and those not completing 12 weeks of treatment were more likely to have an OPU. Youth with advanced illness (i.e., reporting injection drug use and additional health problems) and those receiving ancillary treatments to augment study treatment were more likely to have lower opioid use. Treatment success in the first 2 weeks and completion of 12 weeks of treatment were associated with lower rates of OPU. These findings suggest that youth with advanced illness respond well to Bup/Nal treatment and identify options for tailoring treatment for opioid-dependent youth presenting at community-based settings. Clinical Trial Registration Information: Buprenorphine/Naloxone-Facilitated Rehabilitation for Opioid Dependent Adolescents; http://www.clinicaltrials.gov; NCT00078130. Subramaniam GA, Warden D, Minhajuddin A, Fishman MJ, Stitzer ML, Adinoff B, Trivedi M, Weiss R, Potter J, Poole SA, Woody GE. Predictors of abstinence: National Institute of Drug Abuse multisite buprenorphine/naloxone treatment trial in opioid-dependent youth. J Am Acad Child Adolesc Psychiatry. 2011 Nov; 50(11): 1120-1128.

Brief Strategic Family Therapy versus Treatment As Usual: Results of a Multisite Randomized Trial for Substance Using Adolescents The objective of this study was to determine the effectiveness of brief strategic family therapy (BSFT; an evidence-based family therapy) compared to treatment as usual (TAU) as provided in community-based adolescent outpatient drug abuse programs. A randomized effectiveness trial in the National Drug Abuse Treatment Clinical Trials Network compared BSFT to TAU with a multiethnic sample of adolescents (213 Hispanic, 148 White, and 110 Black) referred for drug abuse treatment at 8 community treatment agencies nationwide. Randomization encompassed both adolescents' families ($n = 480$) and the agency therapists ($n = 49$) who provided either TAU or BSFT services. The primary outcome was adolescent drug use, assessed monthly via adolescent self-report and urinalysis for up to 1 year post randomization. Secondary outcomes included treatment engagement (≥2 sessions), retention (≥8 sessions), and participants' reports of family functioning 4, 8, and 12 months following randomization. No overall differences between conditions were observed in the trajectories of self-reports of adolescent drug use. However, the median number of days of self-reported drug use was significantly higher, $\chi2(1) = 5.40$, $p < .02$, in TAU (Mdn = 3.5, interquartile range [IQR] = 11) than BSFT (Mdn = 2, IQR = 9) at the final observation point. BSFT was significantly more effective than TAU in engaging, $\chi2(1) = 11.33$, $p < .001$, and retaining, $\chi2(1) = 5.66$, $p < .02$, family members in treatment and in improving parent reports of family functioning, $\chi2(2) = 9.10$, $p < .011$. The authors discuss challenges in treatment implementation in community settings and provide recommendations for further research. Robbins MS, Feaster DJ, Horigian VE, Rohrbaugh M, Shoham V, Bachrach K, Miller

M, Burlew KA, Hodgkins C, Carrion I, Vandermark N, Schindler E, Werstlein R, Szapocznik J. Brief strategic family therapy versus treatment as usual: Results of a multisite randomized trial for substance using adolescents. J Consult Clin Psychol. 2011 Dec; 79(6): 713-727. Epub 2011 Oct 3.

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. His was a multisite, 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 study setting comprised ten US sites. Patients were 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 were 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. 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. Trial Registration clinicaltrials.gov Identifier: NCT00316277. 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.

A Multilevel Approach to Predicting Community Addiction Treatment Attitudes about Contingency Management Adoption of contingency management (CM) by the addiction treatment community is limited to date despite much evidence for its efficacy. This study examined systemic and idiographic staff predictors of CM adoption attitudes via archival data collected from treatment organizations affiliated with the National Drug Abuse Treatment Clinical Trials Network. Multilevel modeling analyses evaluated potential predictors from organizational, treatment unit, and workforce surveys. Among these were individual and shared perceptions of staff concerning aspects of their clinic culture and climate. Modeling analyses

identified three systemic predictors (clinic provision of opiate agonist services, national accreditation, and lesser shared perception of workplace stress) and five idiographic predictors (staff with a graduate degree, longer service tenure, managerial position, e-communication facility, and openness to change in clinical procedures). Findings are discussed as they relate to extant literature on CM attitudes and established implementation science constructs, and their practical implications are discussed. Hartzler B, Donovan DM, Tillotson CJ, Mongoue-Tchokote S, Doyle SR, McCarty D. A multilevel approach to predicting community addiction treatment attitudes about contingency management. J Subst Abuse Treat. 2011 Dec 2. [Epub ahead of print].

Major Depression and Treatment Response in Adolescents with ADHD and Substance Use Disorder Major depressive disorder (MDD) frequently co-occurs in adolescents with substance use disorders (SUDs) and attention deficit hyperactivity disorder (ADHD), but the impact of MDD on substance treatment and ADHD outcomes and implications for clinical practice are unclear. Adolescents (n=303; ages 13-18) meeting DSM-IV criteria for ADHD and SUD were randomized to osmotic release methylphenidate (OROS-MPH) or placebo and 16 weeks of cognitive behavioral therapy (CBT). Adolescents with (n=38) and without (n=265) MDD were compared on baseline demographic and clinical characteristics as well as non-nicotine substance use and ADHD treatment outcomes. Adolescents with MDD reported more non-nicotine substance use days at baseline and continued using more throughout treatment compared to those without MDD ($p<0.0001$ based on timeline followback; $p<0.001$ based on urine drug screens). There was no difference between adolescents with and without MDD in retention or CBT sessions attended. ADHD symptom severity (based on DSM-IV ADHD rating scale) followed a slightly different course of improvement although with no difference between groups in baseline or 16-week symptom severity or 16-week symptom reduction. There was no difference in days of substance use or ADHD symptom outcomes over time in adolescents with MDD or those without MDD treated with OROS-MPH or placebo. Depressed adolescents were more often female, older, and not court ordered. These preliminary findings suggest that compared to non-depressed adolescents with ADHD and SUD, those with co-occurring MDD have more severe substance use at baseline and throughout treatment. Such youth may require interventions targeting depression. Warden D, Riggs PD, Min SJ, Mikulich-Gilbertson SK, Tamm L, Trello-Rishel K, Winhusen T. Major depression and treatment response in adolescents with ADHD and substance use disorder. Drug Alcohol Depend. 2012 Jan 1; 120(1-3): 214-219. Epub 2011 Aug 31.

Special CTN Issue of ***The American Journal of Drug and Alcohol Abuse,*** v. 37(5), 2011.

The Design and Analysis of Multisite Effectiveness Trials: A Decade of Progress in the National Drug Abuse Clinical Trials Network This Special Issue brings together articles that reflect 12 years of experience in the Clinical Trials Network (CTN). These include pieces dealing with methodological and statistical issues that arise in the design and conduct of controlled, multi-site, community-based effectiveness trials. To date, the CTN has randomized over 13,000 patients into 27 completed trials, with more trials currently ongoing, providing a wealth of experience in the design, implementation, and analysis of effectiveness trials. Nunes EV. The design and analysis of multisite effectiveness trials: a decade of progress in the National Drug Abuse Clinical Trials Network. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 269-272.

Obituary In Memory of Dr. Malcolm S. Reid Ph.D.
28 September 1962 – 20 April 2010
This special issue on effectiveness trials is dedicated to the memory of our friend and colleague Malcolm S. Reid, who passed away on Friday 20 April 2010, in the prime of his life, after a yearlong struggle with leukemia. Malcolm was an active collaborator in the National Drug Abuse Treatment Clinical Trials Network (NIDA CTN) from its early years, serving as Lead Investigator on CTN-009, a multisite trial of a smoking cessation intervention in community-based addictions treatment programs. Poignantly, 5 years after its completion, and a week before Malcolm's death, CTN-0009 received accolades as a path-breaking study at the Network's 10th Anniversary Celebration in Albuquerque. His last article from that study is published posthumously in this issue. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 273-274

Correction to: Obituary: In memory of Dr. Malcolm S. Reid Ph.D. In *The American Journal of Drug and Alcohol Abuse*, Vol. 37, Issue 5, an error has been brought to our attention. Within the obituary of Dr. Malcolm S. Reid his death date was published as 20 April 2010, but should read 23 April 2010. Informa Healthcare and the authors would like to apologize for this error. Correction to: Obituary: In memory of Dr. Malcolm S. Reid Ph.D. Am J Drug Alcohol Abuse. 2011 Nov 25. [Epub ahead of print].

Ten Take Home Lessons from the First 10 Years of the CTN and 10 Recommendations for the Future The first 10 years of the National Institute on Drug Abuse's Clinical Trials Network (CTN) yielded a wealth of data on the effectiveness of a number of behavioral, pharmacological, and combined approaches in community-based settings. The authors summarize some of the methodological contributions and lessons learned from the behavioral trials conducted during its first ten years, including the capacity and enormous potential of this national research infrastructure. The CTN made contributions to the methodology of effectiveness research; new insights from secondary analyses; the extent to which approaches with strong evidence bases, such as contingency management, extend their effectiveness to real world clinical settings; new data on 'standard treatment' as actually practiced in community programs, the extent to which retention remains a major issue in the field; important data on the safety of specific behavioral therapies for addiction; and heightened the importance of continued sustained attention to bridging the gap between treatment and research. Conclusions: Areas of focus for the CTN's future include defining common outcome measures to be used in treatment outcome studies for illicit drugs; incorporating performance indicators and measures of clinical significance; conducting comparative outcome studies; contributing to the understanding of effective treatments of comorbidity; reaching underserved populations; building implementation science; understanding long-term outcomes of current treatments and sustaining treatment effects; and conducting future trials more efficiently. Carroll KM, Ball SA, Jackson R, Martino S, Petry NM, Stitzer ML, Wells EA, Weiss RD. Ten take home lessons from the first 10 years of the CTN and 10 recommendations for the future. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 275-282.

NIDA's Clinical Trials Network: An Opportunity for HIV Research in Community Substance Abuse Treatment Programs HIV continues to be a significant problem among substance users and their sexual partners in the United States. The National Drug Abuse Treatment Clinical Trials Network (CTN) offers a national platform for effectiveness trials of HIV interventions in community substance abuse treatment programs. This article presents the HIV activities of the CTN during its first 10 years. While emphasizing CTN HIV protocols, this article reviews the (1) HIV context for this work; (2) the collaborative process among providers,

researchers, and National Institute on Drug Abuse CTN staff, on which CTN HIV work was based; (3) results of CTN HIV protocols and HIV secondary analyses in CTN non-HIV protocols; and (4) implications for future HIV intervention effectiveness research in community substance abuse treatment programs. While the feasibility of engaging frontline providers in this research is highlighted, the limitations of small to medium effect sizes and weak adoption and sustainability in everyday practice are also discussed. Tross S, Campbell AN, Calsyn DA, Metsch LR, Sorensen JL, Shoptaw S, Haynes L, Woody GE, Malow RM, Brown LS Jr, Feaster DJ, Booth RE, Mandler RN, Masson C, Holmes BW, Colfax G, Brooks AJ, Hien DA, Schackman BR, Korthuis PT, Miele GM; Clinical Trials Network HIV Special Interest Group. NIDA's Clinical Trials Network: an opportunity for HIV research in community substance abuse treatment programs. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 283-293.

Is Monogamy or Committed Relationship Status a Marker for Low Sexual Risk Among Men in Substance Abuse Treatment? Clinical and Methodological Considerations HIV prevention interventions often promote monogamy to reduce sexual risk. However, there is little consensus about how to define monogamy. The objective of this study was to determine the extent to which recent monogamy and/or being in a committed relationship serve as markers for low sexual risk among men in substance abuse treatment. Participants were 360 men enrolled in the National Institute on Drug Abuse Clinical Trials Network "Real Men Are Safe" protocol who completed all assessments (baseline, 3 months, and 6 months). Self-reported behaviors included number of sexual partners, type of relationships, frequency of vaginal/anal intercourse, and percentage of condom use. The rate of self-reported monogamy in the prior 90 days was stable across assessments (54.2%, 53.1%, 58.3%). However, at each assessment 7.5-10% of monogamous men identified their partner as a casual partner, and only 123 (34.2%) reported being monogamous at every assessment. Of these, 20 (5.6%) reported being monogamous with different partners across assessments. Men with both committed relationship and casual partners reported more condom use with their committed relationship partners than men with only a committed relationship partner. Clinicians and researchers should consider individual relationship context and behavior and avoid assuming that recent monogamy or being in a committed relationship denotes low risk. Scientific Significance: This study provides evidence that, in male drug users, monogamy does not necessarily reflect low sexual risk. Rather, "monogamous" men actually encompass various combinations of partner types and levels of risk behavior that are unstable, even over brief time periods. Clinicians and researchers must take these variations into account. Calsyn DA, Campbell AN, Tross S, Hatch-Maillette MA. Is monogamy or committed relationship status a marker for low sexual risk among men in substance abuse treatment? Clinical and methodological considerations. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 294-300.

Gender Research in the National Institute on Drug Abuse National Treatment Clinical Trials Network: A Summary of Findings The National Institute of Drug Abuse's National Drug Abuse Treatment Clinical Trials Network (CTN) was established to foster translation of research into practice in substance abuse treatment settings. The CTN provides a unique opportunity to examine in multi-site, translational clinical trials, the outcomes of treatment interventions targeting vulnerable subgroups of women; the comparative effectiveness of gender-specific protocols to reduce risk behaviors; and gender differences in clinical outcomes. The objectives of this study were to review gender-related findings from published CTN clinical trials and related studies from January 2000 to March 2010. CTN studies were selected for review if they focused on treatment outcomes or services for special populations of women with

substance use disorders (SUDs) including those with trauma histories, pregnancy, co-occurring eating and other psychiatric disorders, and HIV risk behaviors; or implemented gender-specific protocols. The CTN has randomized 11,500 participants (41% women) across 200 clinics in 24 randomized controlled trials in community settings, of which 4 have been gender-specific. This article summarizes gender-related findings from CTN clinical trials and related studies, focusing on trauma histories, pregnancy, co-occurring eating and other psychiatric disorders, and HIV risk behaviors. These published studies have expanded the evidence base regarding interventions for vulnerable groups of women with SUDs as well as gender-specific interventions to reduce HIV risk behaviors in substance-using men and women. The results also underscore the complexity of accounting for gender in the design of clinical trials and analysis of results. To fully understand the relevance of gender-specific moderators and mediators of outcome, it is essential that future translational studies adopt more sophisticated approaches to understanding and measuring gender-relevant factors and plan sample sizes that are adequate to support more nuanced analytic methods. Greenfield SF, Rosa C, Putnins SI, Green CA, Brooks AJ, Calsyn DA, Cohen LR, Erickson S, Gordon SM, Haynes L, Killeen T, Miele G, Tross S, Winhusen T. Gender research in the National Institute on Drug Abuse National Treatment Clinical Trials Network: a summary of findings. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 301-312.

Comparative Profiles of Men and Women with Opioid Dependence: Results from a National Multisite Effectiveness Trial Accumulating evidence indicates important gender differences in substance use disorders. Little is known, however, about gender differences and opioid use disorders. The objectives of this study were to compare demographic characteristics, substance use severity, and other associated areas of functioning (as measured by the Addiction Severity Index-Lite (ASI-Lite)) among opioid-dependent men and women participating in a multisite effectiveness trial. Participants were 892 adults screened for the National Institute on Drug Abuse Clinical Trials Network investigation of the effectiveness of two buprenorphine tapering schedules. The majority of men and women tested positive for oxycodone (68% and 65%, respectively) and morphine (89% each). More women than men tested positive for amphetamines (4% vs. 1%, $p < .01$), methamphetamine (11% vs. 4%, $p < .01$), and phencyclidine (8% vs. 4%, $p = .02$). More men than women tested positive for methadone (11% vs. 6%, $p = .05$) and marijuana (22% vs. 15%, $p = .03$). Craving for opioids was significantly higher among women ($p < .01$). Men evidenced higher alcohol ($p < .01$) and legal ($p = .04$) ASI composite scores, whereas women had higher drug ($p < .01$), employment ($p < .01$), family ($p < .01$), medical ($p < .01$), and psychiatric ($p < .01$) ASI composite scores. Women endorsed significantly more current and past medical problems. Important gender differences in the clinical profiles of opioid-dependent individuals were observed with regard to substance use severity, craving, medical conditions, and impairment in associated areas of functioning. The findings enhance understanding of the characteristics of treatment-seeking men and women with opioid dependence, and may be useful in improving identification, prevention, and treatment efforts for this challenging and growing population. Back SE, Payne RL, Wahlquist AH, Carter RE, Stroud Z, Haynes L, Hillhouse M, Brady KT, Ling W. Comparative profiles of men and women with opioid dependence: results from a national multisite effectiveness trial. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 313-323.

Conducting Research with Racial/Ethnic Minorities: Methodological Lessons from the NIDA Clinical Trials Network Multiple studies in the National Institute on Drug Abuse Clinical Trials Network (CTN) demonstrate strategies for conducting effective substance abuse treatment research with racial/ethnic minorities (REMs). The objectives of this article are to describe lessons learned within the CTN to (1) enhance recruitment, retention, and other outcomes; (2) assess measurement equivalence; and (3) use data analytic plans that yield more information. This article includes background information and examples from multiple CTN studies on inclusion, measurement, and data analysis. Seven recommendations are included for conducting more effective research on REMs. Burlew AK, Weekes JC, Montgomery L, Feaster DJ, Robbins MS, Rosa CL, Ruglass LM, Venner KL, Wu LT. Conducting research with racial/ethnic minorities: methodological lessons from the NIDA Clinical Trials Network. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 324-332.

Research Partnerships Between Academic Institutions and American Indian and Alaska Native Tribes and Organizations: Effective Strategies and Lessons Learned in a Multisite CTN Study Community Based and Tribally Based Participatory Research (CBPR/TPR) are approaches that can be successful for developing ethical and effective research partnerships between academic institutions and Tribes and Native organizations. The NIDA Clinical Trials Network funded a multi-site, exploratory study using CBPR/TPR to begin to better understand substance abuse issues of concern to some Tribes and Native organizations as well as strengths and resources that exist in these communities to address these concerns. Attention was paid to the development and maintenance of research partnerships in each of the sites. Each of the five partnerships is briefly described and common as well as unique challenges and successes are identified. A summary of the common themes for developing these collaborative research efforts is provided. Conclusion: True, collaborative research partnerships require a great deal of time and effort in order to develop mutual trust, understanding, knowledge, and collaboration that will guide research that is rigorous as well as ethical, effective, and culturally appropriate.
As AIAN communities become increasingly sophisticated partners in, and consumers of, research, CBPR and TPR are emerging as effective, ethical, culturally appropriate, and acceptable approaches. This can serve to improve the science we engage in with AIAN communities, add to the scarce literature regarding AIAN communities, and better serve AIAN communities in addressing health disparities and improving health. Thomas LR, Rosa C, Forcehimes A, Donovan DM. Research partnerships between academic institutions and American Indian and Alaska Native Tribes and organizations: effective strategies and lessons learned in a multisite CTN study. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 333-338.

Determining the Primary Endpoint for a Stimulant Abuse Trial: Lessons Learned from STRIDE (CTN 0037) No consensus is available for identifying the best primary outcome for substance use disorder trials, making interpretation across trials difficult. Abstinence is the most desirable treatment outcome although a wide variety of other endpoints have been used. This report provides a framework for determining an optimal primary endpoint and the relevant measurement approach for substance use disorder treatment trials. The framework was developed based on a trial for stimulant abuse using exercise as an augmentation treatment, delivered within the NIDA Clinical Trials Network. The use of a common endpoint across trials will facilitate comparisons of treatment efficacy. Primary endpoint options in existing substance abuse studies were evaluated. This evaluation included surveys of the literature for endpoints and measurement approaches, followed by assessment of endpoint choices against study design issues, population characteristics, tests of sensitivity, and tests of clinical meaningfulness. The

authors concluded that the best current choice for a primary endpoint is percent days abstinent, as measured by the Time Line Follow Back interview conducted three times a week with recall aided by a take-home Substance Use Diary. To improve the accuracy of the self-reported drug use, the results of qualitative urine drug screens will be used in conjunction with the Time Line Follow Back results. There is a need for a standardized endpoint in this field to allow for comparison across treatment studies, and we suggest that the recommended candidate endpoint be considered. However, the study design and goals ultimately must guide the final decision. Trivedi MH, Greer TL, Potter JS, Grannemann BD, Nunes EV, Rethorst C, Warden D, Ring KM, Somoza E. Determining the primary endpoint for a stimulant abuse trial: lessons learned from STRIDE (CTN 0037). Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 339-349.

Power of Automated Algorithms for Combining Time-line Follow-back and Urine Drug Screening Test Results in Stimulant-abuse Clinical Trials In clinical trials of treatment for stimulant abuse, researchers commonly record both Time-Line Follow-Back (TLFB) self-reports and urine drug screen (UDS) results. The objectives of this study were to compare the power of self-report, qualitative (use vs. no use) UDS assessment, and various algorithms to generate self-report-UDS composite measures to detect treatment differences via t-test in simulated clinical trial data. The authors performed Monte Carlo simulations patterned in part on real data to model self-report reliability, UDS errors, dropout, informatively missing UDS reports, incomplete adherence to a urine donation schedule, temporal correlation of drug use, number of days in the study period, number of patients per arm, and distribution of drug-use probabilities. Investigated algorithms include maximum likelihood and Bayesian estimates, self-report alone, UDS alone, and several simple modifications of self-report (referred to here as ELCON algorithms) which eliminate perceived contradictions between it and UDS. Among the algorithms investigated, simple ELCON algorithms gave rise to the most powerful t-tests to detect mean group differences in stimulant drug use. Further investigation is needed to determine if simple, naïve procedures such as the ELCON algorithms are optimal for comparing clinical study treatment arms. But researchers who currently require an automated algorithm in scenarios similar to those simulated for combining TLFB and UDS to test group differences in stimulant use should consider one of the ELCON algorithms. This analysis continues a line of inquiry which could determine how best to measure outpatient stimulant use in clinical trials (NIDA. NIDA Monograph-57: Self-Report Methods of Estimating Drug Abuse: Meeting Current Challenges to Validity. NTIS PB 88248083. Bethesda, MD: National Institutes of Health, 1985; NIDA. NIDA Research Monograph 73: Urine Testing for Drugs of Abuse. NTIS PB 89151971. Bethesda, MD: National Institutes of Health, 1987; NIDA. NIDA Research Monograph 167: The Validity of Self-Reported Drug Use: Improving the Accuracy of Survey Estimates. NTIS PB 97175889. GPO 017-024-01607-1. Bethesda, MD: National Institutes of Health, 1997). Oden NL, VanVeldhuisen PC, Wakim PG, Trivedi MH, Somoza E, Lewis D. Power of automated algorithms for combining time-line follow-back and urine drug screening test results in stimulant-abuse clinical trials. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 350-357.

Assessing Drug Use during Follow-up: Direct Comparison of Candidate Outcome Definitions in Pooled Analyses of Addiction Treatment Studies Selection of appropriate outcome measures is important for clinical studies of drug addiction treatment. Researchers use various methods for collecting drug use outcomes and must consider substances to be included in a urine drug screen (UDS); accuracy of self-report; use of various instruments and procedures for collecting self-reported drug use; and timing of outcome assessments. The authors sought to define a set of candidate measures to (1) assess their intercorrelation and (2) identify any

differences in results. Data were combined from completed protocols in the National Institute on Drug Abuse Clinical Trials Network (CTN), with a total of 1897 participants. The authors defined nine outcome measures based on UDS, self-report, or a combination. Multivariable, multilevel generalized estimating equation models were used to assess subgroup differences in intervention success, controlling for baseline differences and accounting for clustering by CTN protocols. There were high correlations among all candidate outcomes. All outcomes showed consistent overall results with no significant intervention impact on drug use during follow-up. However, with most UDS variables, but not with self-report or "corrected self-report," the authors observed a significant gender-ethnicity interaction with benefit shown in African American women, White women, and Hispanic men. Despite strong associations between candidate measures, they found some important differences in results. In this study, the authors demonstrated the potential utility and impact of combining UDS and self-report data for drug use assessment. Their results suggest possible differences in intervention efficacy by gender and ethnicity, but highlight the need to cautiously interpret observed interactions. Korte JE, Magruder KM, Chiuzan CC, Logan SL, Killeen T, Bandyopadhyay D, Brady KT.. Assessing drug use during follow-up: direct comparison of candidate outcome definitions in pooled analyses of addiction treatment studies. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 358-366.

Zero-inflated and Hurdle Models of Count Data with Extra Zeros: Examples from an HIV-risk Reduction Intervention Trial In clinical trials of behavioral health interventions, outcome variables often take the form of counts, such as days using substances or episodes of unprotected sex. Classically, count data follow a Poisson distribution; however, in practice such data often display greater heterogeneity in the form of excess zeros (zero-inflation) or greater spread in the values (overdispersion) or both. Greater sample heterogeneity may be especially common in community-based effectiveness trials, where broad eligibility criteria are implemented to achieve a generalizable sample. This article reviews the characteristics of Poisson model and the related models that have been developed to handle overdispersion (negative binomial (NB) model) or zero-inflation (zero-inflated Poisson (ZIP) and Poisson hurdle (PH) models) or both (zero-inflated negative binomial (ZINB) and negative binomial hurdle (NBH) models). All six models were used to model the effect of an HIV-risk reduction intervention on the count of unprotected sexual occasions (USOs), using data from a previously completed clinical trial among female patients (N = 515) participating in community-based substance abuse treatment (Tross et al. Effectiveness of HIV/AIDS sexual risk reduction groups for women in substance abuse treatment programs: Results of NIDA Clinical Trials Network Trial. J Acquir Immune Defic Syndr 2008; 48(5):581-589). Goodness of fit and the estimates of treatment effect derived from each model were compared. The ZINB model provided the best fit, yielding a medium-sized effect of intervention. This article illustrates the consequences of applying models with different distribution assumptions on the data. If a model used does not closely fit the shape of the data distribution, the estimate of the effect of the intervention may be biased, either over- or underestimating the intervention effect. Hu MC, Pavlicova M, Nunes EV. Zero-inflated and hurdle models of count data with extra zeros: examples from an HIV-risk reduction intervention trial. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 367-375.

Some Considerations for Excess Zeroes in Substance Abuse Research Count data collected in substance abuse research often come with an excess of "zeroes," which are typically handled using zero-inflated regression models. However, there is a need to consider the design aspects of those studies before using such a statistical model to ascertain the sources of zeroes. The authors sought to illustrate hurdle models as alternatives to zero-inflated models to validate a two-stage

decision-making process in situations of "excess zeroes." They use data from a study of 45 cocaine-dependent subjects where the primary scientific question was to evaluate whether study participation influences drug-seeking behavior. The outcome, "the frequency (count) of cocaine use days per week," is bounded (ranging from 0 to 7). The authors fit and compare binomial, Poisson, negative binomial, and the hurdle version of these models to study the effect of gender, age, time, and study participation on cocaine use. The hurdle binomial model provides the best fit. Gender and time are not predictive of use. Higher odds of use versus no use are associated with age; however once use is experienced, odds of further use decrease with increase in age. Participation was associated with higher odds of no-cocaine use; once there is use, participation reduced the odds of further use. Age and study participation are significantly predictive of cocaine-use behavior. Scientific Significance: The two-stage decision process as modeled by a hurdle binomial model (appropriate for bounded count data with excess zeroes) provides interesting insights into the study of covariate effects on count responses of substance use, when all enrolled subjects are believed to be "at-risk" of use. Bandyopadhyay D, DeSantis SM, Korte JE, Brady KT. Some considerations for excess zeroes in substance abuse research. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 376-382.

Modeling Site Effects in the Design and Analysis of Multi-site Trials Careful consideration of site effects is important in the analysis of multi-site clinical trials for drug abuse treatment. The statistical choices for modeling these effects have implications for both trial planning and interpretation of findings. Three broad approaches for modeling site effects are presented: omitting site from the analysis; modeling site as a fixed effect; and modeling site as a random effect. Both the direct effect of site and the interaction of site and treatment are considered. Methods: The statistical model, and consequences, for each approach are presented along with examples from existing clinical trials. Power analysis calculations provide sample size requirements for adequate statistical power for studies utilizing 6, 8, 10, 12, 14, and 16 treatment sites. Results of the power analyses showed that the total sample required falls rapidly as the number of sites increases in the random effect approach. In the fixed effect approach in which the interaction of site and treatment is considered, the required number of participants per site decreases as the number of sites increases. Ignoring site effects is not a viable option in multi-site clinical trials. There are advantages and disadvantages to the fixed effect and random effect approaches to modeling site effects. The distinction between efficacy trials and effectiveness trials is rarely sharp. The choice between random effect and fixed effect statistical modeling can provide different benefits depending on the goals of the study. Feaster DJ, Mikulich-Gilbertson S, Brincks AM. Modeling site effects in the design and analysis of multi-site trials. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 383-391.

An Exploration of Site Effects in a Multisite Trial of OROS-methylphenidate for Smokers with Attention Deficit/Hyperactivity Disorder Multisite trials, the gold standard for conducting studies in community-based settings, can mask variability across sites resulting in misrepresentation of effects in specific sites. In a placebo-controlled trial of osmotic-release oral system methylphenidate (OROS-MPH) as augmentation treatment for smokers with attention deficit hyperactivity/impulsivity disorder (ADHD), three types of sites were selected according to their clinical research specialty (ADHD, smoking cessation, and general mental health). Analysis was conducted to determine if clinical outcomes, that is, reduction in ADHD symptoms and smoking cessation rates, and the effect of treatment on these outcomes would differ by type of site. A total of 255 adult smokers diagnosed with ADHD were enrolled in three clinic types: 72 in ADHD, 79 in tobacco dependence, and 104 in the mental health clinics. The three site-

types were similar in demographic characteristics, smoking history, baseline level of ADHD symptoms, and history of psychiatric illness. Site-type but not a site-type by treatment interaction predicted prolonged smoking abstinence. A significant three-way interaction of site-type, treatment, and time-predicted improvement in ADHD symptoms. Moderate to strong effects of OROS-MPH relative to placebo were observed in the mental health and the ADHD clinics; a weak effect was observed in the tobacco dependence clinics. OROS-MPH benefit varied by site for reducing ADHD symptoms but not for improving smoking abstinence. Assessment of site-type effects can indicate the generalizability of findings from multisite trials and should be routinely incorporated in the design of multisite trials. Covey LS, Hu MC, Green CA, Brigham G, Hurt RD, Adler L, Winhusen T. An exploration of site effects in a multisite trial of OROS-methylphenidate for smokers with attention deficit/hyperactivity disorder. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 392-399.

