RESEARCH FINDINGS

BASIC NEUROSCIENCES RESEARCH

Reinforcement-Related Regulation of AMPA Glutamate Receptor Subunits in the Ventral Tegmental Area Enhances Motivation for Cocaine Chronic cocaine use produces numerous biological changes in brain, but relatively few are functionally associated with cocaine reinforcement. Here the authors show that daily intravenous cocaine self-administration, but not passive cocaine administration, induces dynamic upregulation of the AMPA glutamate receptor subunits GluR1 and GluR2 in the ventral tegmental area (VTA) of rats. Increases in GluR1 protein and GluR1(S845) phosphorylation are associated with increased GluR1 mRNA in self-administering animals, whereas increased GluR2 protein levels occurred despite substantial decreases in GluR2 mRNA. The authors investigated the functional significance of GluR1 upregulation in the VTA on cocaine self-administration using localized viral-mediated gene transfer. Overexpression of GluR1(WT) in rat VTA primarily infected dopamine neurons (75%) and increased AMPA GluR1(WT) overexpression potentiated locomotor responses to intra-VTA AMPA, but not NMDA, infusions. In cocaine self-administering animals, overexpression of GluR1(WT) in the VTA markedly increased the motivation for cocaine injections on a progressive ratio schedule of cocaine reinforcement. In contrast, overexpression of protein kinase A-resistant GluR1(S845A) in the VTA reduced peak rates of cocaine self-administration on a fixed ratio reinforcement schedule. Neither viral vector altered sucrose self-administration, and overexpression of GluR1(WT) or GluR1(S845A) in the adjacent substantia nigra had no effect on cocaine self-administration. Together, these results suggest that dynamic regulation of AMPA receptors in the VTA during cocaine self-administration contributes to cocaine addiction by acting to facilitate subsequent cocaine use. Choi KH, Edwards S, Graham DL, Larson EB, Whisler KN, Simmons D, Friedman AK, Walsh JJ, Rahman Z, Monteggia LM, Eisch AJ, Neve RL, Nestler EJ, Han MH, Self DW. Reinforcement-related regulation of AMPA glutamate receptor subunits in the ventral tegmental area enhances motivation for cocaine. J Neurosci. 2011 May 25; 31(21): 7927-7937.

Distribution of Phosphorylated Trkb Receptor in the Mouse Hippocampal Formation Depends on Sex and Estrous Cycle Stage Tropomyosin-related kinase B receptor (TrkB) is a neurotrophin receptor important for the synaptic plasticity underlying hippocampal-dependent learning and memory. Because this receptor is widely expressed in hippocampal neurons, the precise location of TrkB activation is likely important for its specific actions. The goal of this study was to identify the precise sites of TrkB activation in the mouse hippocampal formation and to determine any changes in the distribution of activated TrkB under conditions of enhanced brain-derived neurotrophic factor (BDNF) expression and hippocampal excitability. Using electron microscopy, the authors localized TrkB phosphorylated at tyrosine 816 (pTrkB) in the hippocampal formation of male and female mice under conditions of naturally low circulating estradiol and naturally high circulating estradiol, when BDNF expression, TrkB signaling, and synaptic plasticity are enhanced. To compare relative amounts of pTrkB in each group, they counted profiles containing pTrkB-immunoreactivity (pTrkB-ir) in all hippocampal subregions. pTrkB-ir was in axons, axon terminals, dendrites, and dendritic spines of neurons in the hippocampal formation, but the majority of pTrkB-ir localized to presynaptic profiles. pTrkB-ir

also was abundant in glial profiles, which were further identified as microglia using immunofluorescence and confocal microscopy. Axonal and glial pTrkB-ir and pTrkB-ir in the CA1 stratum radiatum were more abundant in high-estradiol states (proestrus females) than lowestradiol states (estrus and diestrus females and males). These findings suggest that presynaptic TrkB is positioned to modulate estradiol-mediated and BDNF-dependent synaptic plasticity. Furthermore, they suggest a novel role for TrkB in microglial function in the neuroimmune system. Spencer-Segal JL, Waters EM, Bath KG, Chao MV, McEwen BS, Milner TA. Distribution of phosphorylated TrkB receptor in the mouse hippocampal formation depends on sex and estrous cycle stage. J Neurosci. 2011 May 4 ;31(18): 6780-6790.