Site Selection in Community-based Clinical Trials for Substance Use Disorders: Strategies for Effective Site Selection The importance of conducting substance use disorder treatment research in real-world settings is now well recognized. While this approach to clinical trials research offers a variety of benefits, challenges also arise. Selecting high-quality sites to participate is critical to recruitment, retention, and overall trial performance when conducting multi-site, community-based clinical trials of treatments for substance use disorders. Over the past 10 years, the National Institute on Drug Abuse-sponsored National Drug Abuse Treatment Clinical Trials Network (CTN) has strived to conduct high-quality, well-managed clinical trials. This includes developing methods for site selection to be used by investigators conducting CTN trials. The authors review site selection strategies from two community-based multi-site clinical trials conducted under the auspices of the National Drug Abuse Treatment Clinical Trials Network. Issues relevant to site selection include the clinical trial design, availability of appropriate clinical population, and organizational attributes of potential clinical research sites. Site selection strategies include reviewing regional epidemiologic data, collecting standard site selection surveys, evaluating clinic data on existing patient populations, and site selection interviews and visits. This article describes considerations for selecting research sites and identifies specific strategies to employ when selecting community-based sites for participation in clinical trials. Potter JS, Donovan DM, Weiss RD, Gardin J, Lindblad R, Wakim P, Dodd D. Site selection in community-based clinical trials for substance use disorders: strategies for effective site selection. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 400-407.

How Practice and Science are Balanced and Blended in the NIDA Clinical Trials Network: The Bidirectional Process in the Development of the STAGE-12 Protocol as An Example Bidirectional, collaborative partnerships between academic researchers and practitioners have been a fundamental vehicle to achieve the National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN) goal of improving outcomes of community-based drug treatment. These partnerships blend clinical perspectives of practitioners and methodological expertise of researchers working together to address clinically meaningful issues through randomized clinical trials conducted in community treatment settings. Bidirectionality is a guiding principle of the CTN, but its operationlization at the practical level in protocol development and implementation has not been articulated. This descriptive article presents the development of one protocol as an example and model of this bidirectional, collaborative, iterative partnership between researchers and practitioners. This article illuminates several specific issues encountered while developing STAGE-12, a behavioral intervention to facilitate 12-step mutual support group involvement, as well as the rationale for decisions taken to resolve each. The STAGE-12 protocol was

successfully developed through a series of decisions taking into account both design factors and clinical practice needs and realities, thus maintaining a balance between methodological rigor and generalizability. The review demonstrates the process by which research and practice have been blended in protocol development, exemplifying the underlying principle of bidirectionality, a key element in the success of the NIDA CTN. Bidirectional partnerships as derived in the CTN, employing a hybrid model of efficacy-effectiveness research, are capable of designing and implementing protocols that are both methodologically rigorous and clinically meaningful, thus increasing likelihood of adoption and eventual improvement in public health. Donovan DM, Daley DC, Brigham GS, Hodgkins CC, Perl HI, Floyd AS. How practice and science are balanced and blended in the NIDA Clinical Trials Network: the bidirectional process in the development of the STAGE-12 protocol as an example. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 408-416.

Design of NIDA CTN Protocol 0047: Screening, Motivational Assessment, Referral, and Treatment in Emergency Departments (SMART-ED) Medical settings such as emergency departments (EDs) present an opportunity to identify and provide services for individuals with substance use problems who might otherwise never receive any form of assessment, referral, or intervention. Although screening, brief intervention, and referral to treatment models have been extensively studied and are considered effective for individuals with alcohol problems presenting in EDs and other medical settings, the efficacy of such interventions has not been established for drug users presenting in EDs. This article describes the design of a NIDA Clinical Trials Network protocol testing the efficacy of an screening, brief intervention, and referral to treatment model in medical EDs, highlighting considerations that are pertinent to the design of other studies targeting substance use behaviors in medical treatment settings. The protocol is described, and critical design decisions are discussed. Design challenges included defining treatment conditions, study population, and site characteristics; developing the screening process; choosing the primary outcome; balancing brevity and comprehensiveness of assessment; and selecting the strategy for statistical analysis. Many of the issues arising in the design of this study will be relevant to future studies of interventions for addictions in medical settings. Optimal trial design is critical to determining how best to integrate substance abuse interventions into medical care. Bogenschutz MP, Donovan DM, Adinoff B, Crandall C, Forcehimes AA, Lindblad R, Mandler RN, Oden NL, Perl HI, Walker R. Design of NIDA CTN Protocol 0047: screening, motivational assessment, referral, and treatment in emergency departments (SMART-ED). Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 417-425.

Relation of Study Design to Recruitment and Retention in CTN Trials Recruitment and retention in randomized clinical trials are difficult in general and particularly so in trials of substance abuse treatments. Understanding trial design characteristics that could affect recruitment and retention rates would help in the design of future trials. The objective of this study was to test whether any of the following factors are associated with recruitment or retention: type of intervention, type of therapy, duration of treatment, total duration of trial, number of treatment sessions, number of follow-up visits, number of primary assessments, timing of primary assessments, number of case report form (CRF) pages at baseline, and number of CRF pages for the entire trial. Recruitment and retention data from 24 Clinical Trials Network (CTN) trials conducted and completed between 2001 and 2010 were analyzed using single-factor analysis of variance and single-predictor regression methods to test their association with trial design characteristics. Almost all of the analyses performed did not show statistically significant patterns between recruitment and retention rates and the trial design characteristics

considered. In CTN trials, the relationship between assessment burden on participants and length of trial, on the one hand, and recruitment and retention, on the other, is not as strong and direct as expected. Other factors must impinge on the conduct of the trial to influence trial participation. Researchers may deem slightly more justifiable to permit inclusion of some of the design features that previously were assumed to have a strong, negative influence on recruitment and retention, and should consider other strategies that may have a stronger, more direct effect on trial participation. Wakim PG, Rosa C, Kothari P, Michel ME. Relation of Study Design to Recruitment and Retention in CTN Trials. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 426-433.

Standardized Patient Walkthroughs in the National Drug Abuse Treatment Clinical Trials Network: Common Challenges to Protocol Implementation Training research staff to implement clinical trials occurring in community-based addiction treatment programs presents unique challenges. Standardized patient walkthroughs of study procedures may enhance training and protocol implementation. The objectives of this study were to examine and discuss cross-site and cross-study challenges of participant screening and data collection procedures identified during standardized patient walkthroughs of multi-site clinical trials. Actors portrayed clients and "walked through" study procedures with protocol research staff. The study completed 57 walkthroughs during implementation of 4 clinical trials. Observers and walkthrough participants identified three areas of concern (consent procedures, screening and assessment processes, and protocol implementation) and made suggestions for resolving the concerns. Standardized patient walkthroughs capture issues with study procedures previously unidentified with didactic training or unscripted rehearsals. Clinical trials within the National Drug Abuse Treatment Clinical Trials Network are conducted in addiction treatment centers that vary on multiple dimensions. Based on walkthrough observations, the national protocol team and local site leadership modify standardized operating procedures and resolve cross-site problems prior to recruiting study participants. The standardized patient walkthrough improves consistency across study sites and reduces potential site variation in study outcomes. Fussell HE, Kunkel LE, McCarty D, Lewy CS. Standardized patient walkthroughs in the National Drug Abuse Treatment Clinical Trials Network: common challenges to protocol implementation. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 434-439.

Strategies for Safety Reporting in Substance Abuse Trials Reporting all adverse events (AEs) and serious adverse events (SAEs) in substance use disorder (SUD) clinical trials has yielded limited relevant safety information and has been burdensome to research sites. This article describes a new strategy utilizing standard data elements for AE and SAEs that defines a threshold to reduce unnecessary safety reporting burden in SUD clinical trials and describes retrospective review and prospective preliminary data on the strategy's safety reporting impact. Thje authors developed a new strategy to standardize safety reporting and tailor reporting to the trial intervention risk. Protocols and safety data from 17 SUD clinical trials were reviewed. Retrospective analysis of five of these studies and prospective application to new studies is described. Across the 17 previously completed trials, a total of 11,220 AEs and 1330 SAEs were reported in the 6737 participants. Wide variability in AE and SAE reporting rates were noted based on trial type and inconsistent reporting strategies. Application of the new, tailored safety strategy retrospectively and prospectively reduces reporting burden of irrelevant safety events. Comparison of the previous reporting strategies used in SUD trials to the new strategy demonstrates a more consistent safety system with a reduction in safety reporting burden while maintaining appropriate safety monitoring. Safety assessments should be tailored to the participant risks based on the trial intervention. The current strategies could be applied to safety

assessments across all clinical trials in SUDs. Lindblad R, Campanella M, Styers D, Kothari P, Sparenborg S, Rosa C. Strategies for safety reporting in substance abuse trials. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 440-445.

Baseline Matters: The Importance of Covariation for Baseline Severity in the Analysis of Clinical Trials Clinical trials testing the effectiveness of interventions for addictions, HIV transmission risk, and other behavioral health problems are important to advancing evidence-based treatment. Such trials are expensive and time-consuming to conduct, but the underlying effect sizes tend to be modest, and often findings are disappointing, failing to show evidence of treatment effects. The objectives of this study were to demonstrate how appropriate covariation for baseline severity can enhance detection of treatment effects. The study methodology was explication and case example. Baseline severity (the score of the outcome measure at baseline, prior to randomization) is often strongly associated with outcome in such studies. Covariation for baseline score may enhance detection of treatment effects, because the variance explained by the baseline score is removed from the error variance in the estimate of the difference in outcome between treatments. Alternatively, the effect of treatment may manifest in the form of a baseline-by-treatment interaction. Common interaction patterns include that treatment may be more effective among patients with higher levels of baseline severity, or treatment may be more effective among patients with low severity at baseline ('relapse prevention' effect). Such effects may be important to developing treatment guidelines and offer clues toward understanding the mechanisms of action of treatments and of the disorders. This article illustrates principles of covariation for baseline and the baseline-by-treatment interaction in nontechnical graphical terms, and discusses examples from clinical trials. Implications for the design and analysis of clinical trials are discussed, and it is argued that covariation for baseline severity of the outcome measure and testing of the baseline-by-treatment interaction should be considered for inclusion in the primary outcome analyses of treatment effectiveness trials of substantial size. Nunes EV, Pavlicova M, Hu MC, Campbell AN, Miele G, Hien D, Klein DF. Baseline matters: the importance of covariation for baseline severity in the analysis of clinical trials. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 446-452.

Participant Characteristics and Buprenorphine Dose Clinical parameters for determining buprenorphine dose have not been adequately examined in treatment outcome research. This study is a secondary analysis of data collected in a recently completed comparison of buprenorphine taper schedules conducted as part of the National Institute on Drug Abuse's Clinical Trials Network to assess whether participant baseline characteristics are associated with buprenorphine dose. After 3 weeks of flexible dosing, 516 participants were categorized by dose provided in the final dosing week (9.3% received a final week dose of 8 mg buprenorphine, 27.3% received 16 mg, and 63.4% received 24 mg). Findings show that final week dose groups differed in baseline demographic and drug use characteristics including education, heroin use, route of drug administration, withdrawal symptoms, and craving. These groups also differed in opioid use during the four dosing weeks, with the lowest use in the 8 mg group and highest use in the 24 mg group ($p < .0001$). Additional analyses address withdrawal symptoms and craving. Final week dose groups differed in demographic and drug use characteristics, and the group receiving the largest final week dose had the highest rate of continued opioid use. These findings may contribute to the development of clinical guidelines regarding buprenorphine dose in the treatment of opioid dependence; however, further investigations that include random assignment to dose by baseline characteristics are needed. Hillhouse M, Canamar CP, Doraimani G, Thomas

C, Hasson A, Ling W. Participant characteristics and buprenorphine dose. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 453-459.

Rates and Influences of Alcohol Use Disorder Comorbidity Among Primary Stimulant Misusing Treatment-seekers: Meta-analytic Findings Across Eight NIDA CTN Trials There is need to improve treatment effectiveness for stimulant misusers, and one means of doing so is by tailoring services to account for common diagnostic comorbidities and psychosocial challenges they face. Using its publicly available datasets, this CTN-approved secondary analysis project examined prevalence of alcohol use disorders (AUDs) among primary stimulant misusing treatment-seekers as well as impact of AUD comorbidity on their pre-treatment psychosocial functioning. Upon identifying a primary stimulant misuser subsample (N = 1133) from among aggregated treatment-seekers across eight CTN trials, diagnostic data were used to document lifetime AUD rates. Paired comparisons, stratified by stimulant drug type (e.g., amphetamine, cocaine) then tested the influence of AUD comorbidity on psychosocial indices from the Addiction Severity Index – Lite. A high AUD rate (45%) was found in this client population. Among primary cocaine misusers, those with AUD were more likely to: (i) show elevated Addiction Severity Index composite scores, (ii) perceive greater importance of drug treatment, and (iii) endorse psychiatric symptoms and perceived need for their treatment. Among primary amphetamine misusers, those with AUD were more likely to endorse specific psychiatric symptoms. Study findings document AUD comorbidity as a fairly common diagnostic feature of primary stimulant misusers, and suggest it is a pervasive influence on the pre-treatment psychosocial functioning of cocaine misusers. This study demonstrates the utility of CTN common assessment battery for secondary analysis projects, though challenges noted during its conduct highlight the value of consistent data collection and documentation within and across CTN trials. Hartzler B, Donovan DM, Huang Z. Rates and influences of alcohol use disorder comorbidity among primary stimulant misusing treatment-seekers: meta-analytic findings across eight NIDA CTN trials. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 460-471.

Smoking Cessation Treatment Among Patients In Community-Based Substance Abuse Rehabilitation Programs: Exploring Predictors Of Outcome As Clues Toward Treatment Improvement Predictors of smoking cessation (SC) treatment outcome were explored in a multisite clinical trial of SC treatment at community-based, outpatient, substance abuse rehabilitation programs affiliated with the National Drug Abuse Treatment Clinical Trials Network. The objectives of this study were to explore baseline demographic and clinical predictors of abstinence during treatment. Cigarette smokers from five methadone maintenance programs and two drug and alcohol dependence treatment programs were randomly assigned to SC treatment as an adjunct to substance abuse treatment as usual or to substance abuse treatment as usual. SC treatment consisted of group counseling (weeks 1-8) plus transdermal nicotine patch treatment (21 mg/day, weeks 1-6; 14 mg/day, weeks 7-8). Demographic and clinical predictors of smoking abstinence were evaluated among those patients assigned to the active SC condition (N = 153) using logistic regression. Abstinence during treatment was positively associated with younger age, Hispanic or Caucasian (as opposed to African American) ethnicity/race, employment or student status, fewer cigarettes per day at baseline, lower severity of the primary substance problem at baseline, and higher methadone doses (among the subsample in methadone treatment). During future efforts to improve SC treatments among drug- and alcohol-dependent patients, consideration should be given to adequate treatment to reduce the severity of the primary drug or alcohol problem, tailoring treatments for patients with greater severity of smoking and of the primary substance problem, and culturally sensitive interventions. Analysis

of predictors of outcome may be a useful tool for treatment development. Reid MS, Jiang H, Fallon B, Sonne S, Rinaldi P, Turrigiano E, Arfken C, Robinson J, Rotrosen J, Nunes EV. Smoking cessation treatment among patients in community-based substance abuse rehabilitation programs: exploring predictors of outcome as clues toward treatment improvement. Am J Drug Alcohol Abuse. 2011 Sep; 37(5): 472-478.

INTERNATIONAL RESEARCH

HHH Fellow: Isidore Obot, Nigeria, 1991-1992

PLoS Med. 2011 Nov;8(11):e1001122. Epub 2011 Nov 15.

Evidence-Based Guidelines for Mental, Neurological, and Substance Use Disorders in Low- and Middle-Income Countries: Summary of WHO Recommendations

Dua T, Barbui C, Clark N, Fleischmann A, Poznyak V, van Ommeren M, Yasamy MT, Ayuso-Mateos JL, Birbeck GL, Drummond C, Freeman M, Giannakopoulos P, Levav I, Obot IS, Omigbodun O, Patel V, Phillips M, Prince M, Rahimi-Movaghar A, Rahman A, Sander JW, Saunders JB, Servili C, Rangaswamy T, Unützer J, Ventevogel P, Vijayakumar L, Thornicroft G, Saxena S. The authors summarize the recent WHO Mental Health Gap Action Programme (mhGAP) intervention guide that provides evidence-based management recommendations for mental, neurological, and substance use (MNS) disorders.

HHH Fellow: Flavio Pechansky, Brazil, 1993-1994

Int J Drug Policy. 2011 Nov 15. [Epub ahead of print]

Awareness Of Legal Blood Alcohol Concentration Limits Amongst Respondents Of A National Roadside Survey For Alcohol And Traffic Behaviours In Brazil

da Conceição TV, De Boni R, Duarte PD, Pechansky F. In Brazil the legal blood alcohol content (BAC) allowed for driving was changed to zero in 2008. If the BAC found is above 0.6g/L, drivers may be arrested. However, there are limited data on drivers' awareness of such limits. Drivers from 27 major metropolitan areas (n=3397) were randomly asked to participate in roadside survey from 12 a.m. to 12 p.m. on Fridays and Saturdays. They were breathalized by highway patrol officers, and after consent interviewers collected data on drinking behaviours, knowledge about the law, and breath tests results. The mean age was 37.3±11.3 years; 94.3% were male and 26.5% had some college education. When asked about the BAC that could result in arrest, 34.5% of the subjects claimed to know it. However, only 23.5% (8.1% of the total sample) provided correct answers. Factors associated with the right answers were: male gender ($p=0.04$; OR=2.08; CI=1.01-4.27); higher education ($p<0.0001$); negative BAC or self-report of driving under the influence (DUI) ($p=0.02$); higher family income ($p=0.01$) and non-professional driving ($p=0.041$). Age was not statistically different between groups. After multivariate analysis, male gender ($p=0.002$), higher education ($p<0.0001$) and negative BAC or DUI ($p=0.046$) remained in the model. The knowledge that BAC levels over 0.6g/L may result in arrest is sparse amongst Brazilian drivers, notably amongst women, the less educated and those who drink and drive. Educational programmes targeted at those specific groups may be necessary in order to increase awareness about the legal BAC limit and its consequences.

HHH Fellow: Taiwo Adamson, Nigeria, 1992-1993

Subst Abuse Treat Prev Policy. 2011 Sep 18;6:25.

A Descriptive Survey Of Types, Spread and Characteristics Of Substance Abuse Treatment Centers In Nigeria

Onifade PO, Somoye EB, Ogunwobi OO, Ogunwale A, Akinhanmi AO, Adamson TA. Nigeria, the most populous country in Africa and the 8th most populous in the world with a population of over 154 million, does not have current data on substance abuse treatment demand and treatment facilities; however, the country has the highest one-year prevalence rate of Cannabis use (14.3%) in Africa and ranks third in Africa with respect to the one-year prevalence rate of cocaine (0.7%) and Opioids (0.7%) use. This study aimed to determine the types, spread and characteristics of the substance abuse treatment centers in Nigeria. The study was a cross sectional survey of

substance abuse treatment centers in Nigeria. Thirty-one units were invited and participated in filling an online questionnaire, adapted from the European Treatment Unit/Program Form (June 1997 version). All the units completed the online questionnaire. A large proportion (48%) was located in the South-West geopolitical zone of the country. Most (58%) were run by Non-Governmental Organizations. Half of them performed internal or external evaluation of treatment process or outcome. There were a total of 1043 for all categories of paid and volunteer staff, with an average of 33 staff per unit. Most of the funding came from charitable donations (30%). No unit provided drug substitution/maintenance therapy. The units had a total residential capacity of 566 beds. New client admissions in the past one year totalled 765 (mean = 48, median = 26.5, min = 0, max = 147) and 2478 clients received services in the non-residential units in the past year. No unit provided syringe exchange services. The study revealed a dearth of substance abuse treatment units (and of funds for the available ones) in a country with a large population size and one of the highest prevalence rates of substance abuse in Africa. The available units were not networked and lacked a directory or an evaluation framework. To provide an environment for effective monitoring, funding and continuous quality improvement, the units need to be organized into a sustainable network.

HHH Fellow: Arun Kumar Sharma, India, 2004-2005

Stud Health Technol Inform. 2011;169:960-4.

Evaluation of Computer Usage in Healthcare Among Private Practitioners of NCT Delhi

Ganeshkumar P, Arun Kumar S, Rajoura OP. The objectives of this study were: 1. To evaluate the usage and the knowledge of computers and Information and Communication Technology in health care delivery by private practitioners. 2. To understand the determinants of computer usage by them. A cross sectional study was conducted among the private practitioners practising in three districts of NCT of Delhi between November 2007 and December 2008 by stratified random sampling method, where knowledge and usage of computers in health care and determinants of usage of computer was evaluated in them by a pre-coded semi open ended questionnaire. About 77% of the practitioners reported to have a computer and had the accessibility to internet. Computer availability and internet accessibility was highest among super speciality practitioners. Practitioners who attended a computer course were 13.8 times [OR: 13.8 (7.3 - 25.8)] more likely to have installed an EHR in the clinic. Technical related issues were the major perceived barrier in installing a computer in the clinic. Practice speciality, previous attendance of a computer course, age of started using a computer influenced the knowledge about computers. Speciality of the practice, presence of a computer professional and gender were the determinants of usage of computer.

HHH Fellow: Riza Sarasvita, Indonesia, 2003-2004

J Subst Abuse Treat. 2011 Sep 21. [Epub ahead of print]

Predictive Factors For Treatment Retention In Methadone Programs In Indonesia

Sarasvita R, Tonkin A, Utomo B, Ali R. This article presents the results of a 6-month prospective cohort study of methadone maintenance treatment (MMT) in Indonesia. The study aimed to investigate the predictor variables of retention in MMT in Indonesia. The duration of treatment (in days) was the main outcome of the study. For the study, program, client, social network, and accessibility factors were investigated as potential predictors of retention. The study analyzed the relative weight of each factor in predicting treatment retention. The sample consisted of 178 clients drawn from three participating clinics: Rumah Sakit Ketergantungan Obat and Tanjung Priok in Jakarta and Sanglah in Bali. The 3- and 6-month retention rates were 74.2% and 61.3%, respectively. These rates are comparable with previous studies conducted in

developed countries. A survival analysis using a robust estimation for the Cox PH regression found that the strongest predictors of retention were methadone dose followed by an interaction between take-home dose and the experience of the clinic providing this treatment. Other significant predictor variables included age, perceived clinic accessibility, and client's belief in the program. The study concludes that MMT cannot solely rely on the pharmacology for retention but should also promote informed access to take-home doses.

HHH Fellow: Olga Toussova, Russia, 2001-2002

Eur J Public Health. 2011 Oct;21(5):613-9. Epub 2010 Aug 26.

Estimates of HIV Incidence among Drug Users in St. Petersburg, Russia: Continued Growth of a Rapidly Expanding Epidemic

Niccolai LM, Verevochkin SV, Toussova OV, White E, Barbour R, Kozlov AP, Heimer R.

Russia has one of the world's fastest growing HIV epidemics and it has been largely concentrated among injection drug users (IDU). St Petersburg, Russia's second largest city, is one of the country's regions that has been most affected by the HIV epidemic. To monitor the current epidemic situation, we sought to estimate recent HIV incidence among IDU in St Petersburg. In a cross-sectional study of 691 IDU recruited during 2005-08, HIV incidence was estimated by two methods: a retrospective cohort analysis and BED capture enzyme immunoassay (EIA) results. Socio-demographic and behavioural correlates of incident infections and spatial patterns were examined. In the retrospective cohort analysis, the incidence rate was estimated to be 14.1/100 person-years [95% confidence interval (CI) 10.7-17.6]. Using results of BED EIA and two correction formulas for known misclassification, incidence estimates were 23.9 (95% CI 17.8-30.1) and 25.5 (95% CI 18.9-32.0) per 100 person-years. Independent correlates of being recently infected included current unemployment (P=0.004) and not having injected drugs in the past 30 days (P=0.03). HIV incident cases were detected in all but one district in the city, with focal areas of transmission observed to be expanding. High HIV incidence among IDU in St. Petersburg attests to continued growth of the epidemic. The need for expansion of HIV prevention interventions targeted to vulnerable populations throughout the city is urgent. These results also suggest that the BED EIA may over-estimate incidence even after correction for low specificity.

AIDS Behav. 2011 Jul 29. [Epub ahead of print]

Age at First Alcoholic Drink as Predictor of Current HIV Sexual Risk Behaviors Among a Sample of Injection Drug Users (IDUs) and Non-IDUs who are Sexual Partners of IDUs, in St. Petersburg, Russia

Abdala N, Hansen NB, Toussova OV, Krasnoselskikh TV, Kozlov AP, Heimer R.

This study investigates whether age at first alcoholic drink is associated with sexual risk behaviors among injection drug users (IDUs) and non-IDUs who are sexual partners of IDUs in St. Petersburg, Russia. A path analysis was used to test a model of age at first drink, age at sexual debut, age at first drug use, current substance use patterns and current sexual risk behaviors among 558 participants. Results revealed that age at first drink had an effect on multiple sex partners through age at sexual debut and injection drug use, but no effect on unprotected sex. Age at first drug use was not related to sexual risk behaviors. Investigation of age of drinking onset may provide useful information for programs to reduce sexual risk behaviors and injection drug use. Different paths leading to unprotected sex and multiple sexual partners call for different approaches to reduce sexual risk behaviors among this population.

HHH Fellow: David Otiashvili, Georgia, 2003-2004
Drug Alcohol Depend. 2011 Jul 8. [Epub ahead of print]
Drug Use and HIV Risk Outcomes In Opioid-Injecting Men In The Republic Of Georgia: Behavioral Treatment+Naltrexone Compared To Usual Care
Otiashvili D, Kirtadze I, O'Grady KE, Jones HE. The purpose of this study was to test the initial feasibility of a novel 22-week comprehensive intervention pairing behavioral treatment with naltrexone that aimed at engaging, retaining, and treating opioid-injecting men in the Republic of Georgia. Forty opioid-injecting male and their drug-free female partners participated in a two-group randomized clinical trial at the field site of the Union Alternative Georgia, in Tbilisi, Republic of Georgia. The comprehensive intervention that paired behavioral treatment with naltrexone for the male participants (n=20) included counseling sessions using Motivational Interviewing for both the male participant and the couple, monetary incentives for drug abstinence, and research-supported detoxification followed by naltrexone treatment. Male participants in the usual care condition (n=20) had the opportunity to attend once-a-week individualized education sessions and upon request receive referrals to detoxification programs and aftercare that could or could not have included naltrexone. Outcome measures included entry into inpatient detoxification and naltrexone treatment, urine drug screening, reduction in illicit substance use, use of benzodiazepines, injection of buprenorphine, and needle and syringe sharing. The comprehensive intervention condition showed significantly more weekly urine samples negative for illicit opioids during weeks 1-22 (7.0 vs. 1.4; $p<.001$) and reported significant declines in use of benzodiazepines and injection of buprenorphine (both $ps<.004$). 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.

HHH Fellow: Roumen Sedefov, Bulgaria, 1994-1995
Drug Test Anal. 2011 Jul;3(7-8):454-63. doi: 10.1002/dta.312. Epub 2011 Jul 13.
The Pharmacology and Toxicology Of the Synthetic Cathinone Mephedrone (4-Methylmethcathinone)
Dargan PI, Sedefov R, Gallegos A, Wood DM.
Mephedrone (4-methylmethcathinone) is a synthetic cathinone that is used as a recreational drug. It has been available since 2007 but its availability and use increased significantly during 2009 and 2010. In this review article the authors summarize the available literature on the sources, availability, and prevalence of the use of mephedrone. They also discuss the pharmacology of mephedrone, the patterns of acute toxicity associated with its use, the reports of fatalities associated with its use, and the potential for mephedrone dependence.

HHH Fellow: Sandra Reid, Trinidad and Tobago, 1992-1993
J Int Assoc Physicians AIDS Care (Chic). 2011 Aug 4. [Epub ahead of print]
Alcohol, Drugs, Sexual Behavior, and HIV in Trinidad and Tobago: The Way Forward
Reid SD, Malow RM, Rosenberg R. The HIV epidemic in Trinidad and Tobago is primarily heterosexual, fueled by a high level of risky sex, gender inequality, and alcohol and drug use; however, the influence of alcohol and drugs has been neglected in the literature. Research shows that current HIV prevention approaches have failed to substantially impact sexual behavior change. This may be so because they do not incorporate a comprehensive understanding of the sociocultural factors underlying sexual behavior. There is an urgent need to understand how socially accepted patterns of alcohol and drug use contribute to sexual behaviors and HIV risk in Trinidad and Tobago. Moreover, specialized, evidence-based interventions are needed for HIV-

infected substance abusers. Using an adaptation of the cognitive behavioral stress management (CBSM) protocol, this intervention project aimed to assess effectiveness in reducing relapse and risky behaviors among recovering HIV-infected substance abusers in Trinidad and Tobago.

HHH Fellow: Tomas Zabransky, Czech Republic, 2003-2004

Cent Eur J Public Health. 2011 Sep;19(3):152-7.

Mortality Of Cohort Of Very Young Injecting Drug Users In Prague, 1996-2010

Zábranský T, Csémy L, Grohmannová K, Janíková B, Brenza J. The aim of this study was to determine the mortality in a cohort of very young injecting drug users (IDUs), and the factors associated with it. A database linkage prospective (follow-up) cohort study. A convenience sample of clients of 2 low-threshold facilities, 1 drug treatment clinic, and one special facility for children with severe behavioural disorders, who were all younger than 19 and older than 15, was interviewed one or more times in 1996-8 and asked to agree with their being interviewed again after 10 or more years. Participants were 151 (65 male, 86 female) IDUs recruited in October 1996 - December 1998. This database linkage study compared unique identifiers (IDs) of the recruited subjects with the general register of deaths to determine the life status, and the causes of death of those deceased. Where necessary, the authors examined the death protocols directly. Altogether, 8 deaths were registered between recruitment and 31st December 2008 (1,660 person-years). All the deceased were male, and all their deaths were "unnatural"– that is, caused by drug overdose or accident. This translates into the crude mortality rates for the whole cohort being 4.8 deaths per 1,000 person-years (PY), and into a specific mortality ratio in the males SMR=14.4 with the peak at the age of 15-20 (SMR=60.1), declining to SMR=8.2 at the age of 25-30. Except gender, the authors found no "predictors of death" in this high-risk cohort. The overall mortality in the cohort was substantially higher than in the general population; in the male part of the cohort of young injecting drug users it was excessively high in the first three years after recruitment, and caused by external causes exclusively; the mortality in the female sub-cohort was zero, i.e., lower than in the general population of the same age range. These findings suggest a need to develop targeted prevention of overdoses and other unnatural deaths in young male drug injectors.

HHH Fellow: Arthur Guerra de Andrade, Brazil, 1991-1992

J Nerv Ment Dis. 2011 Nov;199(11):866-71.

Perceptions Of and Attitudes Toward Antidepressants: Stigma Attached To Their Use-A Review

Castaldelli-Maia JM, Scomparini LB, Andrade AG, Bhugra D, de Toledo Ferraz Alves TC, D'Elia G. The aim of this study was to ascertain whether there is any evidence of stigma related to the use of antidepressants. Using the PubMed and MEDLINE databases, the authors searched for the terms stigma, antidepressants, and depression. A protocol was developed to extract information from the papers, which were identified and explored further. Thirty-two papers were identified. TheWe found that the stigma against depression differs from stigma against the use of antidepressants. Stigma against depression does not impact on therapeutic adherence to antidepressant use. Stigma related to antidepressant use appears to be linked with perceived emotional weakness, severity of illness, an inability to deal with problems, and a lack of belief in the therapeutic efficacy of antidepressants. Stigma against medication can be a useful target for interventions, just like the stigma related to depression. However, clinicians must be careful in avoiding the medicalization of symptoms.

INVEST Fellow: Min Zhao, China, 2001-2002

PLoS One. 2011;6(8):e22923. Epub 2011 Aug 17.

Role of Novelty Seeking Personality Traits as Mediator of the Association between COMT and Onset Age of Drug Use in Chinese Heroin Dependent Patients

Li T, Yu S, Du J, Chen H, Jiang H, Xu K, Fu Y, Wang D, Zhao M. Personality traits such as novelty seeking (NS) are associated with substance dependence but the mechanism underlying this association remains uncertain. Previous studies have focused on the role of the dopamine pathway. The objective of this study was to examine the relationships between allelic variants of the catechol-O- methlytransferase (COMT) gene, NS personality traits, and age of onset of drug use in heroin-dependent subjects in China. The 478 heroin dependent subjects from four drug rehabilitation centers in Shanghai who were genotyped for eight tagging single nucleotide polymorphisms (SNP) on the COMT gene completed the NS subscale from the Temperament and Character Inventory. Multivaritate analyses were used to assess the potential mediating role of NS personality traits in the association between COMT gene variants and the age of onset of heroin use. In the univariate analysis the COMT rs737866 gene variants were independently associated with both NS and age of onset of drug use: those with the TT genotype had higher NS subscale scores and an earlier onset age of heroin use than individuals with CT or CC genotypes. In the multivariate analysis the inclusion of the NS subscore variable weakened the relationship between the COMT rs737866 TT genotype and an earlier age of onset of drug use. These findings that COMT is associated with both NS personality traits and with the age of onset of heroin use helps to clarify the complex relationship between genetic and psychological factors in the development of substance abuse.

Addiction. 2011 Jul 27. doi: 10.1111/j.1360-0443.2011.03490.x. [Epub ahead of print]

Effects Of A Randomized Contingency Management Intervention On Opiate Abstinence and Retention In Methadone Maintenance Treatment In China

Hser YI, Li J, Jiang H, Zhang R, Du J, Zhang C, Zhang B, Evans E, Wu F, Chang YJ, Peng C, Huang D, Stitzer ML, Roll J, Zhao M. 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 employed 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 comprised 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. Outcome measures 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.

INTRAMURAL RESEARCH

Office of the Scientific Director

Excitatory Transmission From the Amygdala To Nucleus Accumbens Facilitates Reward Seeking The basolateral amygdala (BLA) has a crucial role in emotional learning irrespective of valence. The BLA projection to the nucleus accumbens (NAc) is thought to modulate cue-triggered motivated behaviours, but our understanding of the interaction between these two brain regions has been limited by the inability to manipulate neural-circuit elements of this pathway selectively during behaviour. To circumvent this limitation, IRP scientists used in vivo optogenetic stimulation or inhibition of glutamatergic fibres from the BLA to the NAc, coupled with intracranial pharmacology and ex vivo electrophysiology. Here they show that optical stimulation of the pathway from the BLA to the NAc in mice reinforces behavioural responding to earn additional optical stimulation of these synaptic inputs. Optical stimulation of these glutamatergic fibres required intra-NAc dopamine D1-type receptor signalling, but not D2-type receptor signalling. Brief optical inhibition of fibres from the BLA to the NAc reduced cue-evoked intake of sucrose, demonstrating an important role of this specific pathway in controlling naturally occurring reward-related behaviour. Moreover, although optical stimulation of glutamatergic fibres from the medial prefrontal cortex to the NAc also elicited reliable excitatory synaptic responses, optical self-stimulation behaviour was not observed by activation of this pathway. These data indicate that whereas the BLA is important for processing both positive and negative affect, the glutamatergic pathway from the BLA to the NAc, in conjunction with dopamine signalling in the NAc, promotes motivated behavioural responding. Thus, optogenetic manipulation of anatomically distinct synaptic inputs to the NAc reveals functionally distinct properties of these inputs in controlling reward-seeking behaviours. Stuber GD, Sparta DR, Stamatakis AM, van Leeuwen WA, Hardjoprajitno JE, Cho S, Tye KM, Kempadoo KA, Zhang F, Deisseroth K, Bonci A. Excitatory transmission from the amygdala to nucleus accumbens facilitates reward seeking. Nature. 2011 Jun 29; 475(7356): 377-380

Optogenetic Interrogation Of Dopaminergic Modulation Of the Multiple Phases Of Reward-Seeking Behavior Phasic activation of dopaminergic neurons is associated with reward-predicting cues and supports learning during behavioral adaptation. While noncontingent activation of dopaminergic neurons in the ventral tegmental are (VTA) is sufficient for passive behavioral conditioning, it remains unknown whether the phasic dopaminergic signal is truly reinforcing. In this study, IRP researchers first targeted the expression of channelrhodopsin-2 to dopaminergic neurons of the VTA and optimized optogenetically evoked dopamine transients. Second, we showed that phasic activation of dopaminergic neurons in freely moving mice causally enhances positive reinforcing actions in a food-seeking operant task. Interestingly, such effect was not found in the absence of food reward. The authors further found that phasic activation of dopaminergic neurons is sufficient to reactivate previously extinguished food-seeking behavior in the absence of external cues. This was also confirmed using a single-session reversal paradigm. Collectively, these data suggest that activation of dopaminergic neurons facilitates the development of positive reinforcement during reward-seeking and behavioral flexibility. Adamantidis AR, Tsai HC, Boutrel B, Zhang F, Stuber GD, Budygin EA, Touriño C, Bonci A, Deisseroth K, de Lecea L. Optogenetic interrogation of dopaminergic modulation of the multiple phases of reward-seeking behavior. J Neurosci. 2011 Jul 27; 31(30): 10829-19835.

Endocytosis Promotes Rapid Dopaminergic Signaling D(1) dopamine receptors are primary mediators of dopaminergic signaling in the CNS. These receptors internalize rapidly following agonist-induced activation, but the functional significance of this process is unknown. IRP scientists investigated D(1) receptor endocytosis and signaling in HEK293 cells and cultured striatal neurons using real-time fluorescence imaging and cAMP biosensor technology. Agonist-induced activation of D(1) receptors promoted endocytosis of receptors with a time course overlapping that of acute cAMP accumulation. Inhibiting receptor endocytosis blunted acute D(1) receptor-mediated signaling in both dissociated cells and striatal slice preparations. Although endocytic inhibition markedly attenuated acute cAMP accumulation, inhibiting the subsequent recycling of receptors had no effect. Further, D(1) receptors localized in close proximity to endomembrane-associated trimeric G protein and adenylyl cyclase immediately after endocytosis. Together, these results suggest a previously unanticipated role of endocytosis, and the early endocytic pathway, in supporting rapid dopaminergic neurotransmission. Kotowski SJ, Hopf FW, Seif T, Bonci A, von Zastrow M. Endocytosis promotes rapid dopaminergic signaling. Endocytosis promotes rapid dopaminergic signaling. Neuron. 2011 Jul 28; 71(2): 278-290.

The SK Channel As A Novel Target For Treating Alcohol Use Disorders IRP researchers recently described the SK-type potassium channel as a novel target for treatment of excessive alcohol intake.1 SK channel function is reduced in the nucleus accumbens (NAcb) core in rats consuming alcohol under intermittent (IAA) but not continuous (CAA) access, and the FDA-approved SK activator chlorzoxazone reduces the excessive alcohol intake in IAA rats but not the more moderate intake in CAA rats. Here, they discuss the implications of these and related findings for SK as a treatment for alcohol use disorders. In addition, they report that many NAcb core electrophysiological parameters related to action potential waveform or basal parameters were not altered in alcohol-drinking rats. These results are in strong contrast to those reported for cocaine, where several NAcb ion channels show adaptations after cocaine exposure. These results suggest that alcohol intake is associated with only limited ion channel neuro-adaptations in the NAcb relative to cocaine, and support the hypothesis that SK represents a selective and potent intervention to reduce excessive alcohol intake. Hopf FW, Seif T, Bonci A. The SK channel as a novel target for treating alcohol use disorders. Channels (Austin). 2011 Jul-Aug; 5(4): 289-292.

Cellular Neurobiology Research Branch

Electrophysiology Research Section

Altered Dopamine Metabolism and Increased Vulnerability To MPTP In Mice With Partial Deficiency Of Mitochondrial Complex I In Dopamine Neurons A variety of observations support the hypothesis that deficiency of complex I [reduced nicotinamide-adenine dinucleotide (NADH):ubiquinone oxidoreductase] of the mitochondrial respiratory chain plays a role in the pathophysiology of Parkinson's disease (PD). However, recent data from a study using mice with knockout of the complex I subunit NADH:ubiquinone oxidoreductase iron-sulfur protein 4 (Ndufs4) has challenged this concept as these mice show degeneration of non-dopamine neurons. In addition, primary dopamine (DA) neurons derived from such mice, reported to lack complex I activity, remain sensitive to toxins believed to act through inhibition of complex I. The authors tissue-specifically disrupted the Ndufs4 gene in mouse heart and

found an apparent severe deficiency of complex I activity in disrupted mitochondria, whereas oxidation of substrates that result in entry of electrons at the level of complex I was only mildly reduced in intact isolated heart mitochondria. Further analyses of detergent-solubilized mitochondria showed the mutant complex I to be unstable but capable of forming supercomplexes with complex I enzyme activity. The loss of Ndufs4 thus causes only a mild complex I deficiency in vivo. The authors proceeded to disrupt Ndufs4 in midbrain DA neurons and found no overt neurodegeneration, no loss of striatal innervation and no symptoms of Parkinsonism in tissue-specific knockout animals. However, DA homeostasis was abnormal with impaired DA release and increased levels of DA metabolites. Furthermore, Ndufs4 DA neuron knockouts were more vulnerable to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine. Taken together, these findings lend in vivo support to the hypothesis that complex I deficiency can contribute to the pathophysiology of PD. Sterky FH, Hoffman AF, Milenkovic D, Bao B, Paganelli A, Edgar D, Wibom R, Lupica CR, Olson L, Larsson NG. Altered dopamine metabolism and increased vulnerability to MPTP in mice with partial deficiency of mitochondrial complex I in dopamine neurons. Hum Mol Genet. 2011; Dec 7. [Epub ahead of print]

Molecular Neuropsychiatry Research Branch

Long-Term Protective Effects Of Methamphetamine Preconditioning Against Single-Day Methamphetamine Toxic Challenges Methamphetamine (METH) use is associated with neurotoxic effects which include decreased levels of dopamine (DA), serotonin (5-HT) and their metabolites in the brain. IRP researchers have shown that escalating METH dosing can protect against METH induced neurotoxicity in rats sacrificed within 24 hours after a toxic METH challenge. The purpose of the current study was to investigate if the protective effects of METH persisted for a long period of time. They also tested if a second challenge with a toxic dose of METH would cause further damage to monoaminergic terminals. Saline-pretreated rats showed significant METH-induced decreases in striatal DA and 5-HT levels in rats sacrificed 2 weeks after the challenge. Rats that received two METH challenges showed no further decreases in striatal DA or 5-HT levels in comparison to the single METH challenge. In contrast, METH-pretreated rats showed significant protection against METH-induced striatal DA and 5-HT depletion. In addition, the METH challenge causes substantial decreases in cortical 5-HT levels which were not further potentiated by a second drug challenge. METH preconditioning provided almost complete protection against METH -induced 5-HT depletion. These results are consistent with the idea that METH pretreatment renders the brain refractory to METH-induced degeneration of brain monoaminergic systems. Hodges AB, Ladenheim B, McCoy MT, Beauvais G, Cai N, Krasnova IN, Cadet JL. Curr Neuropharmacol. Mar; 9(1): 35-39, 2011.

Neural Protection and Regeneration Section

Post-Treatment With Amphetamine Enhances Reinnervation Of the Ipsilateral Side Cortex In Stroke Rats Amphetamine (AM) treatment has been shown to alter behavioral recovery after ischemia caused by embolism, permanent unilateral occlusion of the common carotid and middle cerebral arteries, or unilateral sensorimotor cortex ablation in rats. However, the behavioral results are inconsistent possibly due to difficulty controlling the size of the lesion before treatment. There is also evidence that AM promotes neuroregeneration in the cortex

contralateral to the infarction; however, the effects of AM in the ipsilateral cortex remain unclear. The purpose of this study was to employ T2-weighted imaging (T2WI) to establish controlled criteria for AM treatment and to examine neuroregenerative effects in both cortices after stroke. Adult rats were anesthetized, and the right middle cerebral artery was ligated for 90min to generate lesions in the ipsilateral cortex. Animals were separated into two equal treatment groups (AM or saline) according to the size of infarction, measured by T2WI at 2days after stroke. AM or saline was administered to stroke rats every third day starting on day 3 for 4weeks. AM treatment significantly reduced neurological deficits, as measured by body asymmetry and Bederson's score. T2WI and diffusion tensor imaging (DTI) were used to examine the size of infarction and axonal reinnervation, respectively, before and following treatment on days 2, 10 and 25 after stroke. AM treatment reduced the volume of tissue loss on days 10 and 25. A significant increase in fractional anisotropy ratio was found in the ipsilateral cortex after repeated AM administration, suggesting a possible increase in axonal outgrowth in the lesioned side cortex. Western analysis indicated that AM significantly increased the expression of synaptophysin ipsilaterally and neurofilament bilaterally. AM also enhanced matrix metalloproteinase (MMP) enzymatic activity, determined by MMP zymography in the lesioned side cortex. qRT-PCR was used to examine the expression of trophic factors after the 1st and 2nd doses of AM or saline injection. The expression of BDNF, but not BMP7 or CART, was significantly enhanced by AM in the lesioned side cortex. In conclusion, post-stroke treatment with AM facilitates behavioral recovery, which is associated with an increase in fractional anisotropy activity, enhanced fiber growth in tractography, synaptogenesis, upregulation of BDNF, and MMP activity mainly in the lesioned cortex. These data suggest that the ipsilateral cortex may be the major target of action in stroke brain after AM treatment. Liu HS, Shen H, Harvey BK, Castillo P, Lu H, Yang Y, Wang Y. Post-treatment with amphetamine enhances reinnervation of the ipsilateral side cortex in stroke rats. Neuroimage. 2011; 56: 280-289.

Clinical Pharmacology and Therapeutics Research Branch

Treatment Section

Stress In The Daily Lives Of Cocaine and Heroin Users: Relationship To Mood, Craving, Relapse Triggers, and Cocaine Use Quantitative real-time data on the stress experienced by drug misusers in their daily lives may provide additional insight into stress's role in drug use. The purpose of this study is to evaluate stress in relation to craving, mood, relapse-trigger exposure, and cocaine use in cocaine-dependent outpatients. Methadone-maintained cocaine- and heroin- abusing outpatients(N = 114) provided ecological momentary assessment data on handheld computers. Ratings of stress were compared to those of craving and mood and past-hour exposure to putative drug-use triggers in randomly prompted entries and in the 5 h prior to participant- initiated cocaine use reports. Stress had significant positive relationships with current ratings of craving for cocaine, heroin, and tobacco and with ratings of tiredness, boredom, and irritation, and had significant negative relationships with ratings of happiness and relaxation. Stress was significantly greater in entries in which participants also reported past-hour exposure to negative-mood triggers, most of the drug- exposure triggers, or any trigger involving thoughts about drugs (e.g., tempted out of the blue). The linear increase in stress during the 5-h preceding individual episodes of cocaine use was not significant ($p = 0.12$), though there was a trend for such an increase before the use episodes that participants attributed to stressful states when they

occurred (p = 0.087). The findings suggest a complex role of stress in addiction. Stress reported in real time in the natural environment showed strong cross-sectional momentary relationships with craving, mood, and exposure to drug- use trigger. However, the prospective association between stress ratings and cocaine-use episodes was, at best, weak. Preston KL, Epstein DH. Psychopharmacology 2011; 218: 29-37.

Clonidine Blocks Stress-Induced Craving In Cocaine Users Reactivity to stressors and environmental cues, a putative cause of relapse in addiction, may be a useful target for relapse-prevention medication. In rodents, alpha-2 adrenergic agonists such as clonidine block stress-induced reinstatement of drug seeking, but not drug cue-induced reinstatement. The objective of this study is to test the effect of clonidine on stress- and cue-induced craving in human cocaine users. Healthy, non-treatment-seeking cocaine users (n=59) were randomly assigned to three groups receiving clonidine 0, 0.1, or 0.2 mg orally under double-blind conditions. In a single test session, each participant received clonidine or placebo followed 3 h later by exposure to two pairs of standardized auditory-imagery scripts (neutral/stress and neutral/drug). Subjective measures of craving were collected. Subjective responsivity ("crave cocaine" Visual Analog Scale) to stress scripts was significantly attenuated in the 0.1- and 0.2-mg clonidine groups; for drug-cue scripts, this attenuation occurred only in the 0.2-mg group. Other subjective measures of craving showed similar patterns of effects but Dose × Script interactions were not significant. Clonidine was effective in reducing stress-induced (and, at a higher dose, cue-induced) craving in a pattern consistent with preclinical findings, although this was significant on only one of several measures. These results, though modest and preliminary, converge with other evidence to suggest that alpha-2 adrenergic agonists may help prevent relapse in drug abusers experiencing stress or situations that remind them of drug use. Jobes ML, Ghitza UE, Epstein DH, Phillips KA, Heishman SJ, Preston KL. Psychopharmacology 2011; 218: 83-88.

Nicotine Psychopharmacology Section

The Older Smoker Smoking prevalence is lower for older adults (≥ 65 years of age; 8.3%) compared with younger adults (≤ 64 years; 22.2%); however, the likelihood of trying to quit smoking in older adults (25.3%) is half that of smokers aged 18 to 24 years (53.1%). Decreases in smoking rates between 1965 and 1994 were smaller for individuals 65 or older (5.9% reduction) compared with younger adults (≤ 64 years; 18.4% reduction). Research indicates that quitting smoking at any age can increase life expectancy and improve health and quality of life. Accordingly, the Clinical Practice Guideline for the Treatment of Tobacco Use and Dependence highlights older smokers as a subpopulation for which treatments might require tailoring because of unique age-related characteristics. Clinicians should consider that older smokers will be an increasing proportion of the patient population and that these smokers might require modification of treatment for smoking cessation. Kleykamp BA, Heishman SJ. The older smoker. JAMA 2011; 306: 876-877.

Effects of Varenicline on Cognitive Biomarkers in Smokers and Nonsmokers with Schizophrenia Nicotine administration transiently improves many neurobiological and cognitive functions in schizophrenia, leading to the pharmaceutical effort to target neuronal nicotinic acetylcholine receptors (nAChRs) for novel CNS drug development. It is not yet clear which nAChR subtype(s) is responsible for these seemingly pervasive nicotinic effects in

schizophrenia. α4β2 is a key nAChR subtype for nicotinic actions. The authors investigated the effect of varenicline, a relatively specific α4β2 partial agonist/antagonist, on key biomarkers that are associated with schizophrenia and are previously shown to be responsive to nicotinic challenge in humans. This was a double-blind, parallel, randomized, placebo controlled trial in schizophrenia patients to examine effects of varenicline on biomarkers at short-term (2 week) and long-term (8 week), using a slow titration and moderate dosing strategy for retaining α4β2 specific effect while minimizing side effects. The study was conducted in an outpatients setting where 69 smoking and nonsmoking patients were randomized; 64 completed week 2; 59 completed week 8. The intervention was varenicline and the main outcome measures included: prepulse inhibition, sensory gating, antisaccade, spatial working memory, eyetracking, processing speed, and sustained attention. A moderate dose of varenicline 1) reduced P50 sensory gating deficit after a long-term ($p=0.006$) but not short-term treatment; significant in nonsmokers but not in smokers; 2) reduced startle reactivity ($p=0.015$) regardless of baseline smoking status; and 3) improved executive function by reducing antisaccade error rate ($p=0.034$) regardless of smoking status. Moderate dose varenicline had no significant effect on spatial working memory, predictive and maintenance pursuit, processing speed, or sustained attention by Connor's CPT. Clinically, there was no evidence of exacerbation of psychiatric symptoms, psychosis, depression, or suicidality using a gradual titration, 1 mg daily dose. Instead, the study showed nonsignificant trends toward improving psychosis ($p=0.053$) and overall psychiatric symptoms ($p=0.074$) compared with placebo. The authors conclude that moderate dose varenicline has a unique treatment profile on core schizophrenia related biomarkers. Further development is warranted for specific nAChR compounds and dosing/duration strategy to target subgroup of schizophrenia patients with specific biological deficits. Hong LE, Thaker GK, McMahon RP, Summerfelt A, RachBeisel J, Fuller RL, Wonodi I, Buchanan RW, Myers C, Heishman SJ, Yang J, Nye A. Effects of moderate-dose treatment with varenicline on neurobiological and cognitive biomarkers in smokers and nonsmokers with schizophrenia or schizoaffective disorder. Arch Gen Psychiatry 2011; 68: 1195-1206.

Oral Fluid Nicotine Markers to Assess Smoking Status and Recency of Use Oral fluid collection is non-invasive and easily observed making it an attractive matrix for objectively determining smoking status. Despite large inter-subject variability, cotinine oral fluid concentrations correlate with cigarettes smoked per day (CPD). Few studies, however, assessed nicotine markers in oral fluid other than cotinine; other markers might improve smoking status assessment and/or time of last cigarette. Smoking histories and oral fluid specimens were collected from non-treatment-seeking light (1-10 CPD) and heavy smokers (>10 CPD), and from environmentally exposed and nonexposed nonsmokers who provided written informed consent for this Institutional Review Board-approved study. Nicotine, cotinine, hydroxycotinine (OH-cotinine) and norcotinine oral fluid concentrations were quantified via liquid chromatography tandem mass spectrometry (LCMSMS). Results comprised cmparison of 1, 3 and 10ng/mL oral fluid LCMSMS cutoffs demonstrated that 10ng/mL cutoffs performed optimally for cotinine, OH-cotinine, nicotine and norcotinine identifying 98, 97, 88 and 15% of self-reported smokers; 1% nonsmokers had >10ng/mL cotinine. No self-reported nonsmoker had >10ng/mL OH-cotinine, nicotine or norcotinine. Norcotinine was only identified in smokers' oral fluid. Oral fluid nicotine, cotinine and nicotine/cotinine ratios were negatively correlated with time of last smoking ($r=-0.53$, -0.23, and -0.51; $p<0.05$) and CPD ($r=0.35$, 0.26 and 0.33; $p<0.01$), respectively. OH-cotinine performed slightly better than cotinine for distinguishing smokers from nonsmokers and should be considered as an additional oral fluid smoking indicator. Further research is required to determine if oral fluid norcotinine is a marker for distinguishing light and

heavy smokers. Moderate correlations suggest nicotine, cotinine and nicotine/cotinine ratios may be useful for determining smoking recency in "spot samples" collected during nicotine cessation treatment. Scheidweiler KB, Marrone GF, Shakleya DM, Singleton EG, Heishman SJ, Huestis MA. Oral fluid nicotine markers to assess smoking status and recency of use. Ther Drug Monitoring 2011; 33: 609-618.

Chemical Biology Research Branch

Drug Design and Synthesis Section

Diastereoselective One-Pot Synthesis of 7- and 8-Substituted 5-Phenylmorphans
Novel 7- and 8-alkyl and aryl substituted 5-phenylmorphans were synthesized from substituted allyl halides and N-benzyl-4-aryl-1,2,3,6-tetrahydropyridine by a highly efficient and diastereoselective reaction series, "one-pot" alkylation and ene-imine cyclization followed by sodium borohydride reduction. Mild cyclization conditions gave the desired substituted 5-phenylmorphans in good yield as a single diastereomer. Lim HJ, Deschamps JR, Jacobson AE, Rice KC . Org Lett. 2011 Oct 7; 13(19): 5322-5325. Epub 2011 Sep 12.

GABAB 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-3*H*-benzofuran-2-one (rac-BHFF) at γ-aminobutyric acid B (GABAB) receptors in different brain regions. Using quantitative autoradiography, we measured GABAB receptor-stimulated binding of guanosine 5′-*O*-(3-[35S]thiotriphosphate) ([35S]GTPγS) to G proteins in medial prefrontal cortex (mPFC), hippocampus, and cerebellum. CGP7930 and rac-BHFF enhanced baclofen-stimulated [35S]GTPγS binding similarly in mPFC and hippocampus, but were more effective in cerebellum. CGP7930 (100 μM) increased [35S]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 [35S]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 [35S]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 [35S]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 [35S]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 GABAB receptor-positive modulators enhance [35S]GTPγS binding stimulated by GABAB receptor agonists in a brain region-dependent manner. This regionally selective enhancement is further evidence of pharmacologically distinct GABAB receptor populations, possibly allowing for more selective therapeutic targeting of the GABAB system. Hensler JG, Advani T, Burke TF, Cheng K, Rice KC, Koek W. J. Pharmacol. Exp. Ther. 2012 Jan 340: 19-26. Epub 2011 Sep 27.

Effects of Peripherally Restricted Kappa Opioid Receptor Agonists on Pain-Stimulated and Pain-Depressed Behavior in Rats Kappa opioid receptor agonists that do not readily cross the blood-brain barrier are peripherally restricted and distribute poorly to the central nervous system after systemic administration. Peripherally restricted kappa agonists have promise as candidate analgesics because they may produce antinociception mediated by peripheral kappa receptors more potently than they produce undesirable sedative and psychotomimetic effects mediated by central kappa receptors. The present study used assays of pain-related stimulation and depression of behavior in rats to compare effects of (a) two peripherally restricted kappa agonists [the tetrapeptide D-Phe-D-Phe-D-Ile-D-Arg-NH2 (ffir) and the nonpeptidic compound ICI204448], (b) a centrally penetrating kappa agonist (salvinorin A), and (c) several reference drugs including a nonsteroidal anti-inflammatory drug (NSAID; ketoprofen). Intraperitoneal injection of dilute lactic acid served as a noxious stimulus to stimulate a stretching response and to depress intracranial self-stimulation (ICSS) maintained by delivery of electrical brain stimulation to the medial forebrain bundle. Acid-stimulated stretching was blocked by ketoprofen, the peripherally restricted kappa agonists, and salvinorin A. However, acid-induced depression of ICSS was blocked only by ketoprofen. The peripherally restricted kappa agonists had little effect, and salvinorin A exacerbated acid-induced depression of ICSS. These results suggest that peripherally restricted kappa agonists may be safer than centrally penetrating kappa agonists but less efficacious than NSAIDS or mu opioid receptor agonists to block pain-related depression of behavior; however, the peripheral selectivity of ffir and ICI204448 is limited, and future studies with kappa agonists capable of greater peripheral selectivity are warranted. Negus SS, O'Connell R, Morrissey E, Cheng K, Rice KC. J. Pharmacol. Exp. Ther. Epub 2011 Nov 29.

Inhibiting the TLR4-Myd88 Signalling Cascade by Genetic or Pharmacological Stratigies Reduces Acute Alcohol-Induced Sedation and Motor Impairment in Mice Emerging evidence implicates a role for toll-like receptor 4 (TLR4) in the central nervous system effects of alcohol. The current study aimed to determine whether TLR4-MyD88-dependent signalling was involved in the acute behavioural actions of alcohol and if alcohol could activate TLR4-downstream MAPK and NFκB pathways. The TLR4 pathway was evaluated using the TLR4 antagonist (+)-naloxone (μ-opioid receptor-inactive isomer) and mice with null mutations in the *TLR4* and *MyD88* genes. Sedation and motor impairment induced by a single dose of alcohol were assessed by loss of righting reflex (LORR) and rotarod tests, separately. The phosphorylation of JNK, ERK, and p38, and levels of IκBα were measured to determine the effects of acute alcohol exposure on MAPK and NFκB signalling. After a single dose of alcohol, both pharmacological inhibition of TLR4 signalling with (+)-naloxone and genetic deficiency of TLR4 or MyD88 significantly ($p < 0.0001$) reduced the duration of LORR by 45-78%, and significantly ($p < 0.05$) decreased motor impairment recovery time to 62-88% of controls. These behavioural actions were not due to changes in the peripheral or central alcohol pharmacokinetics. IκBα levels responded to alcohol by 30 min in mixed hippocampal cell samples, from wild-type mice, but not in cells from TLR4 or MyD88 deficient mice. These data provide new evidence that TLR4-MyD88 signalling is involved in the acute behavioural actions of alcohol in mice. Wu Y, Lousberg EL, Moldenhauer LM, Hayball JD, Robertson SA, Coller JK, Rice KC, Watkins LR, Somogyi AA, Hutchinson MR. British J. Pharmacol. Epub 2011 Sep 29.