Cannabinoid Receptor Agonists Potentiate Action Potential Independent Release Of GABA in the Dentate Gyrus Through A CB1 Receptor Independent Mechanism The authors report a novel excitatory effect of cannabinoid agonists on action potential independent GABAergic transmission in the rat dentate gyrus. Specifically, they find that both WIN55,212-2 and anandamide increase the frequency of miniature IPSCs (mIPSCs) recorded from hilar mossy cells without altering event amplitude, area, rise time, or decay. The effect of WIN55,212-2 on mIPSCs is insensitive to AM251 and preserved in CB1-/- animals indicating that it does not depend on activation of CB1 receptors. It is also insensitive to AM630 and unaffected by capsazepine suggesting that neither CB2 nor TRPV1 receptors are involved. Further, it is blocked by pre-incubation in suramin, is blocked by a selective protein kinase A inhibitor (H-89), and is mimicked (and occluded) by bath application of forskolin. Similar CB1 receptor independent facilitation of exocytosis is not apparent when recording evoked IPSCs in the presence of AM251, suggesting that the exocytotic mechanism that produces WIN55,212-2 sensitive mIPSCs is distinct from that which produces CB1 sensitive and action potential dependent release. Despite clear independence from action potentials, WIN55,212-2 mediated facilitation of mIPSCs requires calcium, and yet is insensitive to chelation of calcium in the postsynaptic cell. Finally, the authors demonstrate that both bath application of 2-arachidonoyl-glycerol (2-AG) and depolarization induced release of endogenous cannabinoids have minimal effect on mIPSC frequency. Cumulatively, these results indicate that cannabinoid ligands can selectively facilitate action potential independent exocytosis of GABA in the rat dentate gyrus, and further emphasize that this new cannabinoid sensitive signaling system is distinct from previously described CB1 receptor dependent systems in numerous respects. Hofmann ME, Bhatia C, Frzier CJ. Cannabinoid receptor agonists potentiate action potential independent release of GABA in the dentate gyrus through a CB1 receptor independent mechanism. J Physiol. 2011 Jun 6. [Epub ahead of print]

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, the authors 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 controling 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. doi: 10.1038/nature10194. [Epub ahead of print].

Fatty Acid Amide Hydrolase Blockade Attenuates the Development Of Collagen-Induced Arthritis and Related Thermal Hyperalgesia in Mice Fatty acid amide hydrolase (FAAH) is the primary degradative enzyme of the endocannabinoid anandamide (N-arachidonoyl ethanolamine), which activates cannabinoid CB(1) and CB(2) receptors. FAAH disruption reduces nociception in a variety of acute rodent models of inflammatory pain. The present study investigated whether these actions extend to the chronic, collagen-induced arthritis (CIA) model. The authors investigated the anti-arthritic and anti-hyperalgesic effects of genetic deletion or pharmacological inhibition of FAAH in the CIA model. FAAH (-/-) mice, and FAAH-NS mice that express FAAH exclusively in nervous tissue, displayed decreased severity of CIA and associated hyperalgesia. These phenotypic anti-arthritic effects were prevented by repeated daily injections of the CB(2) receptor antagonist, SR144528, but not the CB(1) receptor antagonist rimonabant. Similarly, repeated administration of URB597 reduced CIA severity, and acute administration of rimonabant, but not SR144528, blocked the anti-hyperalgesic effects of prolonged FAAH inhibition, suggesting that prolonged CB(2) receptor activation reduces the severity of CIA, whereas acute CB(1) receptor activation reduces CIA-induced hyperalgesia. In contrast, acute administration of the FAAH inhibitor, URB597, elicited a CB(1) receptordependent anti-hyperalgesic effect. The observed anti-arthritic and anti-hyperalgesic properties of FAAH inhibition, coupled with a lack of apparent behavioral alterations, suggest that endocannabinoid modulating enzymes offer a promising therapeutic target for the development of novel pharmacological approaches to treat rheumatoid arthritis and associated hyperalgesia. Kinsey SG, Naidu PS, Cravatt BF, Dudley DT, Lichtman AH. Fatty acid amide hydrolase blockade attenuates the development of collagen-induced arthritis and related thermal hyperalgesia in mice. Pharmacol Biochem Behav. 2011 Jun 29. [Epub ahead of print]