Recombinant Cannabinoid Type 2 (CB2) Receptor in Liposome Model Activates G Protein in Response to Anionic Lipid Constituents Human cannabinoid type 2 (CB2) receptor expressed in E. coli was purified and successfully reconstituted in the functional form into lipid bilayers composed of POPC, POPS, and CHS. Reconstitution was performed by detergent removal from the protein/lipid/detergent mixed micelles either on an adsorbent column, or by rapid dilution to below the critical micelle concentration of detergent followed by removal of detergent monomers on a concentrator. Proteoliposomes prepared at a protein/phospholipid/CHS molar ratio of 1/620-650/210-220 are free of detergent shown by 1H NMR, have a homogeneous protein/lipid ratio shown by isopycnic gradient ultracentrifugation, and are small in size with a mean diameter of 150-200 nm as measured by dynamic light scattering. Functional integrity of the reconstituted receptor was confirmed by quantitative binding of 2H-labeled agonist CP-55,940-d6 measured by 2H magic-angle spinning NMR as well as by activation of G protein. The efficiency of G protein activation by agonist-bound CB2 receptor was affected by negative electric surface potentials of proteoliposomes controlled by the content of anionic CHS or POPS. The activation was highest at an anionic lipid content of about 50 mol%. There was no correlation between the efficiency of G protein activation and an increase of hydrocarbon chain order induced by CHS or cholesterol. The results suggest importance of anionic lipids in regulating signal transduction by CB2 receptor and other class-A GPCR. The successful reconstitution of milligram quantities of pure, functional CB2 receptor enables a wide variety of structural studies. Kimura T, Yeliseev AA, Vukoti K, Rhodes SD, Cheng K, Rice KC, Gawrisch K. J. Biol. Chem. Epub 2011 Dec 1.

The Neuropharmacology of Prolactin Secretion Elicited by 3,4-Methylenedioxy-methamphetamine ("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, we evaluated the role of the serotonin transporter and the 5-HT2A 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-HT2A 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-HT2A receptors. Accordingly, these findings inform our understanding of the neuropharmacology of both S,R(±)-MDMA and R(-)-MDMA and the regulation of prolactin secretion. Murname KS, Kimmel HL, Rice KC, Howell LL. Horm. Behav. Epub 2011 Dec 14.

Translational Pharmacology Research Section

The Designer Methcathinone Analogs, Mephedrone and Methylone, Are Substrates For Monoamine Transporters In Brain Tissue The nonmedical use of 'designer' cathinone analogs, such as 4-methylmethcathinone (mephedrone) and 3,4-methylenedioxymethcathinone (methylone), is increasing worldwide, yet little information is available regarding the mechanism of action for these drugs. Here, the authors employed in vitro and in vivo methods to compare neurobiological effects of mephedrone and methylone with those produced by the structurally related compounds, 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamine. In vitro release assays using rat brain synaptosomes revealed that mephedrone and methylone are nonselective substrates for plasma membrane monoamine transporters, similar to MDMA in potency and selectivity. In vivo microdialysis in rat nucleus accumbens showed that i.v. administration of 0.3 and 1.0 mg/kg of mephedrone or methylone produces dose-related increases in extracellular dopamine and serotonin (5-HT), with the magnitude of effect on 5-HT being greater. Both methcathinone analogs were weak motor stimulants when compared with methamphetamine. Repeated administrations of mephedrone or methylone (3.0 and 10.0 mg/kg, s.c., 3 doses) caused hyperthermia but no long-term change in cortical or striatal amines, whereas similar treatment with MDMA (2.5 and 7.5 mg/kg, s.c., 3 doses) evoked robust hyperthermia and persistent depletion of cortical and striatal 5-HT. These data demonstrate that designer methcathinone analogs are substrates for monoamine transporters, with a profile of transmitter-releasing activity comparable to MDMA. Dopaminergic effects of mephedrone and methylone may contribute to their addictive potential, but this hypothesis awaits confirmation. Given the widespread use of mephedrone and methylone, determining the consequences of repeated drug exposure warrants further study. Baumann, M, Ayestas MA, Partilla JS, Sink JR, Shulgin AT, Daley PF, Brandt SD, Rothman RB, Ruoho AE Cozzi NV. Neuropsychopharmacology 2011 Dec 14, [Epub ahead of print]

Molecular Targets and Medications Discovery Research Branch

Psychobiology Section

Decreases In Cocaine Self-Administration With Dual Inhibition Of The Dopamine Transporter and Σ Receptors Sigma receptor (σR) antagonists attenuate many behavioral effects of cocaine, but typically not its reinforcing effects in self-administration procedures. However, the σR antagonist rimcazole and its N-propylphenyl analogs, SH 3-24 and SH 3-28, dose-dependently decreased the maximal rates of cocaine self administration without affecting comparable responding maintained by food reinforcement. In contrast, a variety of σR antagonists (AC927, BD 1008, BD 1047, BD 1063, NE-100) had no effect on cocaine self-administration across the range of doses that decreased rates of food-maintained responding. Rimcazole analogs differed from selective σR antagonists in their dual affinities for σRs and the dopamine transporter (DAT) assessed with radioligand binding. Selective DAT inhibitors and σR antagonists were studied alone and in combination on cocaine self-administration to determine whether actions at both σRs and the DAT were sufficient to reproduce the effects of rimcazole analogs. Typical DAT inhibitors (WIN 35,428, methylphenidate, nomifensine) dose-dependently shifted the cocaine dose-effect curve leftward. Combinations of DAT-inhibitor and σR-antagonists doses that were behaviorally inactive alone decreased cocaine self-administration

without effects on food-maintained responding. Additionally, whereas the DAT inhibitors were self-administered at rates similar to those of cocaine, neither rimcazole analogs nor typical σR antagonists (NE-100, AC927) maintained responding above control levels across a wide range of doses. These findings suggest that unique effects of rimcazole analogs are due to dual actions at the DAT and σRs, and that a combined target approach may have utility in development of medical treatments for cocaine abuse. Hiranita, T., Soto, P.L., Kohut, S.J., Kopajtic, T., Cao, J., Newman, A.H., Tanda, G., Katz, J.L. Decreases in cocaine self-administration with dual inhibition of the dopamine transporter and σ receptors. Journal of Pharmacology and Experimental Therapeutics, 339: 662-677, 2011.

Medicinal Chemistry Section

Probing the Binding Pocket Of the Serotonin Transporter By Single Molecular Force Spectroscopy On Living Cells The serotonin transporter (SERT) terminates neurotransmission by removing serotonin from the synaptic cleft. In addition, it is the site of action of antidepressants (which block the transporter) and of amphetamines (which induce substrate efflux). The forces involved in binding to and blocking of the transporter are unknown. Here, IRP researchers used atomic force microscopy (AFM) to probe single molecular interactions between the serotonin transporter and MFZ2-12 (a potent cocaine analog) in living CHOK1 cells. For the AMF measurements MFZ2-12 was immobilized on AFM tips by using a heterobifunctional crosslinker. By varying the pulling velocity in force distance cycles drug/transporter complexes were ruptured at different force loadings allowing for mapping of the interaction energy landscape. The authors derived chemical rate constants from these recordings and compared them with those inferred from inhibition of transport and ligand binding: k_{off} values were in good agreement with those derived from uptake experiments; in contrast, the k_{on} values were scaled down when determined by AFM. Their observations generated new insights into the energy landscape of the interaction between SERT and inhibitors. They thus provide a useful framework for molecular dynamics simulations by defining the range of forces that operate during the binding reaction. Wildling L, Rankl C, Haselgrubler T, Gruber HJ, Holy M, Newman AH, Zou, MF, Freissmuth M, Sitte HH, Hinterdorfer P. Probing the binding pocket of the serotonin transporter by single molecular force spectroscopy on living cells. J. Biol. Chem., 2011, e-pub October 27, 2011.

CNS Receptor-Receptor Interactions Unit

Dopamine D4 Receptor, But Not the ADHD-Associated D4.7 Variant, Forms Functional Heteromers With the Dopamine D2S Receptor In the Brain Polymorphic variants of the dopamine D4 receptor have been consistently associated with attention-deficit hyperactivity disorder (ADHD). However the functional significance of the risk polymorphism (variable number of tandem repeats in exon 3) is still unclear. Here IRP scientists show that whereas the most frequent 4-repeat (D4.4) and the 2-repeat (D4.2) variants form functional heteromers with the short isoform of the dopamine D2 receptor (D2S), the 7-repeat risk allele (D4.7) does not. D2 receptor activation in the D2S-D4 receptor heteromer potentiates D4 receptor-mediated MAPK signaling in transfected cells and in the striatum, which did not occur in cells expressing D4.7 or in the striatum of knock-in mutant mice carrying the 7 repeats of the human D4.7 in the third intracellular loop of the D4 receptor. In the striatum D4 receptors are localized in cortico-striatal

glutamatergic terminals, where they selectively modulate glutamatergic neurotransmission by interacting with D2S receptors. This interaction shows the same qualitative characteristics than the D2S-D4 receptor heteromer-mediated MAPK signaling and D2S receptor activation potentiates D4 receptor-mediated inibition of striatal glutamate release. It is therefore postulated that dysfunctional D2S-D4.7 heteromers may impair presynaptic dopaminergic control of corticostriatal glutamatergic neurotransmission and explain functional deficits associated with ADHD. González S, Rangel-Barajas C, Peper M, Lorenzo R, Moreno E, Ciruela F, Borycz J, Ortiz J, Lluís C, Franco R, McCormick PJ, Volkow ND, Rubinstein M, Floran B, Ferré S. Mol Psychiatry. 2011 Aug 16. doi: 10.1038/mp.2011.93.

Molecular Neurobiology Research Branchndings

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. A single administration of methamphetamine to mice early in the light period decreases running wheel activity observed during the dark period. Brain Res. 2012 Jan 6; 1429:155-63. PMID: 22079320

Meta-Analysis and Genome-Wide Interpretation Of Genetic Susceptibility To Drug Addiction Classical genetic studies provide strong evidence for heritable contributions to usceptibility 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 researchers 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, we linked a total of 843 haplotypes to addiction susceptibility. They 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 they compared the lists of genes identified by association studies and those identified by molecular biological studies of drug-regulated genes, they 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. Meta-analysis and genome-wide interpretation of genetic susceptibility to drug addiction. BMC Genomics. 2011 Oct 15; 12: 508. PMID: 21999673

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. They 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. Genomic regions identified by overlapping clusters of nominally-positive SNPs from genome-wide studies of alcohol and illegal substance dependence. 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. Effects of neurotensin gene knockout in mice on the behavioral effects of cocaine. Psychopharmacology (Berl). 2012 Jan; 219(1): 35-45.

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. The authors 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. Menthol Preference Among Smokers: Association With TRPA1 Variants. Nicotine Tob Res. 2011 Dec;13(12):1311-5. 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. Decreased response to social defeat stress in μ-opioid-receptor knockout mice. Pharmacol Biochem Behav. 2011 Oct; 99(4): 676-682.

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. CHRNA3 rs1051730 genotype and short-term smoking cessation. Nicotine Tob Res. 2011 Oct; 13(10): 982-988. 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. Histamine H3 receptor agonists decrease hypothalamic histamine levels and increase stereotypical biting in mice challenged with methamphetamine. Neurochem Res. 2011 Oct; 36(10): 1824-1833

Behavioral Neuroscience Research Branch

Behavioral Neuroscience Section

Differentiating the Rapid Actions Of Cocaine The subjective effects of intravenous cocaine are felt almost immediately, and this immediacy plays an important part in the drug's rewarding impact. The primary rewarding effect of cocaine involves blockade of dopamine reuptake; however, the onset of this action is too late to account for the drug's initial effects. Recent studies suggest that cocaine-predictive cues--including peripheral interoceptive cues generated by cocaine itself--come to cause more direct and earlier reward signalling by activating excitatory inputs to the dopamine system. The conditioned activation of the dopamine system by cocaine-predictive cues offers a new target for potential addiction therapies. Wise RA 2011 Jun 2; 12(8): 479-484. doi: 10.1038/nrn3043.

Linking Context With Reward: A Functional Circuit From Hippocampal CA3 To Ventral Tegmental Area Reward-motivated behavior is strongly influenced by the learned significance of contextual stimuli in the environment. However, the neural pathways that mediate context-reward relations are not well understood. We have identified a circuit from area CA3 of dorsal hippocampus to ventral tegmental area (VTA) that uses lateral septum (LS) as a relay. Theta frequency stimulation of CA3 excited VTA dopamine (DA) neurons and inhibited non-DA neurons. DA neuron excitation was likely mediated by disinhibition because local antagonism of γ-aminobutyric acid receptors blocked responses to CA3 stimulation. Inactivating components of the CA3-LS-VTA pathway blocked evoked responses in VTA and also reinstatement of cocaine-seeking by contextual stimuli. This transsynaptic link between hippocampus and VTA appears to be an important substrate by which environmental context regulates goal-directed behavior. Luo AH, Tahsili-Fahadan P, Wise RA, Lupica CR, Aston-Jones G. Science. 2011 Jul 15; 333(6040): 353-357.

Preclinical Pharmacology Section

Varenicline Decreases Nicotine Self-Administration and Cue-Induced Reinstatement Of Nicotine-Seeking Behaviour In Rats When A Long Pretreatment Time Is Used Effects of varenicline (Champix), a nicotinic partial agonist, were evaluated on subjective effects of nicotine (drug discrimination), motivation for nicotine taking (progressive-ratio schedule of intravenous nicotine self-administration) and reinstatement (cue-induced reinstatement of previously extinguished nicotine-seeking behaviour). Effects on motor performance were assessed in rats trained to discriminate nicotine (0.4 mg/kg) from saline under a fixed-ratio (FR 10) schedule of food delivery and in rats trained to respond for food under a progressive-ratio schedule. At short pretreatment times (5-40 min), varenicline produced full or high levels of partial generalization to nicotine's discriminative-stimulus effects and disrupted responding for food, while there were low levels of partial generalization and no disruption of responding for food at 2- or 4-h pretreatment times. Varenicline (1 and 3 mg/kg, 2-h pretreatment time) enhanced discrimination of low doses of nicotine and to a small extent decreased discrimination of the training dose of nicotine. It also dose-dependently decreased nicotine-taking behaviour, but had no effect on food-taking behaviour under progressive-ratio schedules. Finally, varenicline significantly reduced the ability of a nicotine-associated cue to reinstate extinguished nicotine-seeking behaviour. The ability of varenicline to reduce both nicotine-taking and

nicotine-seeking behaviour can contribute to its relatively high efficacy in treating human smokers. Le Foll B, Chakraborty-Chatterjee M, Lev-Ran S, Barnes C, Pushparaj A, Gamaleddin I, Yan Y, Khaled M, Goldberg SR**.** International Journal of Neuropsychopharmacology, 2011; 23: 1-10.

Effects Of Endocannabinoid System Modulation On Cognitive and Emotional Behavior Cannabis has long been known to produce cognitive and emotional effects. Research has shown that cannabinoid drugs produce these effects by driving the brain's endogenous cannabinoid system and that this system plays a modulatory role in many cognitive and emotional processes. This review focuses on the effects of endocannabinoid system modulation in animal models of cognition (learning and memory) and emotion (anxiety and depression). The authors review studies in which natural or synthetic cannabinoid agonists were administered to directly stimulate cannabinoid receptors or, conversely, where cannabinoid antagonists were administered to inhibit the activity of cannabinoid receptors. In addition, studies are reviewed that involved genetic disruption of cannabinoid receptors or genetic or pharmacological manipulation of the endocannabinoid-degrading enzyme, fatty acid amide hydrolase (FAAH). Endocannabinoids affect the function of many neurotransmitter systems, some of which play opposing roles. The diversity of cannabinoid roles and the complexity of task-dependent activation of neuronal circuits may lead to the effects of endocannabinoid system modulation being strongly dependent on environmental conditions. Recent findings are reviewed that raise the possibility that endocannabinoid signaling may change the impact of environmental influences on emotional and cognitive behavior rather than selectively affecting any specific behavior. Zanettini C, Panlilio LV, Alicki M, Goldberg SR, Haller J, Yasar S. Frontiers in Behavioral Neuroscience, 2011; 5:57, 1-21.

Blockade Of Dopamine D4 Receptors Attenuates Reinstatement Of Extinguished Nicotine-Seeking Behavior In Rats Since cloning of the dopaine receptor D4 (DRD4), its role in the brain has remained unclear. It has been reported that polymorphism of the DRD4 gene in humans is associated with reactivity to cues related to tobacco smoking. However, the role of DRD4 in animal models of nicotine addiction has seldom been explored. In this study, male Long-Evans rats learned to intravenously self-administer nicotine under a fixed-ratio (FR) schedule of reinforcement. Effects of the selective DRD4 antagonist L-745,870 were evaluated on nicotine self-administration behavior and on reinstatement of extinguished nicotine-seeking behavior induced by nicotine-associated cues or by priming injections of nicotine. L-745,870 was also tested on reinstatement of extinguished food-seeking behavior as a control. In addition, the selective DRD4 agonist PD 168,077 was tested for its ability to reinstate extinguished nicotine-seeking behavior. Finally, L-745,870 was tested in Sprague Dawley rats trained to discriminate administration of 0.4 mg/kg nicotine from vehicle under an FR schedule of food delivery. L-745,870 significantly attenuated reinstatement of nicotine-seeking induced by both nicotine-associated cues and nicotine priming. In contrast, L-745,870 did not affect established nicotine self-administration behavior or reinstatement of food-seeking behavior induced by food cues or food priming. L-745,870 did not produce nicotine-like discriminative-stimulus effects and did not alter discriminative-stimulus effects of nicotine. PD 168,077 did not reinstate extinguished nicotine-seeking behavior. As DRD4 blockade by L-745,870 selectively attenuated both cue- and nicotine-induced reinstatement of nicotine-seeking behavior, without affecting cue- or food-induced reinstatement of food-seeking behavior, DRD4 antagonists are potential therapeutic agents against tobacco smoking. Yan Y, Pushparaj A, Le Strat Y, Gamaleddin I, Barnes C,

Justinova Z, Goldberg SR, Le Foll B. Neuropsychopharmacology, 2011; Oct 26. doi: 10.1038/npp.2011.245. [Epub ahead of print] PMID: 22030716.

The Anandamide Transport Inhibitor AM404 Reduces the Rewarding Effects Of Nicotine and Nicotine-Induced Dopamine Elevations In The Nucleus Accumbens Shell In Rats The fatty-acid amide hydrolase (FAAH) inhibitor URB597 can reverse the abuse-related behavioral and neurochemical effects of nicotine in rats. FAAH inhibitors block the degradation (and thereby magnify and prolong the actions) of the endocannabinoid anandamide (AEA), and also the non-cannabinoid fatty acid ethanolamides oleoylethanolamide (OEA) and palmitoylethanolamide (PEA). OEA and PEA are endogenous ligands for peroxisome proliferator-activated receptor-alpha (PPAR-α). Since recent evidence indicates that PPAR-α can modulate nicotine reward, it is unclear whether AEA plays a role in the effects of URB597 on nicotine reward. A way to selectively increase endogenous levels of AEA without altering OEA or PEA levels is to inhibit AEA uptake into cells by administering the AEA transport inhibitor N-(4-hydroxyphenyl)-arachidonamide (AM404). To clarify AEA's role in nicotine reward, IRP scientists investigated the impact of AM404 on conditioned place preference (CPP), reinstatement of extinguished CPP, locomotor suppression and anxiolysis in an open field, and dopamine elevations in the nucleus accumbens shell induced by nicotine in Sprague Dawley rats. AM404 prevented development of nicotine-induced CPP and impeded nicotine-induced reinstatement of extinguished CPP. Furthermore, AM404 reduced nicotine-induced increases in dopamine levels in the nucleus accumbens shell, the terminal area of the brain's mesolimbic reward system. AM404 did not alter the locomotor suppressive or anxiolytic effect of nicotine. Conclusions and implications: These findings suggest that AEA transport inhibition can counteract the addictive effects of nicotine and that AEA transport may serve as a new target for development of medications for treatment of tobacco dependence. Scherma M, Justinova Z, Zanettini C, Mascia P, Fadda P, Fratta W, Makriyannis A, Vadivel SK, Gamaleddin I, Le Foll B, Goldberg SR**.** British Journal of Pharmacology, 2011 May 9. doi: 10.1111/j.1476-5381.2011.01467.x. [Epub ahead of print] PMID: 21557729.

Cannabinoid Facilitation Of Behavioral and Biochemical Hedonic Taste Responses Cannabinoid receptor agonists are known to stimulate feeding in humans and animals and this effect is thought to be related to an increase in food palatability. On the other hand, highly palatable food stimulates dopamine (DA) transmission in the shell of the nucleus accumbens (NAc) and this effect undergoes one trial habituation. In order to investigate the relationship between the affective properties of tastes and the response of NAc shell DA IRP scientists studied the effect of delta-9-tetrahydrocannabinol (THC) on behavioral taste reactivity to intraoral infusion of appetitive (sucrose solutions) and aversive (quinine and saturated NaCl solutions) tastes and on the response of in vivo DA transmission in the NAc shell to intraoral sucrose. Rats were implanted with intraoral cannulae and the effect of systemic administration of THC on the behavioral reactions to intraoral infusion of sucrose and of quinine or saturated NaCl solutions were scored. THC increased the hedonic reactions to sucrose but did not affect the aversive reactions to quinine and NaCl. The effects of THC were completely blocked by the CB1 receptor inverse agonist/antagonist rimonabant given at doses that do not affect taste reactivity to sucrose. In rats implanted with microdialysis probes and with intraoral cannulae, THC, made sucrose effective in raising dialysate DA in the shell of the NAc. As in the case of highly palatable food (Fonzies, sweet chocolate), the stimulatory effect of sucrose on shell DA under THC underwent one trial habituation. Altogether, these findings demonstrate that stimulation of CB1 receptors specifically increases the palatability of hedonic taste without affecting that of

aversive tastes. Consistent with the ability of THC to increase sucrose palatability is the observation that under THC pretreatment sucrose acquires the ability to induce a release of DA in the shell of the NAc and this property undergoes adaptation after repeated exposure to the taste (habituation). This article is part of a Special Issue entitled 'Central Control of Food Intake'. De Luca MA, Solinas M, Bimpisidis Z, Goldberg SR, Di Chiara G. Neuropharmacology. 2011; Nov 2. [Epub ahead of print] PMID: 22063718.

Neurobiology of Relapse Section

Effect Of Prazosin and Guanfacine On Stress-Induced Reinstatement Of Alcohol and Food Seeking In Rats Relapse to alcohol use during abstinence or maladaptive eating habits during dieting is often provoked by stress. The anxiogenic drug yohimbine, which causes stress-like responses in humans and nonhumans, reliably reinstates alcohol and food seeking in a rat relapse model. Yohimibine is a prototypical alpha-2 adrenoceptor antagonist but results from studies on noradrenaline's role in yohimbine-induced reinstatement of drug and food seeking are inconclusive. Here IRP researchers further addressed this issue by studying the effect of the alpha-1 adrenoceptor antagonist prazosin and the alpha-2 adrenoceptor agonist guanfacine on yohimbine-induced reinstatement. In Exp. 1, the authors trained rats to self-administer alcohol (12% w/v, 1-h/day) and after extinction of the alcohol-reinforced lever-presses we tested prazosin's (0.5, 1.0, and 2.0 mg/kg, i.p.) or guanfacine's (0.125, 0.25, and 0.5 mg/kg, i.p.) effect on yohimbine (1.25 mg/kg, i.p.)-induced reinstatement; they also examined prazosin's effect on intermittent-footshock-stress-induced reinstatement. In Exp. 2, they trained food-restricted rats to self-administer 45 mg food pellets and first examined prazosin's or guanfacine's effects on food-reinforced responding. They then assessed prazosin's or guanfacine's effects on yohimibine-induced reinstatement after extinction of lever presses. Prazosin (0.5-2.0 mg/kg) blocked yohimbine-induced reinstatement of food and alcohol seeking, as well as footshock-induced reinstatement of alcohol seeking. Guanfacine attenuated yohimbine-induced reinstatement of alcohol seeking at the highest dose (0.5 mg/kg) but its effect on yohimbine-induced reinstatement of food seeking was not significant. Neither prazosin nor guanfacine affected high rate food-reinforced responding. Results demonstrate an important role of postsynaptic alpha-1 adrenoceptors in stress-induced reinstatement of alcohol and food seeking. Lê AD, Funk D, Juzytsch W, Coen K, Navarre BM, Cifani C, Shaham Y. Effect of prazosin and guanfacine on stress-induced reinstatement of alcohol and food seeking in rats. Psychopharmacology. 2011; 218: 89–99.

Heroin and Cocaine *Addictions*: The Differences Do Matter The publication of the psychomotor stimulant theory of addiction in 1987 and the demonstration that addictive drugs increase dopamine concentrations in the rat mesolimbic system in 1988 have led to a predominance of psychobiological theories that consider addiction to opiates (heroin, morphine) and psychostimulants (cocaine, amphetamine, methamphetamine) as essentially identical phenomena. Indeed, current theories of addiction—hedonic allostasis, incentive sensitization, aberrant learning, and fronto-striatal dysfunction—all argue for a unitary account of drug addiction. This view is challenged by behavioral, cognitive, and neurobiological findings in laboratory animals and humans. Here the authors argue that opiate addiction and psychostimulant addiction are behaviorally and neurobiologically distinct and that the differences have important implications for addiction treatment, addiction theories, and future research. Badiani A, Belin D, Epstein DH, Calu D, Shaham Y. Heroin and cocaine *addictions*:

the differences do matter. Nature Reviews Neuroscience. 2011; 12: 685-700 (invited review for a special issue on drug addiction).

Critical Role Of Peripheral Actions Of Intravenous Nicotine In Mediating Its Central Effects In addition to its direct action on central neurons, nicotine (NIC) activates multiple nicotinic acetylcholine receptors localized on afferent terminals of sensory nerves at the sites of its administration. Although the activation of these receptors is important in mediating the primary sensory and cardiovascular effects of NIC, their role in triggering and maintaining the neural effects of NIC remains unclear. Using high-speed EEG and EMG recordings in freely moving rats, we showed that NIC at low intravenous doses (10-30 μg/kg) induced rapid, strong and prolonged EEG desynchronization both in the cortex and ventral tegmental area (with decreases in alpha and robust increases in beta and gamma frequencies) and neck EMG activation that began during the injection (~5 s). EEG and EMG effects of NIC were drastically reduced by pre-treatment with hexamethonium, a peripherally acting NIC antagonist, and the immediate EEG effects of NIC were strongly inhibited during urethane anesthesia. Although NIC pyrrolidine methiodide, a quaternary NIC analogue that cannot enter the brain, also induced rapid EEG desynchronization, its effects were much shorter and weaker than those of NIC. Therefore, NIC by acting on peripheral nicotinic receptors provides a major contribution to its rapid, excitatory effects following i.v. administration. Since this action creates a sensory signal that rapidly reaches the brain via neural pathways and precedes the slower and more prolonged direct actions of NIC on brain cells, it could play a major role in associative learning and changes in the behavioral and physiological effects of NIC following its repeated use. Lenoir M, Kiyatkin EA. Critical role of peripheral actions of intravenous nicotine in mediating its central effects. Neuropsychopharmacology 2011; 36: 2125-2138.

PROGRAM ACTIVITIES

CTN UPDATE

Protocols: 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.

Primary outcome papers are published and dissemination materials have been developed with CSAT's ATTC on the following:

Protocol CTN 0001, Buprenorphine/Naloxone versus Clonidine for Inpatient Opiate Detoxification
Protocol CTN 0002, Buprenorphine/Naloxone versus Clonidine for Outpatient Opiate Detoxification
Protocol CTN 0005, MI (Motivational Interviewing) To Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse
Protocol CTN 0006, Motivational Incentives for Enhanced Drug Abuse Recovery: Drug Free Clinics
Protocol CTN 0007, Motivational Incentives for Enhanced Drug Abuse Recovery: Methadone Clinics
Protocol CTN 0010, Buprenorphine/Naloxone-Facilitated Rehabilitation for Heroin Addicted Adolescents/Young Adults

Primary outcome papers are published or in press for:

Protocol CTN 0003, Bup/Nx: Comparison of Two Taper Schedules
Protocol CTN 0004, MET (Motivational Enhancement Treatment) To Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse
Protocol CTN 0008, A Baseline for Investigating Diffusion of Innovation
Protocol CTN 0009, Smoking Cessation Treatment with Transdermal Nicotine Replacement Therapy in Substance Abuse Rehabilitation Programs
Protocol CTN 0011, A Feasibility Study of a Telephone Enhancement Procedure (TELE) to Improve Participation in Continuing Care Activities
Protocol CTN 0012, Characteristics of Screening, Evaluation, and Treatment of HIV/AIDS, Hepatitis C Viral Infection, and Sexually Transmitted Infections in Substance Abuse Treatment Programs
Protocol CTN 0013, Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome In Pregnant Substance Abusers
Protocol CTN 0014, Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT)
Protocol CTN 0015, Women's Treatment for Trauma and Substance Use Disorder: A Randomized Clinical Trial
Protocol CTN 0016, Patient Feedback: A Performance Improvement Study in Outpatient Addiction Treatment
Protocol CTN 0017, HIV and HCV Intervention in Drug Treatment Settings
Protocol CTN 0018, Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment

Protocol CTN 0019, Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment
Protocol CTN 0020, Job-Seekers Training for Patients with Drug Dependence
Protocol CTN 0021, Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse. This is the first Spanish-only protocol in the CTN.
Protocol CTN 0028, Randomized Controlled Trial of Osmotic-Release Methylphenidate (OROS MPH) for Attention Deficit Hyperactivity Disorder (ADHD) in Adolescents with Substance Use Disorders (SUD)
Protocol CTN 0029, A Pilot Study of Osmotic-Release Methylphenidate (OROS MPH) in Initiating and Maintaining Abstinence in Smokers with Attention Deficit Hyperactivity Disorder (ADHD)
Protocol CTN 0030, Prescription Opioid Addiction Treatment Study (POATS)
Protocol CTN 0030A[1]2, Effects of Chronic Opioids in Subjects with a History of Opioid Use: An imaging study

In addition, the following protocols have submitted the primary paper:
Protocol CTN 0027, Starting Treatment with Agonist Replacement Therapies (START) is a randomized, open-label, multi-center study that was developed in collaboration with the Division of Pharmacotherapies & Medical Consequences of Drug Abuse (DPMCDA). The study is completed and the final report has been delivered.
Protocol CTN 0032, HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the U.S.
Protocol CTN 0032A1, Economic Analysis of HIV Rapid Testing in Drug Abuse Treatment Programs. This ancillary study is an assessment of the cost-effectiveness of on-site HIV testing in drug abuse treatment settings vs. referral for off-site testing. The PI is Dr. Bruce Schackman. The project was conducted in collaboration with NIDA's DESPR.
Protocol CTN 0035-Ot, Access to HIV and Hepatitis Screening and Care among Ethnic Minority Drug Users In and Out of Drug Treatment. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and is being conducted in the California/Arizona Node.
Protocol CTN 0036-Ot, Epidemiology and Ethnographic Survey of "Cheese" Heroin Use among Hispanics in Dallas County. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and is being conducted in the Texas Node.

The following protocols have locked data:
Protocol CTN 0027A1, START Pharmacogenetics: Exploratory Genetic Studies In Starting Treatment With Agonist Replacement Therapies. This ancillary study consented 843 of the 1,269 subjects from the START study. Data collection is complete and analysis has begun.
Protocol CTN-0027A2, Retention of Suboxone® Patients in START: Perspectives of Providers and Patients. The overall purposes of the supplemental study are to identify and assess barriers for retaining Suboxone® patients. This ancillary study has completed enrollment, the database has been locked, and analyses are underway.
Protocol CTN 0030A1, Collection of Economic Data for the Prescription Opioid Addiction Treatment Study. This ancillary study was conducted in collaboration with NIDA DESPR; it is in the data analysis phase.

Protocol CTN 0031, Stimulant Abuser Groups to Engage in 12-Step (STAGE-12): Evaluation of a Combined Individual-Group Intervention to Reduce Stimulant and Other Drug Use by Increasing 12-Step Involvement. Recruitment was completed on September 30, 2009, yielding a total of 471 randomized participants across 10 sites. The primary outcome paper is being prepared for submission for peer reviewed publication.
Protocol CTN 0031A1, An Evaluation of Neurocognitive Function, Oxidative Damage, and Their Association with Treatment Outcomes in Methamphetamine and Cocaine Abusers. Recruitment was completed on September 30, 2009, yielding a total of 173 participants across 6 sites completing the data collection and blood draw procedures. The primary outcome paper is being prepared for submission for peer reviewed publication.
Protocol CTN 0031A2, The Role of Alcohol Consumption in Classifications of Alcohol Use Disorders: A Clinical Study. This study investigates the utility of adding a frequency measure of alcohol consumption (i.e., the first three items of the Alcohol Use Disorders Identification Test [AUDIT-C]), to the DSM-IV diagnostic criteria for alcohol use disorders. This study is funded by an MOU between NIDA and NIAAA. The study is now in the data analysis phase.
Protocol CTN 0031A3, Organizational and Practitioner Influences on Implementation of STAGE-12. The study assesses the influence of counselor and organizational variables on fidelity of the STAGE-12 intervention during the clinical trial, tests the impact of fidelity on clinical trial participant outcomes, and explores the influence of counselor and organizational variables on sustainability of the STAGE-12 intervention following completion of the clinical trial. The baseline data obtained in this research formed the foundation for an R01 grant awarded by DESPR to Joseph Guydish, PhD, at the University of California, San Francisco.
Protocol CTN 0033-Ot, Methamphetamine Use among American Indians. The first area of research emphasis in the National Institute on Drug Abuse's Strategic Plan on Reducing Health Disparities (2004 Revision) is the epidemiology of drug abuse, health consequences and infectious diseases among minority populations. The study is a collaboration among four Nodes: Pacific NW, Southwest, Oregon/Hawaii, and Ohio Valley.
Protocol CTN 0034-Ot, Developing Research Capacity and Culturally Appropriate Research Methods: Community-based Participatory Research Manual for Collaborative Research in Drug Abuse for American Indians and Alaska Natives. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and is being conducted in the Pacific Northwest Node.
Protocol CTN 0038-Ot, Barriers to Substance Abuse Treatment among Asian Americans and Pacific Islanders**.** The objective of this study is to gain a better understanding of the factors that may influence the under-utilization of substance abuse treatment services by Asian Americans and Pacific Islanders (AAPIs) and the readiness of substance abuse treatment programs serving AAPIs to participate in clinical trials and adopt evidence based practices. This study is a collaboration with NIH NCMHD.
Protocol CTN 0045-Ot, Rates of HIV Testing and Barriers to Testing in African Americans Receiving Substance Abuse Treatment**.** This is an observational study seeking to: (1) Compare the proportion of African American and non-African Americans receiving treatment at substance abuse treatment clinics that have been tested for HIV within the past 12 months; (2) Observe relationships between rates of African Americans who have not been tested and a) the types of testing offered at substance abuse treatment clinics and b) the types of outreach strategies used to engage persons in HIV testing; and (3) assess African American clients' self-reported barriers to accessing HIV testing, in relation to other ethnicities.
The following protocols have ended new enrollment, and are in the follow-up phase:

Protocol CTN 0030A3, POATS Long-Term Follow Up Study (LTFU) is being conducted at all POATS sites to examine long-term outcomes for individuals who participated in CTN-0030 with opioid analgesic (OA) dependence. This study will follow POATS participants for 42 months after randomization in the POATS study.

Protocols CTN 0037A1, CTN-0044A1, CTN0046A1, and CTN0047A1,
Organizational and Practitioner Influences on Patient Outcomes. This series of ancillary studies is assessing associations between site organizational and practitioner variables and site differences in clinical trial outcomes. Data collection is complete and is being analyzed by the investigators.

Protocol CTN 0044, Web-delivery of Evidence-Based, Psychosocial Treatment for Substance Use Disorders. The purpose of this study is to evaluate the effectiveness of adding an interactive, web-based version of the Community Reinforcement Approach (CRA) intervention plus abstinence incentives as an adjunct to community-based, outpatient substance abuse treatment. Enrollment was completed on August 31, 2011. 507 participants have been randomized at 10 sites. The study is expected to be completed by the end of June, 2012.

Protocol CTN 0044A2, Acceptability of a Web-delivered, Evidence-based, Psychosocial Intervention among Individuals with Substance Use Disorders who Identify as American Indian/Alaska Native. Results from prior research support the efficacy of a web-based version (Therapeutic Education System: TES) of the Community Reinforcement Approach (CRA) with individuals in outpatient substance abuse treatment; however, TES has yet to be tested among American Indian/Alaska Native (AI/AN) populations. The principal objective of this study is to explore the acceptability of TES among a diverse sample of AI/AN enrolled in outpatient substance abuse treatment. Data collection is complete and is being analyzed by the investigators.

Protocol CTN 0046, Smoking-Cessation and Stimulant Treatment (S-CAST): Evaluation of the Impact of Concurrent Outpatient Smoking-Cessation and Stimulant Treatment on Stimulant-Dependence Outcomes**.** The primary objective of this study is to evaluate the impact of substance abuse treatment as usual plus smoking cessation treatment (TAU+SCT), relative to substance abuse treatment as usual (TAU), on drug abuse outcomes. Enrollment was completed on December 1, 2011. 538 participants have been randomized at 12 sites. The study is expected to be completed by the end of June, 2012.

The following protocols are currently enrolling:

Protocol CTN 0037, Stimulant Reduction Intervention Using Dosed Exercise (STRIDE). This randomized clinical trial is testing the efficacy of the addition of exercise to treatment as usual in improving drug abuse treatment outcomes in patients abusing stimulants. As of January 3, 2012, 232 participants have been randomized at nine sites.

Protocol CTN 0047, Screening, Motivational Assessment, Referral and Treatment in Emergency Departments (SMART-ED). The study objective is to evaluate the implementation of, and outcomes associated with, a screening and brief intervention (SBI) process to identify individuals with substance use, abuse, or dependence seen in emergency departments (EDs) and to provide interventions and/or referral to treatment consistent with the severity of their substance use disorder. Recruitment closed in September 2011 at the 2 Wave 1 sites. Recruitment continues at the 4 remaining Wave 2 sites. Total enrollment is 1,181 (target = 1285) as of December 19, 2011.

Protocol CTN 0048, Cocaine Use Reduction with Buprenorphine (CURB). The aim of this study is to investigate the safety and efficacy of buprenorphine in the presence of naltrexone for the treatment of cocaine dependence in a sample of individuals who meet criteria for cocaine

dependence and either past-year opioid dependence or abuse, or past-year opioid use and lifetime opioid dependence. Enrollment is expected to begin in 2011.
Protocol CTN 0050, START Follow-Up Study. The study will follow participants from the CTN 0027 START (Starting Treatment with Agonist Replacement Therapies) study for 3-5 years to assess longer-term outcomes of buprenorphine/naloxone versus methadone treatment and investigate factors associated with post-START treatment access, utilization, and outcomes. Participant interviews are expected to begin in 2011.

The following protocols are in the implementation/development phase:
Protocol CTN 0049, Project HOPE (Hospital Visit as Opportunity for Prevention and Engagement for HIV-Infected Drug Users). This study is in the implementation phase. The study will evaluate the effectiveness of a brief intervention, delivered to HIV-infected drug users recruited from the hospital setting, in achieving viral suppression.
Protocol CTN 0051, Extended-release injectable naltrexone and buprenorphine. This study is under development. Enrollment is expected to begin in 2012.
Protocol CTN 0052, BRAC, Two-Stage Evaluation of Buspirone for Relapse-Prevention in Adults with Cocaine Dependence. This study is under development. Enrollment is expected to begin in 2012.
Protocol CTN 0053, Achieving Cannabis Cessation: Evaluating N-Acetylcysteine Treatment (ACCENT). This study is under development. Enrollment is expected to begin in early 2013.

EXTRAMURAL POLICY AND REVIEW ACTIVITIES

Receipt, Referral, and Review

NIDA received 1512 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 973 applications.
OEA arranged and managed 18 grant review meetings in which 235 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 12 contract proposal and concept review meetings.
NIDA has one standing chartered committee, NIDA-K, which reviewed Career Development applications and Institutional Training Grant applications (T32). There were also 17 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)
- Multi-site Clinical Trials (R01)
- Cutting-Edge Basic Research Awards (CEBRA) (R21)
- Requests for Applications (RFAs)

OEA managed the following RFA reviews:

DA12-002	HIV/AIDS Implementation Science Targeting Drug Using Populations: A Collaboration With PEPFAR (R01)
DA12-005	Medications Development Program Projects for Substance-Related Disorders (P01)
DA12-006	Exploring Drugs of Abuse and Transgenerational Phenotypes (R01)
DA12-007	Remote Monitoring System for Detecting Cocaine Ingestion/Intoxication (R01)

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

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

N01DA-12-8902	Regulatory Affairs Support
N01DA-12-5570	State and Local Planning and Information Development

SBIR Phase I

N43DA-12-2227	Confirming Compliance with Experimental Pharmacotherapy Treatment of Drug Abuse
N43DA-12-2228	Feedback-regulated Naloxone Delivery Device to Prevent Opiate Overdose Deaths
N43DA-12-4415	Recovery Warrior: Behavioral Activation Video Game for Substance Abuse

N43DA-12-5569	Drugged Driving: Future Research Directions
N43DA-12-7783	Smokescreen: Genetic Screening Tool for Tobacco Dependence and Treatment Approaches
N43DA-12-8906	Development of a Solid Dosage Form for Fenobam
N43DA-12-8907	Feasibility of Development of RNAi-based Therapeutics for Treatment of HIV and HCV Infections in Drug Abusing Populations

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

NO1DA-12-1148	Technical Support for Constituency Outreach and Research Dissemination
NO1DA-12-8903	Purity Specifications, Storage and Distribution for Medications Development
NO1DA-12-8904	Preclinical Medications Discovery and Abuse Liability Testing for NIDA

CTN-Related Review Activities

The Data and Safety Monitoring Board(s) met:

- September 6, 2011 to discuss protocol CTN 0047, Screening, Motivational Assessment, Referral and Treatment in Emergency Departments (SMART-ED)
- September 26, 2011 to discuss final study results for protocol CTN 0027, Treatment with Agonist Replacement Therapies (START)
- October 13, 2011 to review protocol CTN 0051, Extended-release injectable naltrexone and buprenorphine
- November 16, 2011 to discuss final results for protocol CTN 0031, Stimulant Abuser Groups to Engage in 12-Step (STAGE-12): Evaluation of a Combined Individual-Group Intervention to Reduce Stimulant and Other Drug Use by Increasing 12-Step Involvement
- December 14, 2011 to discuss protocol CTN 0037, Stimulant Reduction Intervention Using Dosed Exercise (STRIDE)

Certificates of Confidentiality

Between July 23, 2011 and December 28, 2011OEA, processed 119 Certificate of Confidentiality applications, including 12 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 a presentation by Dr. Nicole Lockhart, NCI, about human subjects' issues in biospecimen research and a presentation by Dr. Mark Green, NIDA, about use of Certificates of Confidentiality to protect identities of subjects who participate in NIDA clinical research.

CONGRESSIONAL AFFAIRS SECTION
(Prepared February 3, 2011)

APPROPRIATIONS/BUDGET

On December 23, 2011, the President signed into law H.R. 2055, the Consolidated Appropriations Act, 2012 (P.L. 112-74). This bill, a 9-bill Omnibus which includes funding for the Departments of Labor, HHS, and Education, provides funding for NIH in the amount of $30.689 billion, which is $299 million above last year's level and $758 million below the President's request. For NIDA, the enacted amount is $1.053 billion, which is $3.4 million above last year's level and $27 million below the President's request. (NOTE: The President released his FY 2013 budget too late for inclusion in this report.)
Also note: P.L. 112-74 officially created NIH's newest Center, the National Center for Advancing Translational Sciences (NCATS). See http://ncats.nih.gov for more details.

CONGRESSIONAL BRIEFINGS OF INTEREST

Marijuana -- On October 20, 2011, NIDA staff participated in a briefing focused on marijuana abuse and addiction, with a focus on issues around "medical marijuana." The briefing was requested by staff of the U.S. Senate Caucus on International Narcotics Control. Dr. Susan Weiss led the NIDA team, and focused on NIDA (and NIH) research on the adverse health effects of marijuana use and the variety of cannabinoids-focused research efforts underway. Other HHS participants in the briefing were the FDA, SAMHSA, and the Office of the Assistant Secretary for Health.

Methamphetamine -- At the request of Representative Denny Rehberg (R-MT), Chair, House Appropriations Subcommittee on Labor, HHS, and Education, NIDA Director Dr. Nora Volkow briefed House staffers on NIDA's research on methamphetamine addiction and treatment (November 16, 2011). Representatives from the Meth Project, a national methamphetamine prevention effort that started in Montana, also participated in the briefing. Dr. Volkow also briefed Senate staffers at a second, similar briefing at the request of Senator Michael Bennett (D-CO).

LEGISLATION OF INTEREST

SBIR/STTR - On December 31st, the President signed into law H.R. 1540, the National Defense Authorization Act for FY 2012. This bill included provisions to reauthorize the SBIR and STTR programs for six years. Setaside levels increase – the SBIR setaside increases to 3.2% from 2.5%, and the STTR setaside goes to .45% from .3%. The increases occur over time, reaching these levels in FY 2017. Further, the law allows 1) NIH, the Department of Energy, and the National Science Foundation (NSF) to award up to 25% of the SBIR setaside to venture capital companies, hedge funds, or private equity firms; 2) agencies to apply for waivers to exceed the hard cap on awards (Hard Cap for Phase I-$225,000 and Phase II $1,500,000); and 3) NIH and NSF to make final decisions on proposals not later than 1 year after the solicitation closes.

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. 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.

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 referred to the House Committee on Oversight and Government Reform.

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.

INTERNATIONAL ACTIVITIES

NIDA International Program Announcements Reissued

NIDA has reissued its Program Announcements (PAs) soliciting collaborative research proposals by U.S. investigators working with investigators from other countries. The PAs—International Research Collaboration on Drug Abuse and Addiction—will be in effect until January 8, 2015. Researchers may choose one of three grant programs in response to these broad calls for innovative research proposals: R01 (PA-12-040), R21 (PA-12-041), or R03 (PA-12-042). Priority funding will be given to projects that are collaboratively funded by an agency of the foreign country. Research priority areas include seek-test-treat and retain HIV/AIDS interventions; abuse of amphetamine-type stimulants, synthetic drugs, or other designer drugs; inhalant abuse; smoking during pregnancy and the impact of prenatal tobacco exposure and the effects of early exposure to tobacco in young people and adolescents on development of addiction and other diseases and on cognitive development; and drugged driving.

Research Results

NIDA-Supported Latin American Network Boosts Scientific Exchange

The Red Latinamericano de Investigaciones en Drogas (REDLA) is making an impact on drug abuse and addiction research in Latin America. In the past year, REDLA has published several articles in peer-reviewed journals reporting research findings on such topics as perceptions of risk of drug use, age of onset for alcohol use, and sequence of drug use. The REDLA publications have expanded the reach of these research findings by ensuring that data findings are shared regionally rather than limiting data findings to the country where they originated. REDLA also has been actively involved in the peer review of a new Organization of American States report on drug use in the Americas, a cross-national analysis of drug use in all 36 Inter-American Drug Control Commission (CICAD) member states. REDLA is a joint effort between NIDA and CICAD, with collaboration from the National Hispanic Science Network. Several countries in the region, including Columbia and Argentina, are beginning to build their own national drug research networks using REDLA as a model.

NIDA Grantee Builds Research Capacity in Central and Eastern Europe

Working systematically over the last decade, NIDA grantee Robert Zucker, Ph.D., director of the University of Michigan (UM) Addiction Research Center, has been developing a program to build a substance abuse research infrastructure for Central and Eastern Europe. The program grew from a 2001 NIDA-funded Fogarty International Clinical, Operational and Health Services Research and Training Award (ICOHRTA) grant that supported collaboration between Dr. Zucker, Stanislav Golec, M.D., and the Institute of Psychiatry and Neurology in Warsaw to increase research skills among Polish biomedical and behavioral scientists. The program expanded to Latvia, Slovakia, and Ukraine in 2006 with a second ICOHRTA grant. The program has trained 285 researchers through 11 workshops across the region, and supported a year of mentored research and methodology training in the United States for 12 long-term research fellows. Upon returning home, the 12 long-term fellows carried out pilot research projects developed in collaboration with their U.S. mentors. The program also supported shorter visits to the United States by senior researchers and program directors who completed research projects, established new collaborations, and developed relationships with U.S. substance abuse agencies. In addition, a new curriculum on addiction medicine was established at the Medical University

of Warsaw. UM faculty members now serve as consultants for a component of the Polish Ministry of Health, and one of the former trainees, Marcin Wojnar, M.D., Ph.D., is the permanent advisor to the director of the Polish Ministry of Health. In 2009, the Polish Ministry of Health agreed to support collaborative research projects funded under the NIDA International Research Collaboration on Drug Abuse and Addiction Research Program Announcements, and has forged separate research partnerships with the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the Fogarty International Center.

High Research Productivity at NIDA-Supported Syrian Tobacco Studies Center

A new study on research productivity in Syria puts the Syrian Center for Tobacco Studies (SCTS) as the leading institution for high-quality biomedical research in the nation. The center has far fewer staff members and other resources than many of the institutions with which the study compared it. According to the study, published in the inaugural issue of the *Avicenna Journal of Medicine* (July–September 2011), Syria's Damascus University and its affiliated hospitals generated 56 percent of Syrian clinical and biomedical research, followed by SCTS (15 percent) and the Syrian Ministry of Health and its affiliated hospitals (9 percent). But when the age of the institution is considered, SCTS is the leading institution in research with an annual average of five publications per year. The study authors note the need to promote research capabilities and to bridge the gap in research productivity by Syrian institutions. Initial funding for SCTS came from a 2002 NIDA-supported 5-year Fogarty International Tobacco and Health Research and Capacity-Building Program grant (which has since been renewed) to Wasim Maziak, Ph.D., professor at Florida International University and director of SCTS. The SCTS team also includes collaborating scientists Thomas Eissenberg, Ph.D., Virginia Commonwealth University, and Kenneth Ward, Ph.D., University of Michigan, as well as Syrian scientists and administrators. The center is a model of international cooperation to establish a sustainable research base in a developing country. It addresses the need to create local expertise not only in research methodology, but also in research support and fundraising. The center is currently working to examine patterns and determinants of tobacco use, understand local tobacco use methods, develop effective cessation interventions, and train tobacco control scientists. A regional training course held in Amman, Jordan, last year focused on tobacco dependence treatment.

NIDA-Supported Meetings

Dutch Addiction Program Hosts NIDA at Binational Workshop

The Dutch Addiction Program (DAP) Risk Behaviour and Dependency Programme hosted a binational addiction workshop October 11–12, 2011, in The Hague, The Netherlands. Part of the ongoing collaboration between NIDA and the Research and Development Programme on Substance Use and Addiction of the Netherlands Organization for Health Research and Development (ZonMw), the workshop focused on the progress of current binational research projects, new research initiatives, and future collaboration between NIDA and The Netherlands. NIDA Acting Deputy Director David Shurtleff, Ph.D. IP Director Steven W. Gust, Ph.D., and DAP Chair Sineke ten Horn, Ph.D., hosted a session on future directions and priorities in drug abuse and addiction. Dr. Shurtleff discussed highlights in translational research at NIDA, while Dr. Gust focused on the future of international research collaborations and Dr. ten Horn offered the Dutch perspective. Workshop participants also heard about brain chemistry, brain activity, and pharmacology from jointly funded research teams and researchers funded by the DAP Risk Behavior and Dependency Programme. Meeting participants visited a local coffee shop to hear the owner's interpretation of the Dutch tolerance model for certain drugs, how coffee shops

operate, who their visitors are, and cooperation among coffee shops, addiction clinics, and the police. A local police officer presented the law enforcement perspective on the tolerance model. Joni Rutter, Ph.D., DBNBR, and Dale Weiss, IP, participated in the Binational Workshop, along with three NIDA-supported researchers who are currently working with Dutch partners through U.S.-Netherlands Administrative Supplements: Raymond G. Booth, Ph.D., University of Florida; Daniel D. Langleben, M.D., University of Pennsylvania; and Ingo Willuhn, Ph.D., University of Washington. Dr. Gust also participated in the European Area Research Network on Illicit Drugs conference October 13, 2011. The conference participants discussed some of the policy issues from partnering countries, research underway, and projects planned to help develop evidence-based drug policies. Dr. Gust emphasized the added value of international collaboration in research, especially in saving time and achieving better results.

Experts Share Knowledge on Dual Disorders at International Congress

A recent meeting in Spain brought together professionals in addiction, addiction psychiatry, and mental health to share knowledge and recent research advances about dual disorders. Dual disorders, dual diagnosis, dual pathology, and co-occurrence disorders are all related concepts describing the comorbid presence of substance use disorders and other mental disorders. These disorders are present in an increasing number of patients and pose a significant challenge to the clinician who treats them. NIDA Director Nora D. Volkow, M.D., and Iván Montoya, M.D., M.P.H., Medical Officer, Division of Pharmacotherapies and Medical Consequences of Drug Abuse, attended the second International Congress on Dual Disorders: Addictive Behaviours and Other Mental Disorders in Barcelona on October 5–8, 2011. The meeting was sponsored in part by NIDA and organized by the Spanish Society of Dual Pathology. Dr. Volkow spoke at one of the plenary sessions about recent research efforts to identify genetic and environmental factors underlying mental and addictive disorders and the most effective strategies for their successful treatment. The congress also included symposia, workshops, meetings with experts, educational update sessions, oral communications, and posters. A special 2-day symposium, Parallel Symposia on Self-Medication and Self-Regulation in Dual Diagnosis, reviewed the evidence for and against the theory that some patients use drugs as an attempt to cope with the psychopathological distress they suffer.

DRUID Conference Focuses on Drugged Driving

The European Union (EU) Driving Under the Influence of Drugs, Alcohol and Medicines (DRUID) project met September 27–28, 2011, in Cologne, Germany, marking a 5-year effort to gain insight into the impact of substance abuse on road safety. NIDA IP Director Steven W. Gust, Ph.D. participated in the DRUID conference. Coordinated by the Federal Highway Research Institute of Germany and begun in 2006, DRUID provided scientific support to European Commission (EU) transport policymakers by suggesting guidelines and measures to combat impaired driving. Financed within the EU Sixth Framework Program for Research and Technological Development, with partial support from NIDA, experts from 18 countries representing 37 institutions worked together to gain new insights into the real degree of impairment caused by psychoactive substances such as alcohol, drugs, and certain medicines, and their actual impact on road safety.

NIDA, NIAAA Initiatives Featured at Polish Society for Research on Addictions

The Polish Society for Research on Addictions, formally chartered in 2007, held its third scientific meeting September 26–27, 2011, in Warsaw to provide an update on alcohol and drug research in that nation. Margaret M. Murray, Ph.D., National Institute on Alcohol Abuse and

Alcoholism (NIAAA), reported on the formal collaborative research partnership established between the Polish government and NIAAA to carry out a joint research program on fetal alcohol syndrome. That program also served as the template for a separately funded NIAAA/Fogarty International Center initiative on the development of research capacity in Poland for alcohol and injury research with emergency medicine and public health departments. NIDA IP Director Steven W. Gust, Ph.D., reported on global drug use statistics; emerging trends (especially synthetic drugs in Europe); global commitment to drug abuse through government policies, prevention interventions, and treatment protocols; recent NIDA-funded research advances; and IP activities. The Polish government also has an agreement with NIDA to support collaborative research projects funded under the NIDA International Research Collaboration on Drug Abuse and Addiction Research Program Announcements.

NIDA Supports Young International Investigators at SfN

NIDA organized an Early Career Investigators Poster Session on Friday, November 11, as part of NIDA's mini-convention on Frontiers in Addiction Research at the 2011 Society for Neuroscience Research meeting in Washington, D.C. The invited poster session provides an opportunity for young investigators to speak with mini-convention symposia participants, NIDA staff, and NIDA-supported training directors and researchers while showcasing drug abuse and drug-related neuroscience research. The 12 researchers from 11 countries were supported, in part, by NIDA and the College on Problems of Drug Dependence, International Brain Research Organization, International Cannabinoid Research Society, International Drug Abuse Research Society, International Narcotics Research Conference, and International Union of Basic and Clinical Pharmacology. They included:

- Kiran Akula, Ph.D., India
- Igor Bazov, Ph.D., Sweden
- Laura Caltana, Argentina
- Estefanía Pilar Bello Gay, Argentina
- Carmen Gonzalez, Ph.D., Mexico
- Esther Gramage, Spain
- Mark Hutchinson, Ph.D., Australia
- Philip Kesner, Canada
- Salvatore Lecca, Italy
- Zahra Taslimi, Iran
- Pao Pao Yang, MSc., Taiwan
- Yi Zhang, Ph.D., China

NIDA Supports Researchers at NHSN

Ten researchers received travel awards to present their research at the poster session during the National Hispanic Science Network (NHSN) International Conference, which was held August 24–27, 2011 in Miami, Florida. The NHSN conference International Poster Session showcased ongoing research projects to generate discussion and create linkages for collaborations. NIDA-supported scientists from five nations presented their research at the poster session, including:

- Chile: Luis Caris, University of Chile
- Costa Rica: Julio Bejerano, National Institute on Alcoholism and Drug Dependence
- Mexico: Octavio Campollo, University of Guadalajara; Clara Fleiz, Claudia Rafful Loera, Maria Lourdes Gutierrez Lopez, Natania Oliva Robles, and Jorge Ameth Villatoro Velazquez, National Institute of Psychiatry Ramón de la Fuente Muñiz

- Puerto Rico: Juan Carlos Reyes-Pulliza, University of Puerto Rico
- Spain: Javier Gonzalez-Riera, Jaen Health District, Andalusian Public Health System

Canada – Finland – USA Joint Workshop on "The Early Origins of Addiction". The Division of Clinical Neuroscience and Behavioral Research, NIDA, NIH co-sponsored a meeting along with the Canadian Institutes of Health Research (CIHR) and Academy of Finland (AKA) to build research knowledge through international collaborations on the early origins of addiction from neuroscience, behavioral and environmental perspectives. The successful meeting allowed Finnish and Canadian researchers to network with US investigators who are exploring the integration of neuroscience into adolescent substance abuse treatment and drug policy issues including Dr. Catherine Stanger (University of Arkansas for Medical Sciences); Dr. Cecile Ladouceur (University of Pittsburgh); Dr. Laura MacPherson (University of Maryland); Dr. Mathew Shane (University of New Mexico), Dr. Monique Ernst (NIMH) and Dr. Sara Lynne Landsman (University of Florida). Other highlights included an update on Phenx and potential for common measures for phentotypes and exposures in addiction by Dr. Kevin Conway (DESPR/NIDA). Drs. Terry Jernigan and Anders Dale (University of California, San Diego) gave the US keynote luncheon talk on the Pediatric Imaging, Neurocognition, and Genetics (PING) initiative. The meeting was co-chaired by Dr. Cheryl Anne Boyce (DCNBR)

On October 19, 2011 at the **58th Annual Meeting American Academy of Child and Adolescent Psychiatry** in Toronto, Canada, Drs. Cheryl Anne Boyce and Sarah Lynn Landsman (University of Florida) chaired a session on "Integrating Translational Neuroscience and Adolescent Drug Abuse Treatment." The session highlighted NIDA and NIH funded grants by Dr. Catherine Stanger (University of Arkansas for Medical Sciences), Dr. Cecile Ladouceur (University of Pittsburgh); Dr. Laura MacPherson (University of Maryland); Dr. Mathew Shane (University of New Mexico), Dr. Monique Ernst (NIMH) and Dr. Sara Feldstein-Ewing (University of New Mexico) on innovations in neuroscience which have potential to strengthen adolescent addiction treatments. Also at this international meeting, Dr. Cheryl Anne Boyce chaired and presented at the workshop on NIH Research Priorities and Grant Writing Success. Dr. Ryan Neal (University of Pittsburgh), Dr. Bennett Leventhal (University of Illinois at Chicago), Dr. Kevin Conway (DESPR/NIDA) and Dr. Shelli Avenevoli (NIMH) also presented at the workshop.