Pharmacological Characterization of AM1710, A Putative Cannabinoid CB2 Agonist From the Cannabilactone Class: Antinociception Without Central Nervous System Side-Effects Cannabinoid CB(2) agonists produce antinociception without central nervous system (CNS) side-effects. This study was designed to characterize the pharmacological and antinociceptive profile of AM1710, a CB(2) agonist from the cannabilactone class of cannabinoids. AM1710 did not exhibit off-target activity at 63 sites evaluated. AM1710 also exhibited limited blood brain

barrier penetration. AM1710 was evaluated in tests of antinociception and CNS activity. CNS side-effects were evaluated in a modified tetrad (tail flick, rectal temperature, locomotor activity and rota-rod). Pharmacological specificity was established using CB(1) (SR141716) and CB(2) (SR14528) antagonists. AM1710 (0.1-10mg/kg i.p.) produced antinociception to thermal but not mechanical stimulation of the hindpaw. AM1710 (5mg/kg i.p.) produced a longer duration of antinociceptive action than the aminoalkylindole CB(2) agonist (R,S)-AM1241 (1mg/kg i.p.) at maximally antinociceptive doses. Antinociception produced by the low (0.1mg/kg i.p.) dose of AM1710 was blocked selectively by the CB(2) antagonist SR144528 (6mg/kg i.p.), whereas antinociception produced by the high dose of AM1710 (5mg/kg i.p.) was blocked by either SR144528 (6mg/kg i.p.) or SR141716 (6mg/kg i.p.). AM1710 did not produce hypoactivity, hypothermia, tail flick antinociception, or motor ataxia when evaluated in the tetrad at any dose. In conclusion, AM1710, a CB(2)-preferring cannabilactone, produced antinociception in the absence of CNS side-effects. Thus, any CB(1)-mediated antinociceptive effects of this compound may be attributable to peripheral CB(1) activity. The observed pattern of pharmacological specificity produced by AM1710 is consistent with limited blood brain barrier penetration of this compound and absence of CNS side-effects. Rahn EJ, Thakur GA, Wood JA, Zvonok AM, Makriyannis A, Hohmann AG. Pharmacological characterization of AM1710, a putative cannabinoid CB2 agonist from the cannabilactone class: antinociception without central nervous system side-effects. Pharm Biochem Behav. 2011 Jun;98(4): 493-502.Epub 2011 Mar 5.

Resolution of Inflammation by N-arachidonoylglycine N-arachidonoylglycine (NAgly) is an endogenous signaling lipid that is a member of the eicosanoid super family and is related to anandamide. It shows anti-inflammatory activity in vivo in the mouse peritonitis model where it redues migration of inflammatory leukocytes following injection of pro-inflammatory agents into the peritoneal cavity. Using cell culture models, including GPR18 transfected HEK-293 cells, evidence is presented that the orphan receptor GPR18 is involved in this action. Increases in free arachidonic acid, and robust stimulation of anti-inflammatory eicosanoids were observed at low micro molar concentrations. These included 15-deoxy-delta-13, 14-PGJ(2) and lipoxin A(4) both of which are believed to mediate the resolution stage of inflammation. It was further shown that NAgly might act via GPR18 activation in promoting the number of Trypan Blue stained cells, a possible indicator of programmed cell death. Thus, the authors hypothesize that NAgly induces the death of inflammatory cells, a process that is considered to be important for the resolution of inflammation. Burstein S, McQuain C, Ross A, Salmonsen R, Zurier RE. Resolution of inflammation by N-arachidonoylglycine. J Cell Biochem. 2011 Jul 5. doi: 10.1002/jcb.23245. [Epub ahead of print]