Online Initiatives

NIDA International Wins Web Award

On October 31, 2011, the NIDA IP was awarded the Silver World Wide Web Health Award, an honor bestowed on the nation's best electronic health programs and Web-based tools. The IP Web site, www.international.drugabuse.gov, which was redesigned in June 2011, was chosen among hundreds of local, state, and national U.S. health-related organizations. A panel of health technology professionals judged the Web sites based on content, format, success in reaching the targeted health audience, and overall quality. The IP Web site now makes it easier for visitors to explore fellowship opportunities, connect with international drug abuse researchers, access the free online training tools, and read past issues of the *NIDA International E-News.* A new keyword feature allows for faster access to information by topic area.

Fellowships

NIDA Welcomes New Humphrey Fellows

IP Associate Director Dale Weiss met with the 2011–2012 Hubert H. Humphrey Fellows in September to introduce the NIDA resources and opportunities available to them during their fellowships. Ms. Weiss met with NIDA Hubert H. Humphrey Fellows in Substance Abuse Education, Treatment, and Prevention at Virginia Commonwealth University (VCU) and NIDA Hubert H. Humphrey Fellows in Drug Abuse and Public Health at Johns Hopkins University (JHU). She described several NIDA resources, including the NIDA International Virtual Collaboratory (NIVC)—a password-protected tool to support geographically distant partners in collaborative research, discussion, and education—and met individually with the fellows to discuss their professional affiliation interests. In October, IP Director Steven W. Gust, Ph.D., joined Ms. Weiss at the Humphrey Program Global Leadership Forum, where the U.S. Department of State assembled more than 200 Humphrey Fellows from 93 countries for a 4-day orientation. During the Global Leadership Forum, Ms. Weiss met with interested fellows from several Humphrey campuses to describe NIDA activities, research priorities, and opportunities available to the fellows, emphasizing the that the NIDA research portfolio examines the consequences of drug use on brain development and function, physical and mental health, and social, economic, and criminal justice systems.

The 2011–2012 NIDA-supported Hubert H. Humphrey Fellows at VCU include:

- **Tin Moe Aung (Myanmar [Burma])** Dr. Aung's focus is on relapse prevention and promotion of comprehensive health care among injecting drug users. She hopes to enhance her knowledge and practical skills in the prevention of substance abuse to improve prevention programming and aftercare in Myanmar.
- **Natalia Estoyanoff (Uruguay)** Ms. Estoyanoff would like to improve her knowledge and practical skills related to the design and implementation of effective community-based prevention programs, particularly those designed to target young drug users in high social vulnerability contexts.
- **Rogers Kasirye (Uganda)** Mr. Kasirye wants to learn more about substance prevention and policy work in the United States and explore ways of improving the policy environment in Uganda.
- **Laith R. Khalil (Iraq)** Dr. Khalil's goals are to gain the required knowledge and skills to help addiction sufferers in Iraq by learning about the most effective and proven treatment and prevention practices.
- **Lionel Kulathilake (Sri Lanka)** Mr. Kulathilake plans to enhance his knowledge of substance abuse treatment and prevention, as well as program development and evaluation.
- **Pansak Pramokchon (Thailand)** Mr. Pramokchon's goal is to expand his professional experience in institutional management and policy formation to better prepare the Thai Food and Drug Administration for the challenges of global change.
- **Pedro Augusto de Andrade Rodrigues (Brazil)** Mr. Rodrigues' fellowship goals include developing greater knowledge of crack cocaine addiction and treatment and gaining a better understanding of the causes of recent increases in drug abuse and dependence in Brazil. He aims to enhance his knowledge of successful treatment and prevention programs to adapt them to the specific needs of the Brazilian population.
- **Aizhan Zhumasheva (Kazakhstan)** Dr. Zhumasheva seeks to acquire knowledge and practical experience related to drug abuse treatment and prevention services in the United States,

and to establish new professional contacts, particularly with U.S. antidrug coalition members. She plans to utilize this knowledge so that problems of drug abuse in Kazakhstan can be more effectively addressed.

JHU Hubert H. Humphrey Fellows include:

- **Sumitha Chalil (India)** Ms. Chalil will focus on strategies for improving HIV prevention programs and ensuring sustainable behavior change among men who have sex with men and injecting drug users.
- **Tshegofatso Mmolawa (Botswana)** Ms. Mmolawa is interested in strategies to prevent and reduce excessive use of substances among enlisted men and in research on cognitive decline in relation to prolonged substance use, especially alcohol.
- **Eugene Dordoye (Ghana)** Dr. Dordoye will focus his fellowship training to be able to undertake a baseline survey of the alcohol and drug abuse situation in Ghana.
- **Ivan Y. Quevedo (Chile)** Dr. Quevedo's goal is to improve his knowledge and skills to better conduct clinical and translational research on addiction with a special focus on genetics.
- **Onukogu Uchechi Chinyere (Nigeria)** Ms. Onukogu is interested in improving substance abuse treatment in Nigeria and adapting U.S. relapse prevention models to Nigeria.
- **Elis Haan (Estonia)** Ms. Haan seeks to improve her knowledge and skills for the treatment and prevention of substance abuse among youth. She is also interested in strengthening her leadership skills to improve the management and coordination of mental health services in Estonia.
- **Tshering Dolkar (Bhutan)** Ms. Dolkar's goals are to make international connections and get experience with substance abuse intervention programs.
- **Renata de Cerqueira Campos (Brazil)** Ms. de Cerqueira seeks to improve her knowledge in addiction prevention and treatment and in antitobacco advocacy. Her goal is to improve mental health and addiction treatment in the city and propose a model that can be used by the national health system.

Dutch Summer Institute Enriches Doctoral Student's Research Training

The NIDA-supported participant in the Dutch Summer Institute on Alcohol, Drugs and Addiction, Ms. Cendrine Danae Robinson, a doctoral student at the Uniformed Services University of the Health Sciences, found that the experience exceeded her expectations. Dennis McCarty, Ph.D., the scientific director for the Summer Institute and a professor at Oregon Health & Science University, reported that Ms. Robinson's background in neuroscience contributed to the success of the 2011 class. A joint initiative of The Netherlands Organisation for Health Research and Development (ZonMw) and the University of Amsterdam Graduate School of Social Sciences, the Summer Institute is a 2-week, intensive multidisciplinary program offering graduate-level and continuing professional development training in addiction, while promoting opportunities for international networking.

Humphrey Host Universities Team with Local Colleges

Hubert H. Humphrey Drug Abuse Research Fellowship host universities each have teamed with a local college or university to broaden the impact of the program for the Humphrey fellows as well as to local faculty and students. As part of the Humphrey Associate Campus Partnership, Virginia Commonwealth University (VCU) is partnering with Virginia State University and Johns Hopkins University (JHU) is partnering with Prince George's Community College in Maryland. These partnership programs incorporate a range of professional development and

outreach activities between participating students and faculty and the cohort of Hubert H. Humphrey Fellows. The partnerships also enhance the understanding of health disparities research and community-based approaches to substance abuse issues in impoverished minority populations in the United States. The exchanges take place through formal and informal meetings, guest lectures by the fellows, and university and community events.

CTN INVEST Fellows

The National Institute on Drug Abuse (NIDA) International Program and the Clinical Trials Network (CTN) joined forces to offer fellowships to non-U.S. scientists. The international researcher works with a CTN mentor who is 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. Currently, seven scientists have completed their fellowships and have been successful in continuing their research in their countries; six are currently working on their projects, and one more will start in January 2012. All current fellows plan to visit NIH and NIDA on February 1-3, 2012.

Travel Support

NIDA provided travel support to six researchers who participated in the European and International Congress THS 10 (Addiction – Hepatitis – AIDS), October 11–14, 2011, in Biarritz, France. NIDA-supported plenary session speakers included: Robert E. Booth, Ph.D., University of Colorado Denver, who reported on HIV prevention for injection drug users and barriers to effective interventions in Ukraine; Sandra Comer, Ph.D., New York State Psychiatric Institute, who spoke about the abuse liability of maintenance medications for opioid dependence treatment; Thomas Kerr, Ph.D., University of British Columbia, who described the evaluation of Vancouver's supervised injection site; Herbert Kleber, M.D., Columbia University, who discussed whether opioid maintenance treatment can be ended without risk of relapse; Mary Jeanne Kreek, M.D., Rockefeller University, who spoke on stress and addictions; and Frank Orson, M.D., Baylor College of Medicine, who reported on the status of vaccine development for cocaine addiction. NIDA ARP Director Jacques Normand, Ph.D., and DPMCDA Medical Officer Iván Montoya, M.D., M.P.H., also spoke at plenary sessions during the meeting.

Canada – Finland – USA Joint Workshop on "The Early Origins of Addiction". DCNBR provided international travel support for US researchers: Catherine Stanger (U of AK MS); Cecile Ladouceur (U of Pitt); Laura MacPherson (U of MD); Mathew Shane (U of NM), and Sara Lynne Landsman (U of FL).

Other International Activities

Dr. John Satterlee, DBNBR, helped organize the International Human Epigenome Consortium/European Union Epigenomics Blueprint Kick-Off meeting held October 3-4, 2011 in Amsterdam, Netherlands. He gave presentations entitled "IHEC Goals and Progress" and "NIH Roadmap Epigenomics Program Update" at this meeting.

Dr. Louise Wideroff, DBNBR, described NIDA AIDS research interests to African researchers who attended a September 20-21, 2011 meeting in Nairobi, Kenya about the Human Health and Heredity in Africa Initiative (H3A), a new trans-NIH Common Fund program that will support genomics research in Africa.

Dr. Cora Lee Wetherington, DBNBR and Coordinator, Women and Sex/Gender Differences Research gave an invited lecture, "The Ubiquity of Sex/Gender Differences in Drug Abuse," on the Addiction Course held at the Institute of Drug Abuse, Toxicology and Pharmaceutical Science at Ege University in Izmir, Turkey, August 21-22, 2011.

Drs. Cora Lee Wetherington and Samia Noursi, Deputy Coordinator, Women and Sex/Gender Differences Research organized and co-chaired the symposium, "Sex Differences, Women and Smoking: Biobehavioral, Developmental and Translational Perspectives," at the annual meeting of the Society for Research on Nicotine and Tobacco – Europe, in Antalyla, Turkey, September 8-11, 2011

Dr. Samia Noursi gave an invited lecture, "Techniques and Best Practices of Treatment in Women," at the International Seminar on Women and Addiction held in Santiago, Chile, August 24 - 25, 2011.

Dr. Jag Khalsa, DPMCDA, participated and presented at the Canadian Society of Addiction Medicine (CSAM) in Vancouver, Canada, November 4-6, 2011. He was also invited by CSAM to debate the issue of Medical Marijuana with Dr. Mark Ware of Montreal, Canada. This was written up in the CSAM news bulletin (see NIDANews, January 2012) and by an independent writer, Dr. William Hay (Marijuana Debate-Canadian Society of Addiction Medicine 2011: available at: http://williamhaywriter.blogspot.com/2011/11/marijuana-debate-canadian-society-of.html)

Dr. Jag Khalsa was invited by the Marathwada Institute of Technology in India to participate and deliver a talk on treatment management of dually infected drug abusing populations with emphasis on the use of nanotechnology/nanomedicine at the International Conference on Nanotechnology, December 12-13, 2011, in Mumbai, India, and at a satellite meeting in Aurangabad, India, December 14, 2011. Dr. Khalsa also site-visited a NIDA/OAR-funded study on HIV and drug abuse being conducted in Delhi by Dr. Shilpa Buch of University of Nebraska, Omaha, in an international collaboration with the Indian counterpart scientist, Dr. Pankaj Seth.

Dr. Ivan Montoya, DPMCDA, participated and presented at the International Conference on Dual Diagnosis in Barcelona (Spain).

Ivan Montoya participated and presented at the 10th European and International Congress on Addiction Hepatitis AIDS (THS 10), in Biarritz, France. The title of his presentation was "Medications to Treat Concurrent Opiate and Cocaine Dependence."

Aida Klun, DPMCDA, and Ivan Montoya participated in the 4th Annual Federal Hispanic Career Advancement Summit (FAFHCAS) that took place in Bethesda, MD on September 20th and 21st, 2011.

Dr. Wilson M. Compton, Director, DESPR, co-chaired two panels and presented a paper on "Unemployment and Substance Use Outcomes in the United States" at the International Society on Addiction Medicine, Oslo, Norway, September 7-10, 2011.

Dr. Wilson M. Compton presented a plenary on the "Science of Drug Abuse and Addiction" at the Governmental Expert Group of the Inter-American Drug Abuse Control Commission of the Organization of American States, Washington, District of Columbia, September 27, 2011.

Dr. Wilson M. Compton presented in a panel on "The Science of Drug Abuse and Addiction" at the International Conference on Security and Justice, Puebla, Mexico, November 14, 2011.

Dr. Elizabeth Robertson, DESPR, presented a symposium at the 2nd annual meeting of the European Society for Prevention Research held on December 1 and 2, 2011 in Lisbon, Portugal. The Title of the meeting was: "Synergy in Prevention and Health Promotion: Individual, community and environmental approaches", the symposium Dr. Robertson gave was titled: "The Development of Interventions Involving an Environment/Community Component".

Dr. Eve Reider, DESPR, represented NIDA at the 2nd Annual European Union Society for Prevention Research Meeting, held December 8-9, 2011 in Lisbon, Portugal. The theme of the meeting is "Synergy in prevention and health promotion: individual, community, and environmental approach."

Dr. Eve Reider represented NIDA at a workshop on International Prevention Standards that was held December 7, 2011 in Lisbon, Portugal. The meeting was held at the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) in Lisbon, Portugal.

Dr. Eve Reider is an organizer and theme reviewer for the 5th Annual NIDA International Poster Session, which will be held May 29, 2011 at the 19th Annual Society for Prevention Research Annual Meeting, Washington, D.C.

Dr. Peter Hartsock, DESPR, participated in the World Bank/UNAIDS Commemoration of 30 years of the global AIDS response, September 15, 2011, Washington, D.C. The meeting was led by UNAIDS Executive Director and Under-Secretary General of the UN, Dr. Michel Sidibe.

Dr. Peter Hartsock participated in the three meetings of the Presidential U.S.-Russia Bilateral Commission's Health Working Group, September 18th October 15th and December 7th, 2011 at the Carnegie Endowment for Peace, Washington, D.C. The purpose of the Working Group is to develop stronger cooperation in health between both countries as well as more cooperation between the public and private sectors. Dr. Hartsock's participation continues that which he served in the earlier Gore-Chernomyrdin Commission.

Dr. Peter Hartsock briefed a delegation from Ukraine on NIDA-sponsored research currently taking place in Ukraine and other parts of the former Soviet Union, October 28, 2011 Bethesda, MD. The delegation was led by the Advisor to Prime Minister of Ukraine and the Supreme Council of Ukraine, Committee on Public Health.

Dr. Peter Hartsock participated in the State Department-sponsored conference on "The Consequences of Violence Against Women: Examining the Economic, Health, Legal and Social Costs," November 21, 2011 Washington, D.C. The conference was led by Melanne Verveer, Ambassador-at-Large for Global Women's Issues and was held in honor of the "International Day to Eliminate Violence Against Women" and "16 Days of Activism Against Gender-Based

Violence." Human trafficking was one of the issues discussed and NIDA is developing research on trafficking related to drug abuse, HIV/AIDS, and associated problems.

Dr. Peter Hartsock participated in the Center for Strategic and International Studies (CSIS) Conference on Emerging Practices in Global Health Cooperation: Brazil, China, India, Russia, and South Africa, December 6, 2011 Washington, D.C. Dr. Hartsock reported on NIDA-supported implementation research currently underway in these and other countries.

During this period, the Molecular Neurobiology Branch increased interactions with Japanese scientists and collaborators with a formal gift that will facilitate interactions with scientists from Tohoku University, Sendai, Japan.

International Visitors

A delegation from Colombia visited NIDA on September 28, 2011. The delegation was led by Aldemar Parra Espitia**,** Mental Health and Drug Coordinator within the Ministry of Social Protection. The visitors met with NIDA staff: Acting Deputy Director David Shurtleff, Ph.D, Kevin Conway, Ph.D., DESPR Deputy Director & Acting Chief of Prevention Research Branch, Ivan Montoya, M.D., DPMDCA, Deputy Director, Ruben Baler, Ph.D., OSPC and Dale Weiss, IP.

On October 28, 2011 Ukrainian officials on a methadone study tour organized by the International AIDS Alliance visited NIDA. NIDA staff that met with the group included, Jacques Normand, Ph.D., ARP, Peter Hartsock, Ph.D. and Jeffrey Schulden, M.D. DESPR, Steven Gust, Ph.D. and Dale Weiss, IP.

Dr. Cheryl Anne Boyce met with the Ambassador from Trinidad and Tobago to the United States, Dr. Neil Parson, to brief him on current NIDA initiatives on substance use and HIV and NIH international collaborations on October 24, 2011.

MEETINGS/CONFERENCES

NIDA's Neuroscience Consortium organized the 10th annual **Frontiers in Addiction Research Mini-convention** at the Society for Neuroscience Meeting, November 11, 2011. This year's mini-convention included sessions on autism, addiction and MeCP2; synapse organization and plasticity in drug addiction; using optogenetic tools to shed light on the neural mechanisms of addiction; and neurobiology of behavioral and emotional regulation/dysregulation. The miniconvention was organized by Drs. Antonello Bonci, Mary Kautz, Geraline Lin, Cathrine Sasek, John Satterlee, David Shurtleff, Susan Volman, and Ms. Patricia Anderson, Usha Charya, and Joan Nolan.

The NIDA Neuroscience Consortium sponsored an **NIH Grant Workshop for Early Career Investigators** at the annual Society for Neuroscience meeting, November 14, 2011. This very well attended meeting provided valuable information and insight to those who are at the beginning of their research career. NIDA organizers included Nancy Pilotte, Roger Sorensen and Albert Avila. Kristin Kramer from CSR provided review expertise at the workshop.

Drs. Mary Kautz, DCNBR and Cathrine Sasek, OSPC, chaired the 9th annual **Society for Neuroscience Jacob P. Waletzy Memorial Award Lecture** at the" Frontiers in Addiction Research" Mini-convention at the Society for Neuroscience meeting. This year's winner was Dr. David Jentsch. The Jacob P. Waletzky Memorial Award was established in 2003 to recognize the research contributions made by outstanding junior scientists in the area of drug addiction or alcoholism, and the nervous system.

NIMH, NIDA and NINDS were cosponsors for the **5th Annual Julius Axelrod Lecture** and poster session held November 13, 2011 at the annual Society for Neuroscience Meeting. The winner of this year's prize was Dr. Roger Nicoll from the University of California, San Francisco. The title of his presentation was Deconstructing and Reconstructing Excitatory Synapses.

Dr. John Satterlee, DBNBR, chaired a symposium, **Autism, Addiction, and MeCP2** as part of NIDA's mini-convention "Frontiers in Addiction Research" held in Washington, D.C. on November 11, 2011. Speakers included Janine LaSalle, Ph.D. (UC Davis School of Medicine), Ghazaleh Sadri-Vakili, Ph.D. (Mass General Institute for Neurodegenerative Disease) and Anne E. West, M.D., Ph.D. (Duke University Medical Center).

Dr. Geraline Lin, DBNBR, chaired a symposium titled **Synapse Organization and Plasticity in Drug Addiction** as part of NIDA's mini-convention "Frontiers in Addiction Research" held in Washington, D.C. on November 11, 2011. Speakers included Thomas C. Südhof, M.D. (Stanford University School of Medicine), Thomas Biederer, Ph.D. (Yale University), Veronica A. Alvarez, Ph.D. (National Institute on Alcohol Abuse and Alcoholism) and Marine E. Wolf, Ph.D. (Rosalind Franklin University of Medicine and Science).

Dr. Susan Volman, DBNBR, organized the **Early Career Investigators Poster Session** at the NIDA mini-convention, "Frontiers in Addiction Research" in Washington, D.C. on November 11, 2011. A total of 84 posters were presented, including 12 by international investigators cosponsored by 6 international organizations (CPDD, IBRO, ICRS, IDARS, INRC, and

IUPHAR). This year, the poster session also included 2 posters from the ADHD-200 Global Competition, a competition aimed at identifying algorithms/approaches capable of classifying individual participants based on their functional imaging data.

Drs. David Shurtleff, Acting Deputy Director, NIDA, and Antonello Bonci, Scientific Director, NIDA Intramural Research Program, chaired a symposium titled **Using Optogenetic Tools to Shed Light on the Neural Mechanisms of Addiction** as part of NIDA's mini-convention "Frontiers in Addiction Research" held in Washington, D.C. on November 11, 2011. Speakers included Jin Hyung Lee, Ph.D. (University of California, Los Angeles), Garret Stuber, Ph.D. (University of North Carolina at Chapel Hill School of Medicine), Mary Kay Lobo, Ph.D. (University of Maryland School of Medicine), and Billy T. Chen, Ph.D. (NIDA Intramural Research Program). The discussant session was lead by Dr. Bonci.

Dr. Susan Volman, DBNBR, chaired a symposium titled **Neurobiology of Behavioral and Emotional Regulation/Dysregulation** as part of NIDA's mini-convention "Frontiers in Addiction Research" held in Washington, D.C. on November 11, 2011. Speakers included Anthony A Grace, Ph.D. (University of Pittsburgh), Alison M. Bell, Ph.D. (University of Illinois at Urbana-Champaign) and Elisabeth A. Phelps, Ph.D. (New York University).

Dr. Yu (Woody) Lin, DCNBR, organized a workshop entitled **Pathways Toward Evidence-Based, Personalized Analgesic Medication**. The meeting was sponsored by the NIDA Prescription Opioid and Pain Workgroup and the NIDA DCNBR, was held at NIDA on September 14, 2011. Representatives from FDA and VA pain and analgesia program as well as program staffs from NCCAM, NCRR, NIA and NIAMS participated the meeting. This workshop 1) reviewed the evidence base of patient characteristics, and the association between patient phenotype and genotype and individual heterogeneity in pain and responses to analgesics; and 2) discussed how the present evidence might inform and improve research, clinical practice, and clinical trials to maximize the effectiveness of prescription analgesics based upon individual variation. Given the demand for evidence-based medical use of prescription analgesics for chronic pain, this meeting will help to facilitate advances in future research on pain and analgesia.

The NIDA Asian American/Pacific Islanders Researcher and Scholars (AAPI) workgroup sponsored a training program where six diversity trainees received travel award and attended the 2011 NIDA Neuroscience mini-convention. The program accentuated the workgroup's mission in coaching and training and incorporated two elements, the **AAPI Early Career Investigator Symposium** and the **AAPI Mentoring and Training Session**. Neuroscience Consortium jointly supported the mission and its member, Dr. Yu (Woody) Lin from DCNBR served as a liaison to facilitate the planning and implementation of the AAPI events.

On December 9-10, 2011, NIDA's **African American Researchers and Scholars Workgroup** sponsored a two-day ***"Grant Writing Booster Session"*** at Johns Hopkins University in Baltimore, Maryland. A number of early career investigators who previously attended the Workgroup's July 2011 **Addiction Research Training Institute** came to Baltimore to engage in intensive one-on-one and small group grant writing sessions, under the supervision and mentorship of workgroup members/investigators currently funded by NIDA and the NIH. All participants are expected to submit research applications to the NIH in early 2012.

NIDA's **Asian American/Pacific Islanders Researcher and Scholars (AAPI) workgroup** sponsored a training program in the 2011 NIDA Neuroscience mini-convention for diversity trainees. The workgroup acknowledged 6 mentorship programs in this symposium. The program accentuated the workgroup's mission in coaching and training of socially disadvantaged minority junior investigators. Two sessions were successfully incorporated. The AAPI Early Career Investigator Symposium permitted the junior investigators to interact with AAPI investigators. Research topics presented covered areas from lab study to clinical implication and from addiction research to the interactive effects of addictive substance and HIV. The AAPI Mentoring and Training session consisted of topics on scientific writing, benefit of serving NIH study sections and an orientation for junior investigators to attend NIDA Grant Workshop. Dr. Sulie Chang at Seton Hall University and Dr. Ming Li at University of Virginia served as scientific program organizer of this event who shared with the trainees their own experience and the great benefit of attending and networking at NIDA mini-convention.

On November 7-8, 2011, the Special Populations Office (SPO) convened the **Diversity Alumni Meeting** in Bethesda, Maryland. Coordinated by Flair Lindsey, Program Analyst, SPO, the meeting invited key diversity program stakeholders – those who have been involved as diversity mentors, trainees, grantees, faculty and participants in NIDA and select NIAAA programs over the years -- to identify and discuss program needs, strengths and weaknesses. Moreover, meeting participants shared assessments of what worked, what did not work, and challenges faced as a mentor/faculty/trainee through presentations, open forums and Q&A segments, ultimately providing individual and collective recommendations for strategies to improve current efforts and create new opportunities. Additionally, the participants were canvassed to offer perspectives on causes of low diversity participation rates in the NIH research funding pool and remedies to overcome them, an area of immediate concern for NIH. Formal findings from the meeting will be shared with the NIH Director and NIH colleagues working on diversity issues in other NIH Institutes and Centers. The meeting's keynote speaker was Dr. Frederick T.L. Leong, Michigan State University, who presented "Cultural Dynamics in the Psychology of Science: Impact on Career Development." The meeting also included presentations from an array of Diversity program participants, NIDA staff and colleagues from NIH OD, NIMHD and NIAAA. The agenda was structured around factors considered critical in academic and research success for persons from racial/ethnic minority populations and other disadvantaged groups, namely mentoring, review/evaluation, and institutional home and challenges.

NIDA, in conjunction with NIAAA, NICHD, NIMH and NIDS, hosted the second installment of the **Addressing Health Disparities through Neuroscience Seminar Series** on September 19, 2011 in Bethesda, Maryland. The seminar featured speakers Drs. Bruce McEwen (Rockefeller University) and James S. Jackson (University of Michigan), whose presentations were "Neuroscience Perspectives on Brain and Body Health: Importance of the Social Environment" and "The Affordances Framework for Understanding Population Disparities in Physical and Mental Health" respectively. Flair Lindsey, Program Analyst, Special Populations Office, represented NIDA on the seminar series' planning committee.

As a part of the **NIDA Special Populations Research Development Seminar Series**, Kathy Etz, Ph.D., Chair, American Indian and Alaska Native Coordinating Committee, NIDA and Flair Lindsey, Program Analyst, Special Populations Office, coordinated a 2-day mock review/technical assistance workshop for new investigators with an interest in American Indian/Alaska Native (AI/AN) focused substance abuse and addiction research. Participants

submitted draft research grant proposals, which underwent a mock review, participated in one-on-one consultations with NIH funded investigators/NIH program staff and heard presentations on cutting-edge research methods currently being utilized in AI/AN social science research.

On November 7-8, 2011, a **Joint Workgroup Meeting of NIDA's Racial/Ethnic Minority Work Groups** was held including members of the African American Researchers and Scholars, American Indian/Alaska Native Researchers and Scholars, Asian American/Pacific Islander Researchers and Scholars and the National Hispanic Science Network. The work groups met independently and jointly to discuss common goals, future directions, collaborative opportunities and gaps in opportunities for minority health and health diversity. This meeting was coordinated by Flair Lindsey, Program Analyst, Special Populations Office.

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Lula Beatty, Ph.D., Director, Special Populations Office (detail) gave the presentation "To Build or Not to Build that Research Bridge: Obtaining Support for Your Research Ideas" at the Caribbean Regional Conference of Psychology's annual conference "Psychological Science and Well Being: Building Bridges for Tomorrow" in Nassau, Bahamas on November 17, 2011.

Dr. Lula Beatty gave the presentation "Diversity Program Overview: NIDA" at the NIDA Diversity Alumni meeting in Bethesda, Maryland on Monday, November 7, 2011, in addition to fulfilling roles such as moderator and facilitator.

Ana Anders, M.S.W., Public Health Analyst, Special Populations Office, planned and participated in the National Hispanic Science Network's annual conference in Miami, Florida on August 24-27, 2011.

Ana Anders participated in the Latino Behavioral Health Institute in Los Angeles, California on September 14-16, 2011.

Ana Anders was invited to present at Clinical Rounds at St. Elizabeth's Hospital, Washington, D.C. on September 21, 2011.

Ana Anders, in collaboration with the NIH Hispanic Employment Committee, planned the Hispanic Heritage Month Observance for NIH, on October 5, 2011.

Dr. Mimi Ghim, Deputy Coordinator for Research Training, OSPC, presented on NIDA's research training and related programs at The Diversity Alumni Meeting, held November 7-8, 2011 at the Hyatt Regency in Bethesda, MD.

Dr. Vishnu Purohit and Dr. Rao Rapaka, DBNBR, organized a symposium on Drugs of Abuse, Dopamine, and HAND/HAD in Rockville, Maryland, October 4, 2011. A summary of the symposium will be submitted to the Journal of Neurovirology for publication.

Dr. Rapaka co-organized a symposium on "Lipid mediators, receptors and TRPs" with Carolina Cannabinioid collaborative on October 29-30, 2011, at Research Triangle Park, NC. The proceedings of the symposium will be published in 2012.

Dr. Da-Yu Wu, DBNBR, represented NIDA on the Common Fund Single Cell Analysis Project and participated in drafting and publishing three RFAs in this new research area.

Dr. John Satterlee, DBNBR, chaired a session entitled "Addiction, Autism, and MeCP2" held at the NIDA Frontiers in Neuroscience meeting on Nov 11, 2011 in Washington, DC.

Dr. Jonathan D. Pollock, DBNBR, organized and chaired, the Genetics and Epigenetics of Substance Abuse: NIDA/NIAAA Satellite Symposium at the World Congress on Psychiatric Genetics, Omni Shoreham Hotel, Washington, DC, September 9th, 2011.

Dr. Jonathan D. Pollock organized and chaired a weekly webinar series on molecular neuroanatomy from August 30 through November 8, 2011 with leaders in the field. These webinars were set up to facilitate discussion at the November 11-12, 2011 meeting "Molecular Neuroanatomy: the Next Decade of Decade of Progress" held at the Embassy Suites Hotel, Washington, DC. The meeting was organized by Dr. Pollock in collaboration with program officials at NIMH, NIAAA, NINDS, NEI, NICHD, NIEHS, NIDDK, NLM, NCRR, and NIA. The purpose of the meeting was to review the progress that had been made in the field of molecular neuroanatomy, and develop a strategic plan for the next decade.

Dr. Jonathan D. Pollock organized and co-chaired a panel with Dr. Lei Yu at the American College of Neuropsychopharmacology, entitled, "Role of Phagocytes in Synaptic Plasticity and Remodeling of Tissues in the Nervous System,." Held at the Waikaloa Hilton, Waikaloa, HI, December 7, 2011. The speakers in the panel were Noble Laureate, Dr. Mario Capecchi, Dr. Ben Barres, Dr. Beth Stevens, and Dr. Wenbiao Gan.

Dr. Cora Lee Wetherington, DBNBR, gave an invited presentation, "Sex Differences in Drug Abuse," to the National Institute on Mental Health Women's Team on October 31, 2011 in the Neuroscience Center.

Dr. Cora Lee Wetherington served as a session moderator in the Eight Annual Interdisciplinary Women's Health Symposium sponsored by the NIH Office of Research on Women's Health (ORWH) held November 17, 2011 in Masur Auditorium on the NIH main campus. The annual symposium features research funded by ORWH's P50 and K12 programs and co-funded by NIH ICs, including NIDA.

Dr. Susan Volman and Dr. Jennifer Couch (NCI) moderated and served as discussants for a session at the interagency Multiscale Modeling Consortium meeting, October 5, 2011.

Drs. Ivan Montoya, DPMCDA and Wilson Compton, DESPR, co-chaired a symposium at the Annual Meeting of the American Academy of Addiction Psychiatry in Phoenix, Arizona. The title of the symposium was New Approaches to Treat Tobacco, Stimulants, and Opioid Addiction: Medication Update from NIDA. Dr. Dorothy Hatsukami presented the advances in the development of immunotherapies to treat nicotine and cocaine addiction. Dr. Tom Newton discussed the progress in the development of therapeutics for Stimulant Dependence. Ivan Montoya presented for Katherine Beebe the results of the Phase III clinical trial of an implantable formulation of buprenorphine for the treatment of opioid dependence.

Dr. Steven Grant, DCNBR, and Suzanne Haber co-organized and co-chaired a panel at the 50th Annual Meeting of the American College of Neuropsychopharmacology entitled "New Directions in Understanding the Neurocircuitry of Choice, Value, and Decision-Making" held December 4-8, 2011 in Waikoloa, Hawaii.

Dr. Cheryl Anne Boyce, DCNBR, and Dr. Denise Pintello, OD/NIDA, attended the Translational Research on Child Neglect Consortium Fifth Annual Meeting held on September 8-9, 2011 at the University of Iowa, Iowa City, focused on interventions for neglect child populations where they presented on research funding and mentored early research investigators.

Dr. Nicolette Borek, DCNBR, participated in the Developmental Origins of Health and Disease 7th World Congress, September 18-21, 2011 in Portland, Oregon.

Dr. Nicolette Borek provided technical assistance at the annual meeting of the program project on Neurobiological and Behavioral Consequences of Cocaine Use in Mother/Infant Dyads, in New Haven, CT held on September 23-24, 2011.

Dr. Cheryl Anne Boyce presented on "Finding Funding" at the NIH Postbac Careers in Psychology workshop held on the Bethesda NIH Campus on October 24, 2011. Dr. Kim Nickerson (University of Maryland) and Dr. Audrey Thurm (NIMH Intramural) also participated in the workshop.

NIDA's Child and Adolescent Workgroup (CAWG) chaired by Drs. Cheryl Anne Boyce and Denise Pintello hosted Nataki MacMurray and Peter Gaumond from the White House Office of National Drug Control Policy (ONDCP) at the October 25, 2011 workgroup meeting. An update on current recovery and demand reduction programs relevant to adolescent populations was presented, "Promoting Addiction Recovery for Adolescents."

Dr. Cheryl Anne Boyce presented at the Robert Wood Johnson New Connections Research and Coaching Clinic on "Opportunities and Challenges to Obtaining NIH Funding" on October 28, 2011 in Washington, DC.

Dr. Karen Sirocco, DCNBR, participated in the Early Head Start Partnership Grants: Buffering Children from Toxic Stress Consortium Meeting held on November 2-3, 2011. The meeting was sponsored by the Administration for Children and Families, DHHS.

Dr. Nicolette Borek attended the mHealth Summit December 5-7, 2011 at the National Harbor, Maryland.

Dr. Cheryl Anne Boyce was an invited presenter for the Children's National Medical Center (CNMC) Department of Psychiatry CORE Lecture on "Child Sexual Abuse and Prevention of HIV, Substance Abuse, & Mental Disorders" on January 11, 2012.

Drs. Jessica Chambers and Will Aklin of DCNBR facilitated a Morning Networking Discussion Group on Alcohol and Drug Abuse at the mHealth Summit on December 7, 2011 in Washington DC.

Dr. Lisa Onken, DCNBR, gave a plenary presentation at the October 26-28, 2011 meeting of the Delaware Project on Clinical Science Training: From Intervention Development to Implementation, at the University of Delaware in Newark, Delaware. The Delaware Project aims to redefine psychological clinical science training in ways that emphasize continuity across a spectrum of research activities concerned with (a) basic mechanisms of psychopathology and behavior change, (b) intervention generation and refinement, (c) intervention efficacy and effectiveness, and (d) implementation and dissemination. Dr. Onken's presentation was entitled, "The NIH Stage Model of Intervention Development: A Bidirectional + Translational Conceptual Framework."

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

Dr. Wilson M. Compton 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.

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

Dr. Wilson M. Compton continues to participate in the DSM-V Task Force and DSM-V Substance Use Disorders Workgroup meetings on a continuing basis.

Dr. Wilson M. Compton co-chaired two panels and presented a paper on "Unemployment and Substance Use Outcomes in the United States" at the International Society on Addiction Medicine, Oslo, Norway, September 7-10, 2011.

Dr. Wilson M. Compton gave a plenary lecture on "Mainstreaming Addictions in Medicine" at the annual INEBRIA Conference, Boston, Massachusetts, September 21, 2011.

Dr. Wilson M. Compton presented on "Context of PDMPs: Abuse of Pharmaceuticals in the USA" at the annual meeting of the National Prevention Network, Atlanta, Georgia, September 22, 2011.

Dr. Wilson M. Compton presented a plenary on the "Science of Drug Abuse and Addiction" at the Governmental Expert Group of the Inter-American Drug Abuse Control Commission of the Organization of American States, Washington, District of Columbia, September 27, 2011.

Dr. Wilson M. Compton presented a plenary on the "Harnessing Healthcare Reform to Improve Substance Abuse Treatment" at the Addiction Healther Services Research conference, Fairfax, Virginia, October 5, 2011.

Dr. Wilson M. Compton presented on "Terminology of Substance Use Disorders for DSM-5" at the annual meeting of the American Public Health Association conference, Washington, District of Columbia, October 31, 2011.

Dr. Wilson M. Compton presented in a panel on "The Science of Drug Abuse and Addiction" at the International Conference on Security and Justice, Puebla, Mexico, November 14, 2011.

Dr. Wilson M. Compton presented a paper on "Unemployment and Substance Outcomes in the United States During Economic Stress" at the American College of Neuropsychopharmacology, Waikaloa, Hawaii, December 7, 2011.

Dr. Wilson M. Compton co-chaired two panels and presented a paper on "Terminology of Substance Use Disorders for DSM-5" at the annual meeting of the American Academy of Addiction Psychiatry, Scottsdale, Arizona, December 8-9, 2011.

Dr. Kevin Conway, DESPR, presented at The National Academies (Board on Children, Youth, and Family) meeting, "Applying the Principles of *The Science of Adolescent Risk-Taking* to the Design and Implementation of Interventions" on September 16, 2011.

Dr. Meyer Glantz, DESPR, presented background information and was subsequently interviewed by members of the Board on Health Care Services, Institute of Medicine, National Academy of Sciences for the IOM study on geriatric mental health and substance abuse.

Dr. Meyer Glantz is NIDA's representative to the Administration on Aging - NIH committee on Depression, Mental Health, & Substance Abuse. He presented a report at the December 6, 2011 meeting which summarized NIDA's activities in the area and some of the complexities of research in the area.

Dr. Elizabeth Robertson, DESPR, was on the planning committee for the Garrison Institute's Initiative on Contemplation and Education symposium. The meeting was titled: "Advancing the Science and Practice of Contemplative Teaching and Learning" and was held on November 4-6, 2011, Garrison, NY.

Dr. Elizabeth Robertson was on the planning committee for the NIH meeting titled "Health Outcomes among Children and Families Living in Rural Communities" held on December 1-2, 2011 at the Masur Auditorium on the NIH campus.
Drs. Elizabeth Robertson, Eve Reider and Wilson Compton, DESPR, are on a program planning committee for a DHHS multi-agency meeting being planned on adoption that will be held in the spring 2012.

The members of the Prevention Research Branch (PRB), NIDA, met with Drs. Kate Nassauer and Ron Hoover, Military Operational Medicine Research Program (MOMRP), on September 23, 2011 to present and discuss mission, goals, portfolios, and opportunities for future collaborations of the MOMRP and PRB. The meeting was held at NIDA.

Dr Elizabeth Robertson presented to the Interagency Working Group on Youth Programs hosted by the Department of Health and Human Services on Prevention Research at the National Institute on Drug Abuse. The meeting was titled: "The Federal Learning Exchange on Directions in Evidence-based Strategies for Youth Programs" and was held at the Madison hotel in Washington, DC on October 12, 2011.

Dr. Eve Reider was invited to attend and represented NIDA at a two-day meeting sponsored by the Defense Health Program (DHP). The purpose of the meeting was a joint DHP Medical Research and Development Program and Veterans Affairs (VA) Office of Research and Development portfolio review of research in the Psychological Health and Traumatic Brain Injury program areas. The meeting was held November 30th and December 1st, 2011 at Fort Detrick, Maryland.

Drs. Eve Reider and Belinda Sims, Prevention Research Branch, participated on the program planning committee for the 20th Annual Society for Prevention Research Annual Meeting that will be held May 29-June 1, 2012 in Washington, D.C.

Dr. Eve Reider, Prevention Research Branch, represents NIDA on a Federal Interagency Committee on Traumatic Brain Injury and attended a meeting that was held at the Parklawn Building on June 16, 2011. The second meeting was held by phone on October 13, 2011.

Dr. Eve Reider presented on "Drug Abuse and Associated Problems among Military Personnel, Veterans & Their Families" at the Office of National Drug Control Policy on August 10, 2011.

Dr. Eve Reider was a speaker at the ICF International Veterans Breakfast Series on "Addressing Substance Abuse in Military and Veteran Populations**."** Other speakers included: Dr. Keita Franklin, Branch Head, Behavioral Health, U.S. Marine Corps, Manpower & Reserve Affairs (MRRO); LTC Sheila Seitz, Army Center for Substance Abuse Programs, U.S. Army; General Arthur T. Dean (Ret. Army), Chairman, Community Anti-Drug Coalition of America (CADCA); and Mr. Mark Mattiko, Substance Abuse Program Manager, U.S. Coast Guard The event was held September 14, 2011 at ICF International in Washington, D.C.

Drs. Aria Crump, Rich Jenkins, and Augusto Diana, DESPR, served as mentors for the NIDA Special Populations Office Research Development Seminar Series meeting held September 28-29^{th,} 2011 in Bethesda, MD to support drug abuse and drug-related HIV research in American Indian and Alaska Native communities.

Drs. Aria Crump, Jacqueline Lloyd, Eve Reider, Elizabeth Robertson, and Belinda Sims, Prevention Research Branch, DESPR, attended the Interagency Working Group on Youth Programs meeting entitled, A Federal Learning Exchange on Directions in Evidence-Based Strategies for Youth Programs, organized by the HHS office of the Assistant Secretary for Planning and Evaluation, in Washington, DC, on October 12, 2011.

Dr. Belinda Sims participated in the Military Family Research Workgroup, in Indianapolis, IN, on September 29, 2011, which was organized by the US Army Medical Research and Materiel Command, Military Operational Medicine Research Program

Dr. Jacqueline Lloyd, DESPR, represented the Prevention Research Branch at the Early Head Start University Partnership Grants: Buffering Children from Toxic Stress Consortium Meeting organized by the Office of Planning, Research, and Evaluation (OPRE) and held in Washington D.C. November 2-3, 2011.

Dr. Augusto Diana, DESPR, participated in a workshop on “Research Funding Opportunities and Data Resources, Research Support Forum” at the American Sociological Association annual conference in Las Vegas, NV, in August 2011.

Dr. Augusto Diana was on the planning committee for and moderated a panel at the NIH meeting titled “Brand Positioning: What Are You Promising Your Target Audience,” held in September, 2011 at the Neuroscience Center in Rockville, MD.

Dr. Augusto Diana moderated a panel on “Innovative Approaches to Preventing Prescription Drug Abuse” at the National Prevention Network Research Conference in Atlanta, GA, in September, 2011.

Dr. Dionne Jones, DESPR, organized and chaired a panel entitled "Empowering Women to be Healthy: Ending Partner Abuse" at the American Psychological Association 119th Annual Meeting in Washington, DC, August 4-7, 2011.

Dr. Dionne Jones moderated a panel "Predictors of Alcohol, Tobacco, and Other Drug Use in Our Youth" at the American Public Health Association Annual Meeting in Washington, DC held October 29-November 2, 2011.

Dr. Dionne Jones moderated a panel "Improving Implementation of Evidence-Based Practice: Initial Findings from the Criminal Justice – Drug Abuse Treatment Studies Research Collaborative” at the American Society of Criminology Annual Meeting in Washington, DC held November 16-19, 2011.

Dr. Sarah Q. Duffy, DESPR, served as the discussant in the session entitled "Research Design, Outcomes, and Policy Implications from Florida Cost Assessment of Addiction Programs (FCAAP), the First State-Wide Assessment of Substance Abuse Treatment Costs" at the October, 2011 Addiction Health Services Research Conference in Fairfax, VA.

Dr. Peter Hartsock, DESPR, co-chaired, with NIDA grantee Dr. Sheryl McCurdy (University of Texas School of Public Health), the inaugural meeting on health held by the African Studies Association (ASA), November 16, 2011, Washington, DC. Dr. McCurdy serves on the Board of Directors of the ASA, which is the largest organization of its kind with members (e.g., economists, political scientists, historians, ethnographers) from around the world whose research concerns the African continent. The ASA has recognized the need for a much stronger involvement in health research and the meeting provided members with the chance to meet with NIH representatives and grantees to discuss shared goals and plan future cooperation. The meeting was also supported by Dr. and Mrs. Steven Alderman, who just received the Presidential Citizens Medal from President Obama for their work in developing medical and mental health training and facilities for 22 post-conflict countries.

Dr. Teri Levitin, Director, OEA, presented a talk on “Challenges to Achieving Diversity on NIH Review Panels” and participated on the panel that discussed these issues at the NIDA Diversity Alumni Meeting held at the Hyatt Regency in Bethesda, November 7-8, 2011.

Drs. Jose Ruiz, OEA, and Joseph Frascella, DCNBR, were co-presenters of the "Grant Writing Workshop" at the 11th Annual International Conference of the National Hispanic Science Network on Drug Abuse in Coral Gables, Florida, August 26, 2011.

Dr. Scott Chen, OEA, participated in NIH testing modifications to the technology developed for Internet Assisted Review (IAR) software in Bethesda, Maryland, September 14, 2011.

The 1st Biennial Global Implementation Conference was held August 15-17, 2011 in Washington, DC. Dr. Harold Perl, CCTN, presented an interactive poster entitled, "Three Strategies to Enhance Implementation of Evidence-Supported Practices."

Dr. Petra Jacobs, CCTN, participated in the 2012 AATOD National Conference Workshop Selection Committee meeting held in Las Vegas, Nevada on August 19, 2011.

The 4th Annual National CTSA Community Engagement Conference was held August 30-31, 2011 in Bethesda, MD.

1) Dr. Barbara Moquin, CCTN, was a member of the Planning Committee and moderated a break-out session on Social Media and Arts.
2) Dr. Betty Tai, Director, CCTN, chaired a "Think Tank" session titled, "Challenges, innovations, and regulations of integrating behavioral health EHRs into meaningful use in primary health care."

The 8th Annual International Network on Brief Interventions for Alcohol Problems (INEBRIA) Conference was held September 21-23, 2011 in Boston, MA. NIDA CTN members and CCTN staff presented the following:

1) Dr. Udi Ghitza, CCTN, chaired a workshop entitled, "NIDA Clinical Trials Network Electronic Health Records Project: Public Opportunity for Input into Standardized Data Elements for Drug Abuse Treatment." Dr. Betty Tai presented a talk titled: "Development of an Electronic Medical (Health) Record in Substance Use Disorders" at this workshop.
2) Dr. Geetha Subramaniam, CCTN, chaired a workshop entitled, "The Development of a Clinical Decision Support for Substance Use in Primary Care." Drs. Betty Tai and Geetha Subramaniam presented along with Dr. Robert Gore-Langton of The EMMES Corporation.
3) Dr. Harold Perl, CCTN, chaired a symposium entitled, "Innovative methodologies for testing SBIRT in six emergency departments: The Clinical Trials Network's SMART-ED Trial."

The National CTN Steering Committee Meetings were held September 26-28, 2011 in Bethesda, Maryland. The following workshops and meetings convened:

Design & Analysis Workshop
CTP and PI Caucuses
Executive Committee
Research Utilization Committee
Research Development Committee
Node Coordinator Workgroup
International Forum with Invest Fellows
Patient Reported Outcomes (PRO)
Steering Committee
Psychopharmacotherapy Special Interest Group

CTN 0037, STRIDE
CTN 0044, Web-based TES
CTN 0047, SMART-ED
CTN 0048, CURB
CTN 0050, START Follow-up
CTN 0051, X:BOT
Electronic Health Record

Dr. Paul Wakim and biostatisticians from CTN's Data and Statistics Center organized a workshop entitled "Determining Stimulant Drug Use by Combining Results from Timeline Follow-Back and Urine Drug Screening". This workshop compared several algorithms to determine drug use, which is the primary outcome in most CTN trials. The workshop was held on September 26, 2011, in conjunction with the CTN Steering Committee meetings.

At the Addiction Health Services Research (AHSR) Conference held October 3-5, 2011 in Fairfax, VA, Dr. Betty Tai presented an address titled, "Measuring Performance to Improve the Quality of Substance Use Disorder Treatment."

The Annual Washington Circle Conference was held on October 11, 2011 in Washington, DC. Dr. Betty Tai delivered a presentation on the EHR's role in Healthcare reform.

The Science Leadership Conference of APA was held on October 23, 2011 in Washington, DC. Dr. Betty Tai presented a talk entitled, "Clinical Trials Network Bridging the Gap between Science & Practice: Translating Addiction Research to Benefit Patients."

Drs. Geetha Subramaniam and Udi Ghitza co-chaired a plenary session at the Annual SAMHSA SBIRT Grantee meeting November 1-2, 2011, to provide an overview on the EHR and common data elements initiative undertaken by NIDA and to present the clinical decision support model for screening for substance use disorders in general medical settings. Drs. Betty Tai, Geetha Subramaniam and Robert Lindblad of The EMMES Corporation presented at this meeting.

The 35th Annual National Conference of the Association for Medical Education and Research in Substance Abuse (AMERSA) was held November 3-5, 2011 in Washington, DC. NIDA CCTN staff presented the following:

1) Drs. Geetha Subramaniam and Udi Ghitza, co-chaired a workshop entitled, "NIDA's Electronic Health Records Project: From Screening to Decision Support (Public Opportunity for Input into Standardized Common Data Elements for Drug Abuse Treatment)." Drs. Betty Tai, Geetha Subramaniam, Richard Saitz from Boston University Schools of Medicine and Public Health, and Robert Lindblad of The EMMES Corporation were also presenters at the session.
2) Dr. Harold Perl taught a skills-based workshop entitled, "Unlock the Mysteries of NIH Research Funding: Improve Your Grant Application and Improve Your Chance at Success."
3) Dr. Betty Tai presented at a breakfast session on the topic of EHR's role in Healthcare reform.

Dr. Geetha Subramaniam was invited to present an expert review of "Pharmacotherapies for the treatment of Substance use disorders in youth" at the SAMHSA sponsored "Children and Youth Substance Abuse Services Expert Panel Meeting" in Washington DC, December 5-6, 2011.

Dr. Jonathan Katz, IRP, presented a seminar entitled "A role for sigma receptors in stimulant self administration and addiction" to the Department of Behavioral Health, National Naval Medical Center, Bethesda, Maryland. September 9, 2011.

Dr. Amy Newman, IRP, gave invited lectures in the Department of Chemistry, University of Massachusetts in September and the Department of Medicinal Chemistry, School of Pharmacy at the Medical College of Virginia, Virginia Commonwealth University, in October.

Dr. Amy Newman chaired a mini-symposium at the 50th Annual American College of Neuropsychopharmacology meeting, in Waikoloa, HI, entitled "Medication Discovery for Addiction: Translating the Dopamine D3 Receptor Hypothesis."

MEDIA AND EDUCATION ACTIVITIES

MEDIA SUPPORT OF EVENTS AND MEETINGS:

Addiction Performance Project
Performances were held in Denver, CO on November 6th and 7th for the Addiction Performance Project (APP). APP is a continuing medical education (CME) program that offers healthcare providers the opportunity 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 NIDAMED, NIDA's outreach program targeted to practicing physicians, physicians in training, and other health professionals. Each performance begins with a dramatic reading of Act III of Eugene O'Neill's "Long Day's Journey into Night" by award-winning, professional actors. The reading is followed by a brief expert panel presentation and facilitated audience discussion on caring for drug-addicted patients. Activities supporting this project included planning and executing each performance; marketing the program to promote registration among physicians, residents, and medical school faculty; and conducting outreach to national, local, trade, and social media to raise awareness about the project among targeted audiences. Additional information about APP can be found at www.drugabuse.gov/nidamed/APP.

National Drug Facts Week (NDFW)
NIDA utilized traditional media outreach (15 television interviews in major U.S. markets and three national radio interviews) and social media outreach (Twitter, Facebook and bloggers) to promote this year's National Drug Facts Week, held October 31st through November 6th. In addition, new 2011 approaches included targeted outreach through Facebook, partnerships with *Radio One* network and *AOL,* an event on the *Today Show* plaza, and the creation of a Spanish version of the IQ Challenge. Former American Idol judge Kara DioGuardi announced the winner of the MusiCares® and GRAMMY Foundation® Teen Substance Abuse Awareness through Music contest on *Fox and Friends*. A Special Issue of *NIDA in the News* about NDFW's extensive media highlights was distributed in December.

Society for Neuroscience (SfN) Meeting
NIDA coordinated 12 grantee and NIDA staff video interviews at the SfN NIDA Mini-Convention on November 11th in Washington, D.C. These videos will appear on NIDA's website and YouTube site in early 2012 and will be similar in design to the videos created during the 2010 International AIDS Society conference. NIDA also provided logistical support for a NIH press conference that was held during SfN, in which several Institute directors, including Dr. Volkow, highlighted studies presented at SfN. Additionally, NIDA provided logistical support for -- and distributed a Note to Reporters about -- a journalist workshop held by the Addiction Studies Program during the SfN Mini-Convention. This included a Q&A with Dr. Volkow, with over 30 reporters in attendance. NIDA tweeted 54 times from SfN and was re-tweeted 55 times.

National High School Journalist Convention
NIDA organized a prescription drug abuse panel at the National High School Journalist Convention, held on November 18th in Minneapolis, MN. NIDA's Chief Press Officer Stephanie Older, OSPC's Jen Elcano and NIDA grantee Dr. Carol Boyd were among the panel experts. Over 50 student journalists and journalism advisors attended.

Monitoring the Future Press Conference
NIDA hosted its annual Monitoring the Future (MTF) survey results press conference at the National Press Club on December 14, 2011. NIDA Director Dr. Nora Volkow presented the results of the survey, and top tier columnists and reporters, trade press and bloggers were contacted to encourage press coverage. ONDCP Director Gil Kerlikowske, Assistant Secretary for Health at HHS Dr. Howard Koh, and Principal Investigator Dr. Lloyd Johnston also spoke. NIDA hosted a web streaming of the event and prepared a satellite bites and b-roll package to pitch to the media. Media coverage of the event was extensive, including 521 airings reaching more than 36 million viewers. The national network placements included *ABC World News Tonight, CBS Evening News, PBS Newshour* and *America This Morning*. National cable placements included *Morning Express, MSNBC's Morning Joe, Studio B with Shepard Smith,* and *American Morning*. Locally, stories ran in 49 of the top 50 markets, including multiple stations in nine of the top 10 markets. Print coverage highlights included *USA Today, Associated Press, New York Times, San Francisco Chronicle, Reuters, Washington Post, National Journal, Time* and *HealthDay.*

NIDA issued Notes to Reporters on the following topics:

July 26, 2011 — A study, published in *Drug and Alcohol Dependence,* analyzed approximately 15 years of hospital admissions data and death records to show that people admitted to the hospital with conditions related to the abuse of methamphetamine or other amphetamine-like drugs had an increased risk of developing Parkinson's disease or parkinsonism compared to control groups. View study here
http://www.sciencedirect.com/science/article/pii/S0376871611002766

August 5, 2011 — In a NIDA-funded study, published in the *Journal of Pharmacology and Experimental Therapeutics*, mephedrone was self-administered by rats and had lasting effects on the function of serotonin neurons, suggesting possible toxic effects on the brain. View study here
http://jpet.aspetjournals.org/content/early/2011/08/02/jpet.111.184119.full.pdf+html

August 16, 2011 — NIDA's award-winning peer-reviewed journal, *Addiction Science & Clinical Practice (AS&CP)*, transferred to Biomed Central (BMC). It no longer appears in a print edition, but remains available on the web at no charge. NIDA also continues to offer news and analysis of research findings in its bi-monthly *NIDA Notes*, which is transitioning to an all web format.

August 24, 2011 — Published in *Neuron,* NIH-funded research showed that mice exposed repeatedly to cocaine have more severe depressive-like responses to social stress; possibly offering insight into why people addicted to drugs are often also diagnosed with mood disorders, such as depression. View study here
www.sciencedirect.com/science/article/pii/S0896627311005113.

September 14, 2011 — Results of a NIH-funded study, published in the *Journal of Neuroscience*, helped explain the molecular basis of the opposing actions of two different dopamine receptors that mediate the rewarding actions of cocaine. These results add important new information to the understanding of the differential contributions of the two dopamine receptor types to the net rewarding properties of cocaine. View study here www.jneurosci.org/content/31/37/13180.full

September 15, 2011 — NIDA selected the following researchers as the 2011 recipients of the Medications Initiative for Tobacco Dependence (MITD) Phased-Innovation (UH2) Awards: Dr. Selena Bartlett of the Ernest Gallo Clinic and Research Center; Drs. Patrick Griffin and Paul Kenny of Scripps Florida; and Dr. Doris Jane Rouse of the Research Triangle Institute (RTI).

October 31, 2011— Funded by NIDA, the Addiction Studies Program for Journalists workshop was held November 10-11, in Washington, D.C., to coincide with the 2011 Annual Meeting of the Society for Neuroscience (SfN).

November 8, 2011— A preliminary NIDA-funded clinical trial showed that mirtazapine, an FDA-approved medication for the treatment of depression, reduces methamphetamine use as well as associated sexual risk behaviors in men who have sex with men. View study here http://archpsyc.ama-assn.org/cgi/content/full/68/11/1168?maxtoshow=&hits=10&RESULTFORMAT =&fulltext=colfax&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT

November 23, 2011— Two NIDA-funded articles described new potential targets for the treatment of pain without significant side effects that limited their use, including the possibility of addiction. One study was published in the *Proceedings of the National Academy of Sciences* and the other study was published in *Nature Neuroscience*. View studies here www.pnas.org/content/early/2011/11/16/1115231108.full.pdf+html?sid=32540f09-678d-4990-9967-8b9b7ea7526a and www.nature.com/neuro/journal/vaop/ncurrent/full/nn.2986.html

December 8, 2011— An analysis by HHS-funded researchers, published in *Prevention Science*, showed that the Communities That Care prevention program, a public health initiative aimed at reducing risky teen behaviors such as drug use, garners a positive return on investment that increases with time. View study here www.springerlink.com/content/6146270806136053/

December 12, 2011 — Published in *Pediatrics*, NIDA-funded researchers demonstrated that a family-centered program, the Strong African American Families-Teen (SAAF-T), reduces substance use, conduct problems, and symptoms of depression among black adolescents in a geographically rural area by more than 30% (compared to adolescents in a control condition) across nearly two years. View study here http://pediatrics.aappublications.org/content/early/2011/12/07/ peds.2011-0623.abstract?sid=afe79983-5165-4081-9e6e-0f4a0562875b

December 19, 2011 -- NIDA-funded scientists showed that mephedrone and methylone (the active components in bath salts), acted like MDMA (Ecstasy) by binding to monoamine transporters on the surface of some neurons. This in turn led to increases in serotonin and dopamine (to a lesser extent), suggesting a mechanism that could underlie the addictive potential of these compounds. View study here: http://www.nature.com/npp/journal/vaop/ncurrent/full/npp2011304a.html.

NIDA issued the following Media Advisories:

August 1, 2011 — Three-time Oscar nominee Debra Winger to lead an impressive cast in the Addiction Performance Project, an innovative continuing medical education (CME) and continuing education (CE) program for health professionals and those in training, on August 5 and 6 in the Washington, D.C. area.

November 3, 2011— Actress Kathleen Chalfant to lead an impressive cast in the Addiction Performance Project, an innovative continuing medical education (CME) program for doctors and other health providers, on November 6 and 7 in the Denver, Colo. area.

November 7, 2011— NIDA to host a one-day mini-convention on November 11 at the Society for Neuroscience Annual Meeting in Washington, D.C. NIDA-supported scientists will present recent findings and discuss future directions in neuroscience.

December 9, 2011 – NIDA to hold a press conference to announce the results of the 2011 Monitoring the Future survey. The survey, funded by NIDA, tracks annual drug abuse trends of 8th, 10th, and 12th-grade students, including attitudes and perceived risk of specific illicit drugs.