Methamphetamine and HIV-1 gp120 Effects on Lipopolysaccharide Stimulated Matrix Metalloproteinase-9 Production by Human Monocyte-Derived Macrophages
Monocytes/macrophages are a primary source of human immunodeficiency virus (HIV-1) in the central nervous system (CNS). Macrophages infected with HIV-1 produce a plethora of factors, including matrix metalloproteinase-9 (MMP-9) that may contribute to the development of HIV-1-associated neurocognitive disorders (HAND). MMP-9 plays a pivotal role in the turnover of the extracellular matrix (ECM) and functions to remodel cellular architecture. Hje authors have investigated the role of methamphetamine and HIV-1 gp120 in the regulation of lipopolysaccaride (LPS) induced-MMP-9 production in monocyte-derived macrophages (MDM). Here, they show that LPS-induced MMP-9 gene expression and protein secretion are otentiated

by incubation with methamphetamine alone and gp120 alone. Further, concomitant incubation with gp120 and methamphetamine potentiated LPS-induced MMP-9 expression and biological activity in MDM. Collectively methamphetamine and gp120 effects on MMPs may modulate remodeling of the extracellular environment enhancing migration of monocytes/macrophages to the CNS. Reynolds JL, Mahajan SD, Aalinkeel R, Nair B, Sykes DE, Schwartz SA. Methamphetamine and HIV-1 gp120 Effects on Lipopolysaccharide Stimulated Marix Metalloproteinase-9 Production by Human Monocyte-Derived Macrophages. Immunological Investigations. 2011: 40(5): 481-497.

Human Mu Opioid Receptor (OPRM1 A118G) Polymorphism is Associated with Brain mu-opioid Receptor Binding Potential in Smokers Evidence points to the endogenous opioid system, and the mu-opioid receptor (MOR) in particular, in mediating the rewarding effects of drugs of abuse, including nicotine. A single nucleotide polymorphism (SNP) in the human MOR gene (OPRM1 A118G) has been shown to alter receptor protein level in preclinical models and smoking behavior in humans. To clarify the underlying mechanisms for these associations, the authors conducted an in vivo investigation of the effects of OPRM1 A118G genotype on MOR binding potential (BP(ND) or receptor availability). Twenty-two smokers prescreened for genotype (12 A/A, 10 */G) completed two [(11)C]carfentanil positron emission tomography (PET) imaging sessions following overnight abstinence and exposure to a nicotine-containing cigarette and a denicotinized cigarette. Independent of session, smokers homozygous for the wild-type OPRM1 A allele exhibited significantly higher levels of MOR BP(ND) than smokers carrying the G allele in bilateral amygdala, left thalamus, and left anterior cingulate cortex. Among G allele carriers, the extent of subjective reward difference (denicotinized versus nictine cigarette) was associated significantly with MOR BP(ND) difference in right amygdala, caudate, anterior cingulate cortex, and thalamus. Future translational investigations can elucidate the role of MORs in nicotine addiction, which may lead to development of novel therapeutics. Ray R, Ruparel K, Newberg A, Wileyto EP, Loughead JW, Divgi C, Blendy JA, Logan J, Zubieta JK, Lerman C. Human Mu Opioid Receptor (OPRM1 A118G) polymorphism is associated with brain mu-opioid receptor binding potential in smokers. Proc Natl Acad Sci U S A. 2011 May 31; 108(22): 9268-9273. Epub 2011 May 16.