HIGHLIGHTS OF INTERVIEWS: August 2011 – December 2011

Washingtonian Magazine — Dr. Nora Volkow was interviewed and photographed for the issue on "100 Most Powerful Women" feature
Associated Press – Dr. Volkow was interviewed about addiction
New York Times – Dr. Volkow was interviewed about addiction vaccines
New York Times – Dr. Volkow was interviewed about FDA/NIH tobacco research
Bloomberg News – Dr. Volkow was interviewed about obesity/food addiction
USA Today – Dr. Volkow was interviewed about teens and marijuana
BBC Radio — Dr. Volkow was interviewed about cocaine
Time online — Dr. Volkow was interviewed about cocaine
NBC News — Dr. Volkow was interviewed about MTF Survey Results
ABC News — Dr. Volkow was interviewed about MTF Survey Results
CNN En Espanol — Dr. Ruben Baler was interviewed about National Drug Facts Week
NPR — Dr. Steve Grant was interviewed about video game addiction
Nature — Dr. John Satterlee was interviewed about epigenetics
Time — Dr. David Shurtleff was interviewed about opioid abuse
Houston Chronicle — Dr. Shurtleff was interviewed about the Avant-Garde awardees research
New York Times — Dr. Shurtleff was interviewed about drug testing
Time online — Dr. Mike Baumann was interviewed about bath salts

OTHER EDUCATIONAL ACTIVITIES

NIH K-12 LAB Challenge

Dr. Cathrine Sasek, OSPC, has been an active participant in the development of the NIH K-12 Lessons About Bioscience (LAB) Challenge, a call to the nation to submit engaging hands-on science activities for classroom to NIH. The NIH Office of Science Education along with representatives from multiple NIH Institutes (including NIDA) will review the submitted entries, revise as necessary, and then post them on the web for use by students and teachers in kindergarten through twelfth grade. Submissions were due to NIH by December 15, 2011 and review of the submissions is currently ongoing. Winning experiments will be announced on March 1, 2012.

Web-based Games Developed for the Brain Power! Materials

NIDA has developed interactive science based web games to accompany each edition of the Brain Power! materials (grades K-1, 2-3, and 4-5, and middle school). The games were designed for students to use either at home or in the classroom as an adjunct to the current classroom based Brain Power! materials. While the materials have been very successful, having a component that the students could do on their own will further enhance the classroom learning experience while at the same time provide innovative web based activities that captures student's creative energies outside of the classroom. The web games were developed through an OSPC contract on which Dr. Cathrine Sasek served as project officer.

As part of the CCTN Classroom Seminar Series, the following seminars were presented: October 25, 2011, Jia Bei Wang, MD., PhD, Professor of Pharmacology in the School of Pharmacy at the University of Maryland Baltimore presented, "Development of l-tetrahydropalmatine (I-THP) as a New Medication for Cocaine Addiction**."** Levo-tetrahydropalmatine (l-THP) is a key active constituent of herbal preparations containing plant species of the genera Stephania and Corydalis and has been approved and used in China for the last 40 years for a number of clinical indications under the drug name Rotundine. Dr. Wang provided an overview of the pharmacological properties of l-THP and of the preclinical and clinical evidence in support of the development of l-THP as a medication for the treatment of addictive disease. The results of preliminary clinical studies demonstrating efficacy in human drug addicts were described and an overview of the challenges associated with FDA approval of l-THP was discussed.

November 15, 2011, Linda Rosenberg, MSW, President and CEO of the National Council for Community Behavioral Healthcare in Washington DC, presented, "National Policy Trends and Expected Impact on MH/SUD." National health reform is evolving quickly into a practical commitment to successful implementation. Reform has many working parts including insurance, coverage, quality, payment, and information technology - and clear, tactical plans are needed. Ms. Rosenberg focused on operational activities including the integration of behavioral and primary care via Health Homes and Accountable Care Organizations.

RECENT AND UPCOMING CONFERENCES/EXHIBITS

American Academy of Addiction Psychiatry -- Scottsdale, AZ -- December 8-11, 2011

Community Anti-Drug Coalitions of American National Leadership Forum XXII
National Harbor, MD -- February 6-9, 2012

2012 National Science Teachers Association National Conference on Science Education
Indianapolis, IN -- March 29-April 1, 2012

Blending Conference on SBIRT of ASAS Annual Meeting -- Atlanta, GA -- April 19-22, 2012

American Psychiatric Association Annual Meeting -- Philadelphia, PA -- May 5-9, 2012

PLANNED MEETINGS

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

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

The next **National CTN Steering Committee Meetings** will be held April 17-18, 2012 in Atlanta, Georgia in conjunction with the ASAM Pre-conference session (mini-blending sessions).

The National Institute on Drug Abuse (NIDA) is organizing a research track at the **American Psychiatric Association (APA) Annual Meeting in Philadelphia, Pennsylvania, May 5-9, 2012.** NIDA will hold a number of sessions on topics unique to addiction science. Topics include: *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 (TBD) and chaired by NIDA Director, Dr. Nora Volkow, will also be featured at this year's meeting.

The National Institute on Drug Abuse (NIDA) will sponsor a Grant-Writing and Career Development Workshop at the **College on Problems of Drug Dependence (CPDD) Annual Scientific Meeting**. This year's conference will be held in **Palm Springs, California, on June 9–14, 2012**. The Grant/Career Workshop provides new or junior investigators with information and skills to advance their research careers, with a heavy emphasis on NIDA funding opportunities, grantsmanship, and the grant application process. NIDA will also be offering a limited number of travel awards to partially defray the cost of attending this conference. Only NIDA-supported NRSA trainees, NRSA fellows, and Minority Supplement recipients are eligible for this award. The application deadline for these awards is February 27, 2012.

PUBLICATIONS

NIDA PUBLICATIONS

NIDA Notes, Vol. 24, No. 1
In this second Innovations issue of NIDA Notes, NIDA Director Dr. Nora D. Volkow describes how scientists seeking answers to addiction problems make discoveries that have broad implications for human development and health. The first feature in the issue reports on a recently recognized brain circuit--discovered in studies of the resting brain--that correlates with a person's vulnerability to nicotine dependence. The second article presents an *in vitro* demonstration of a prototype skin patch programmable to deliver medication. Another article presents research indicating that disruption of neuron production in the brains of adult rats increases cocaine taking. Additional features report that epigenetic alterations of DNA contribute to persistence of painful memories and that RNA snippets known as microRNAs can either promote or protect against vulnerability to addiction.

NIDA Notes, Vol. 24, No. 2
In the final print issue of NIDA Notes, the first feature reports how brain activity changes when smokers reduce craving by focusing on long-term consequences of cigarette use. The second feature presents evidence that the addictive properties of benzodiazepines rely on a well-known mechanism: reduced control of dopamine-producing neurons. The next article describes animal tests indicating that physical activity reduces return to cocaine-seeking during abstinence. Another article reports that home visits by nurses to low-income, first-time mothers yield benefits for at least a decade and save government money. A "NIDA at Work" report describes the activities of the Institute's Women and Sex/Gender Differences Research Program. In the Director's Perspective, Dr. Nora D. Volkow highlights research focused on groups with high smoking rates.

Seeking Drug Abuse Treatment: Know What to Ask
NIH Pub. No.: 11-7764
This consumer-friendly guide will assist individuals in their search for a drug treatment program. The publication provides questions and answers to ask drug treatment programs to ascertain whether they follow NIDA's *Principles of Drug Abuse Treatment*.

Screening for Drug Use in General Medical Settings
NIH Pub. No.: 11-7384
This is an at-a-glance booklet based on the NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test.

Principles of Drug Abuse Treatment for Criminal Justice Populations (Revised)
NIH Pub. No.: 11-5316
This booklet is designed as a complement to NIDA's *Principles of Drug Addiction Treatment: A Research-Based Guide*, which provides treatment principles and research findings that are of particular relevance to the criminal justice community and to treatment professionals working with drug-abusing offenders

CTN-RELATED PUBLICATIONS

Eight 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 24 CTN studies are now available on the CTN Data Sharing Web Site http://www.nida.nih.gov/CTN/Data.html. 1,200 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.

INTERNATIONAL PROGRAM-RELATED PUBLICATIONS

NIDA International Program E-News

- *October 2011* – This issue reported on the high research productivity of the NIDA-supported Syrian Center for Tobacco Studies, an international meeting on dual diagnosis, and the Hispanic Science Network International Conference. Other stories reported on funding opportunities through the H3Africa initiative, community outreach efforts by Hubert H. Humphrey Fellowship Program host universities, a Fogarty International Center Webinar series on brain disorders, and the new editor for the NIDA journal, *Addiction Science & Clinical Practice.*
- *December 2011* – This issue reported on the reissued Program Announcements supporting International Research Collaboration on Drug Abuse and Addiction Research and on the success of NIDA grantee Robert Zucker, Ph.D., in building research capacity in Central and Eastern Europe. Other stories reported on meetings such as the U.S.-Netherlands Binational Workshop; Driving Under the Influence of Drugs, Alcohol and Medicines (DRUID); and Red Latinamericano de Investigaciones en Drogas (REDLA), the Latin American drug epidemiology group. The issue also introduced the 2011–2012 NIDA Hubert H. Humphrey Fellows and the NIDA-supported participant in the Dutch Summer Institute on Alcohol, Drugs and Addiction.

OTHER PUBLICATIONS

Ali SF, Onaivi ES, Dodd PR, Cadet JL, Schenk S, Kuhar MJ, Koob GF. Understanding the global problem of drug addiction is a challenge for idars scientists. Curr Neuropharmacol. 2011 Mar; 9(1): 2-7.

Bjork JM, Chen G, Hommer DW. Psychopathic tendencies and mesolimbic recruitment by cues for instrumental and passively obtained rewards. Biol Psychol. 2011 Dec 14. [Epub ahead of print].

Bjork JM, Smith AR, Chen G, Hommer DW. Mesolimbic recruitment by nondrug rewards in detoxified alcoholics: effort anticipation, reward anticipation and reward delivery. Human Brain Mapping. [HBM online Early View].

Bjork JM, Smith AR, Chen G, Hommer DW. Psychosocial problems and recruitment of incentive neurocircuitry: exploring individual differences in healthy adolescents. Dev Cogn Neurosci. 2011 Oct1;1(4): 570-577.

Cadet JL, Brannock C, Krasnova IN, Ladenheim B, McCoy MT, Chou J, Lehrmann E, Wood WH, Becker KG, Wang Y. Methamphetamine-induced dopamine-independent alterations in striatal gene expression in the 6-hydroxydopamine hemiparkinsonian rats. PLoS One. 2011; 5(12): e15643.

Cadet JL, Brannock C, Ladenheim B, McCoy MT, Beauvais G, Hodges AB, Lehrmann E, Wood WH 3rd, Becker KG, Krasnova IN. Methamphetamine preconditioning causes differential changes in striatal transcriptional responses to large doses of the drug. Dose Response. 2011; 9(2): 165-181.

Chou J, Greig NH, Reiner D, Hoffer BJ, Wang Y. Enhanced survival of dopaminergic neuronal transplants in hemi-Parkinsonian rats by the p53 inactivator PFT-a. Cell Transplant. 2011; 20: 1351-1359.

Deng P, Pang ZP, Lei Z, Shikano S, Xiong Q, Harvey BK, London B, Wang Y, Li M, Xu ZC. Up-regulation of A-type potassium currents protects neurons against cerebral ischemia. J Cereb Blood Flow Metab. 2011; 31: 1823-1835.

Fernando ABP, Economidou D, Theobald DE, Zou M-F, Newman AH, Spoelder M, Caprioli D, Moreno M, Hipolito L, Aspinall A T, Robbins TW, Dalley JW. Modulation of high impulsivity and attentional performance in rats by selective direct and indirect dopaminergic and noradrenergic receptor agonists. Psychopharmacology, 2011, e-pub July 15, 2011.

Harvey BK, Airavaara MT, Hinzman J, Simons EM, Chiocco MJ, Howard DB, Shen H, Gerhardt GA, Hoffer BJ, Wang Y. Targeted over-expression of glutamate transporter 1 (GLT-1) reduces ischemic brain injury in rat model of stroke. PLoS One. 2011; 6:e22135.

Hiranita T, Soto PL, Kohut SJ, Kopajtic T, Cao J, Newman AH, Tanda G, Katz JL. Decreases in cocaine self-administration with dual inhibition of the dopamine transporter and σ receptors. J Pharmacol Exp Ther. 2011 Nov; 339(2): 662-677.

Hiranita T, Soto PL, Tanda G, Katz JL. Lack of cocaine-like discriminative-stimulus effects of σ-receptor agonists in rats. Behav Pharmacol. 2011 Sep; 22(5-6): 525-530.

Hodges AB, Ladenheim B, McCoy MT, Beauvais G, Cai N, Krasnova IN, Cadet JL. Long-term protective effects of methamphetamine preconditioning against single-day methamphetamine toxic challenges. Curr Neuropharmacol. 2011 Mar; 9(1): 35-39.

Hommer DW, Bjork JM, Gilman JM. Imaging brain response to reward in addictive disorders. Ann N Y Acad Sci. 2011 Jan; 1216: 50-61.

Hong LE, Yang X, Wonodi I, Hodgkinson CA, Goldman D, Stine OC, Stein EA, Thaker GK. A CHRNA5 allele related to nicotine addiction and schizophrenia. Genes, Brain and Behavior 2011; 10: 530-535.

Kahn R, Gorgon L, Jones K, McSherry F, Glover ED, Anthenelli RM, Jackson T, Williams J, Murtaugh C, Montoya I, Yu E, Elkashef A. Selegiline Transdermal System (STS) as an aid for smoking cessation. Nicotine Tob Res. 2011 Aug 16. [Epub ahead of print]

Katz JL, Su TP, Hiranita T, Hayashi T, Tanda G, Kopajtic T, Tsai SY. A role for sigma receptors in stimulant self administration and addiction. pharmaceuticals (Basel). 2011; 4(6): 880-914.

Krasnova IN, Ladenheim B, Hodges AB, Volkow ND, Cadet JL. Chronic methamphetamine administration causes differential regulation of transcription factors in the rat midbrain. PLoS One. 2011; 6(4): e19179.

Lee MR, Gallen CL, Zhang X, Hodgkinson CA, Goldman D, Stein EA, Barr, CS. Functional polymorphism of the Mu opioid receptor influences reinforcement learning in humans. PLoS One, 2011; 6 (9), e24203.

Liu HS, Shen H, Harvey BK, Castillo P, Lu H, Yang Y, Wang Y. Post-treatment with amphetamine enhances reinnervation of the ipsilateral side cortex in stroke rats. Neuroimage. 2011; 56: 280-289.

Matsumoto RR, Li SM, Katz JL, Fantegrossi WE, Coop A. Effects of the selective sigma receptor ligand, 1-(2-phenethyl)piperidine oxalate (AC927), on the behavioral and toxic effects of cocaine. Drug Alcohol Depend. 2011 Oct 1; 118(1): 40-47.

McCoy MT, Jayanthi S, Wulu JA, Beauvais G, Ladenheim B, Martin TA, Krasnova IN, Hodges AB, Cadet JL. Chronic methamphetamine exposure suppresses the striatal expression of members of multiple families of immediate early genes (IEGs) in the rat: normalization by an acute methamphetamine injection. Psychopharmacology (Berl). 2011; 215(2): 353-365.

Pogorelov VM, Nomura J, Kim J, Kannan G, Ayhan Y, Yang C, Taniguchi Y, Abazyan B, Valentine H, Krasnova IN, Kamiya A, Cadet JL, Wong DF, Pletnikov MV. Mutant DISC1 affects methamphetamine-induced sensitization and conditioned place preference: a comorbidity model. Neuropharmacology. 2011 Feb 17.

Rothman RB, Cadet JL, Dersch CM, McCoy MT, Lehrmann E, Becker KG, Bader M, Alenina N, Baumann MH. Altered gene expression in pulmonary tissue of tryptophan hydroxylase-1 knockout mice: implications for pulmonary arterial hypertension. PLoS One 2011; 6(3): e17735

Saha TD, Compton WM, Chou SP, Smith S, Ruan WJ, Huang B, Pickering RP, Grant BF. Analyses related to the development of DSM-5 criteria for substance use related disorders 1. Toward amphetamine, cocaine and prescription drug use disorder continua using Item Response Theory. Drug and Alcohol Dependence 2011 Sep 29 [Epub ahead of print]. PMID: 21963414

Scheidweiler KB, Ladenheim B, Barnes AJ, Cadet JL, Huestis MA. (±)-3,4-methylenedioxymethamphetamine and metabolite disposition in plasma and striatum of wild-type and multidrug resistance protein 1a knock-out mice. J Anal Toxicol 2011; 35(7): 470-480.

Schwilke EW, Gullberg RG, Darwin WD, Chiang CN, Cadet JL, Gorelick DA, Pope HG, Huestis MA. Differentiating new cannabis use from residual urinary cannabinoid excretion in chronic, daily cannabis users. Addiction. 2011; 106(3): 499-506.

Shen H, Harvey BK, Chiang YH, Pick CG, Wang Y. Methamphetamine potentiates behavioral and electrochemical responses after mild traumatic brain injury in mice. Brain Res. 2011; 1368: 248-253.

Shen H, Luo Y, Yu SJ, Wang Y. Enhanced neurodegeneration after a high dose of methamphetamine in adenosine A3 receptor null mutant mice. Neuroscience. 2011; 194: 170-180.

Shin EJ, Duong CX, Nguyen TX, Bing G, Bach JH, Park DH, Nakayama K, Ali SF, Kanthasamy AG, Cadet JL, Nabeshima T, Kim HC. PKCδ inhibition enhances tyrosine hydroxylase phosphorylation in mice after methamphetamine treatment. Neurochem Int. 2011; 59(1): 39-50.

Texel SJ, Camandola S, Ladenheim B, Rothman SM, Mughal MR, Unger EL, Cadet JL, Mattson MP. Ceruloplasmin deficiency results in an anxiety phenotype involving deficits in hippocampal iron, serotonin, and BDNF. J Neurochem. 10.1111/j.1471-4159.2011.07554.x, 2011.

Thiriet N, Agasse F, Nicoleau C, Guégan C, Vallette F, Cadet JL, Jaber M, Malva JO, Coronas V. NPY promotes chemokinesis and neurogenesis in the rat subventricular zone. J Neurochem. 2011; 116(6): 1018-1027.

Wildling L, Rankl C, Haselgrubler T, Gruber HJ, Holy M, Newman AH, Zou M-F, Freissmuth M, Sitte HH, Hinterdorfer P. Probing the binding pocket of the serotonin transporter by single molecular force spectroscopy on living cells. J. Biol. Chem., 2011, e-pub October 27, 2011.

Zhang X, Ross TJ, Salmeron BJ, Yang S, Yang Y and Stein EA. Single subject task-related BOLD signal artifact in a real-time fMRI feedback paradigm. Human Brain Mapp. 2011; 32, 592-600.

Zuo Y, Lu H, Vaupel DB, Zhang Y, Chefer SI, Rea WR, Moore A, Yang Y, Stein, EA. Acute nicotine-induced tachyphylaxis is differentially manifest in the limbic system. Neuropsychopharmacology 2011; 36: 2498-2512.

The Proceedings from the Workshop entitled “Nutrition & addiction” (June 2010), coedited by Rao S. Rapaka. Paul Schnur and David Shurtleff, appeared as a Special Issue, entitled “Addiction & Nutrition”, October 2011, Volume 44, No.2.

STAFF HIGHLIGHTS

Staff Honors and Awards

Dr. Cheryl Anne Boyce, DCNBR, successfully completed the NIH Executive Leadership Program on September 22, 2011 which included completion of a management team project on "Analysis of Centrally Managed Receipt of Property."

Richard Denisco M.D, M.P.H., is a voting member of the FDA Drug Safety and Risk Monitoring (DSaRM) Advisory Committee and temporary voting member of the Anesthetic and Life Support Medications Advisory Committee. Recent meetings include; Long Acting Opioids REMS meeting, dextromethorphan rescheduling meeting, rescheduling GHB-narcolepsy meeting, new formulation Oxycontin meeting, and Vivitrol approval meeting.

Dr. Meyer Glantz, Ph.D., DESPR, was awarded a 2011 Meritorious Research Service Commendation by the American Psychological Association's Board of Scientific Affairs at the December 2011 Board of Directors meeting in Washington, D.C. The award recognizes individuals who have made outstanding contributions to psychological science through their service as employees of the federal government or other organizations.

Dr. Steven Grant, DCNBR, was elected to membership in the American College of Neuropsychopharmacology.

Dr. Jag Khalsa, DPMCDA, received the Lifetime Achievement Award for his 46+ years of contributions to the field of drug research from the Board of Regents of Marathwada Institute of Technology in India (December 14, 2011).

Dr. Teri Levitin, OEA, was appointed to a trans-NIH committee that is reviewing the use of the R21 mechanism. The purpose of the committee is to identify how different institutes are defining and using this mechanism and the success they are having with it in meeting programmatic needs.

Dr. Nadine Rogers, OEA, received a Meritorious Honor Award on December 12, 2011 from the U.S. Department of the State, Embassy—Phnom Penh for her part in hosting an August 2011 delegation of staff from the HHS Appropriations Committee, the CDC Chief of Staff, and the Director of International Research at NIAID. Dr. Rogers had been selected for the HHS-sponsored International Experience & Technical Assistance (IETA) Program and was detailed to CDC Cambodia as part of this program. During this field placement she provided training to local staff regarding the legislative process as it affects HHS appropriations, the structure of HHS, and an in-depth overview of the NIH, with a spotlight on NIDA. In addition, Dr. Rogers provided a one-day workshop on the dissemination of study findings and program results to CDC's partners in the provincial health departments and the Ministry of Health in Cambodia.

Dr. George Uhl, IRP, joined the program committee of the World Congress of Psychiatric Genetics.

Staff Changes

Glenda Conroy joined NIDA in January 2012 to serve as our Executive Officer/Associate Director for Management. Ms. Conroy comes to us from the HHS Program Support Center, where she served as Deputy Chief Financial Officer. Prior to that, she served as Director of Financial Enterprise Solutions and Deputy Director of Financial Management at the Food and Drug Administration. She has a wealth of experience with a background in executive leadership, technology, finance, organizational development, and team building. Glenda has an MBA from St. Francis University and several other academic certifications in project management, contracting, and accounting. She also served in the U.S. military as a Captain in the Air Force Reserves.

Dr. Comfort Boateng joined the Medicinal Chemistry Section, IRP, in November 2011 as an IRTA fellow and recipient of a NIDA SD Diversity in Research Fellowship.

Dr. Michelle Rankin joined the Office of Science Policy and Communications (OSPC) in December. Michele received her Ph.D. from Louisiana State University, where she focused on characterizing the signal transduction pathways of olfactory receptor neurons. She performed her post-doctoral research in the intramural program at NINDS in the Molecular Neuropharmacology Section, focusing on the molecular mechanisms that govern dopamine D_1 receptor signaling. In 2010 she joined the NINDS Extramural Research Program as a Health Program Specialist in the Neurodegeneration Cluster. She is also an Adjunct Associate Professor for UMUC and has taught and guest lectured for the NIH graduate school offered through FAES.

Eric Wargo, Ph.D., joined the Science Policy Branch of the Office of Science Policy and Communications as a Science Writer in January, 2012. He received his Ph.D. in Anthropology from Emory University in 2000. For the past seven years before coming to NIH, he was Editorial Director at the Association for Psychological Science in Washington, DC. There he edited two top-ranked psychology journals, *Current Directions in Psychological Science* and *Psychological Science in the Public Interest*. Eric will be working in the Science Policy Branch on a variety of projects, including but not limited to writing publications for the public and responding to inquiries from NIH, HHS, Congress, and the White House.

Markus Heilig, M.D., Ph.D. has been appointed as the Clinical Director for the joint NIDA-NIAAA clinical program. Dr. Heilig is a world leader in the fields of stress and translational neuroscience.

Dr. Brandon Harvey has been appointed as Director of the Optogenetic and Transgenic Technology Center at NIDA. This center is a unique resource available to all NIH intramural programs and will help develop projects related to the use of optogenetics and transgenic rats.

Geoffrey Schoenbaum, M.D., Ph.D. has been named as Chief, Cellular Neurobiology Research Branch, IRP. Dr. Schoenbaum is renowned as a world authority in the field of cognitive neuroscience.

In June 2011, Dr. Antonello Bonci established the **Office of Education and Career Development (OECD)** within the Office of the Scientific Director (OSD). **Dr. Stephen Heishman** is Director, OECD, **Dr. Mary Pfeiffer** is Assistant Director, and **Ms. Stacey**

Saunders is Administrative Assistant. The OECD serves as a visible and central office to provide the optimal training experience for our postdoctoral fellows, graduate students, post-baccalaureate students, and summer interns. Activities of the OECD include:

- Establishing training and career development programs for NIDA trainees
- Coordinating training activities with NIH Office of Intramural Training and Education
- Implementing a Mentoring Plan for postdoctoral fellows
- Implementing a Graduate Student Incentives Program
- Coordinating the NIH Summer Internship Program
- Coordinating the IRP's involvement in Towson University's Baltimore Excellence in STEM Teaching Project

Dr. Nicolette Borek, DCNBR is on detail to 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) until February 11, 2012.

Dr. Cece Spitznas, DCNBR, is on a 6-month detail to the Office of National Drug Control Policy (ONDCP), Executive Office of the President. Dr. Spitznas will provide support and assistance to the ONDCP in the development and implementation of substance abuse policies and programs to place greater emphasis on recovery, treatment and prevention.

After 32 years of federal service, **Patricia Anderson** retired at the end of 2011. Pat began her federal career at the IRS in their Field Operations Division. She moved to the NIDA Intramural Research Program's Clinical Pharmacology Branch in 1986 where she served as secretary to Branch Chief, Jack Henningfield. In 1994 she joined the Office of Science Policy and Communications (OSPC). Since 1996, Pat has served as publications assistant to Joan Nolan, NIDA's longtime publications and exhibits manager. Pat has always been committed to NIDA and its mission, motivated to reach our audiences, and willing to help people in any way she can. Through her hard work and dedication, she has engendered respect and admiration from her peers for her professionalism.

Janelle Barth will be a Supervisory Program Analyst for the Center for Tobacco Prevention and help to build their new organization. She had been at NIH for 10 years, almost half of which was spent with NIDA. During that time, she helped to establish the Management Analysis Branch and supported many new initiatives for our Institute. She was also an active leader and participant on many NIH committees and workgroups.

Dr. Laurence Stanford has retired from NIDA as the Deputy Director of the Division of Clinical Neuroscience and Behavioral Research on December 31, 2011. He had a long and distinguished career of Federal service working at the NSF and the NIH. Dr. Stanford was a tenured faculty at the University of Wisconsin for over 15 years, where his lab conducted a Federally-funded research program investigating the structure and function of the visual system. He did a sabbatical at the NSF to run the basic developmental neurobiology program within their Division of Integrative Biology and Neuroscience. He then joined the CSR at the NIH, where he was instrumental in the creation of the new neuroscience study sections, becoming the first Chief of the Integrative and Functional Neuroscience IRG. He then headed the Neuroscience and Behavioral Science Review Branch at the NIMH and was the Director of the Division of Scientific Review at the NICHD before coming to NIDA, where he directed the developmental

neurobiology program for the division, and then served as the Deputy Director of DCNBR since 2004. He has worked tirelessly on many workgroups and committees, both across NIDA and the NIH, and has been extremely involved in research training, particularly with underrepresented groups and through the NIH Neuroscience Blueprint. He has overseen NIDA's very successful accomplishments are many, and he will be missed at the NIDA.

Mary Affeldt retired on December 31, 2011. Mary had done an outstanding job as the NIDA Associate Director for Management (Executive Officer) since September 30, 2007. In the process she had transformed NIDA's business operations through innovations in communication, increased efficiencies, coalition, team building and her relentless determination to deliver effective solutions. She had also played a central role in many trans-NIH activities, initiatives, and workgroups that have helped NIH as a corporation carry its mission. Mary's career stretches 35 years and prior to her role as the NIDA Associate Director for Management, she had been the Executive Officer for NHGRI and the Chief of Administrative Management in the NIDA Intramural Program.

GRANTEE HONORS

Dr. Frank I. Carroll, Research Triangle Institute, is the recipient of the 2012 Alfred Burger Award in Medicinal Chemistry, sponsored by GlaxoSmithKline, for his contributions to medicinal chemistry, and in particular, to the development of potential treatments for cocaine and nicotine addiction, and central nervous system disorders. The award will be presented at the American Chemical Society meeting in March 2012.
Adam Aron, Department of Psychology, University of California- San Diego, will receive one of the 2012 Young Investigator Awards from the Cognitive Neuroscience Society.

As part of the Presidential U.S.-Russia Bilateral Commission's meeting in Moscow, November 15, 2011 the research of NIDA grantee **Dr. Douglas Owens** (Stanford University) was presented as a major model on how to support and grow cooperation in civil society and health between the two countries. Dr. Owens' and colleagues' research is the FIRST to be singled out by on the online publishing service, PLoS, for immediate translation—*gratis*--in to the Russian language of all papers produced by Dr. Owens and his group in research which they are conducting on the former Soviet Union (FSU). This will enable faster dissemination usefulness of research findings and will serve as a model for similar efforts with research dealing with other countries outside of the FSU.

Memorial Hermann Prevention & Recovery Center (PaRC), a Community Treatment Program in the CTN Texas Node, received the 2011 President's Cup for Overall Outstanding Performance in Non-Acute Care Services at the Memorial Hermann Annual Meeting on October 11, 2011. The President's Cup is the highest award given annually by Memorial Hermann President and CEO Dan Wolterman. Memorial Hermann, the nation's 10th largest non-profit healthcare system, employs six system strategies that drive its efforts and help the system to fulfill its mission and vision to advance health. The award highlights an entity or division's success during the fiscal year (July 1 – June 30, 2011). In order to be considered for this award, the chosen entity must excel in all six system strategies: Quality, Patients (Satisfaction), Physicians (Satisfaction), People (Employee Satisfaction & Engagement), Operational Excellence, and Growth. PaRC received this acknowledgement in 2006 and 2008; making the 2011 award the third time PaRC has received this recognition. The CTN research team at the PaRC is currently implementing the STRIDE study (CTN 0037) under the leadership of Drs. Angela Stotts (RRTC, Houston) and Tom Northrop (Site PI).