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 genomewide 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 our 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 Jun 15. [Epub ahead of print]

Flotillin-1 is Essential for PKC-Triggered Endocytosis and Membrane Microdomain Localization of DAT Plasmalemmal neurotransmitter transporters (NTTs) regulate the level of neurotransmitters, such as dopamine (DA) and glutamate, after their release at brain synapses. Stimuli including protein kinase C (PKC) activation can lead to the internalization of some NTTs and a reduction in neurotransmitter clearance capacity. The authors found that the protein Flotillin-1 (Flot1), also known as Reggie-2, was required for PKC-regulated internalization of members of two different NTT families, the DA transporter (DAT) and the glial glutamate transporter EAAT2, and we identified a conserved serine residue in Flot1 that is essential for transporter internalization. Further analysis revealed that Flot1 was also required to localize DAT within plasma membrane microdomains in stable cell lines, and was essential for amphetamine-induced reverse transport of DA in neurons but not for DA uptake. In sum, these findings provide evidence for a critical role of Flot1-enriched membrane microdomains in PKC-triggered DT endocytosis and the actions of amphetamine. Cremona ML, Matthies HJ, Pau K, Bowton E, Speed N, Lute BJ, Anderson M, Sen N, Robertson SD, Vaughan RA, Rothman JE, Galli A, Javitch JA, Yamamoto A. Flotillin-1 is essential for PKC-triggered endocytosis and membrane microdomain localization of DAT. Nat Neurosci. 2011 Apr; 14(4): 469-477. Epub 2011 Mar 13.

Epigenetic Silencing of HIV-1 by the Histone H3 lysine 27 Methyltransferase Enhancer of Zeste 2 (EZH2) Latent HIV proviruses are silenced as the result of deacetylation and methylation of histones located at the viral LTR. Inhibition of histone deacetylases (HDACs) leads to the re-emergence of HIV-1 from latency, but the contribution of histone lysine methyltransferases (HKMTs) to maintaining HIV latency remains uncertain. Chromatin immunoprecipitation experiments using latently infected Jurkat T-cell lines demonstrated that the HKMT Enhancer of Zeste 2 (EZH2) was present at high levels at the LTR of silenced HIV proviruses and was rapidly displaced following proviral reactivation. Knockdown of EZH2, a key component of the Polycomb repressive complex 2 (PRC2) silencing machinery, and the enzyme which is required for trimethyl histone lysine 27 (H3K27me3) synthesis, induced up to 40% of the latent HIV proviruses. By contrast, there was less than 5% induction of latent proviruses following knockdown of SUV39H1, which is required for H3K9me3 synthesis. Knockdown of EZH2 also sensitized latent proviruses to external stimuli such as T-cell receptor stimulation and slowed the reversion of reactivated proviruses to latency. Similarly, cell populations that responded poorly to external stimuli carried HIV proviruses that were enriched in H3K27me3 and relatively depleted in H3K9me3. Treating latently infected cells with the HKMT inhibitor DZNep, which targets EZH2, led to the reactivation of silenced proviruses whereas chaetocin and BIX01294 showed only minimal reactivation activity. These findings

suggest that PRC2-mediated silencing is an important feature of HIV latency and that inhibitors of histone methylation may play a useful role in induction strategies designed to eradicate latent HIV pools. Friedman J, Cho WK, Chu CK, Keedy KS, Archin NM, Margolis DM, Karn J. Epigenetic silencing of HIV-1 by the Histone H3 lysine 27 Methyltransferase Enhancer of Zeste 2(EZH2). Virol. 2011 Jun 29. [Epub ahead of print]

Antidepressant Effects of Selective Serotonin Reuptake Inhibitors (SSRIs) Are Attenuated By Antiinflammatory Drugs In Mice and Humans Antiinflammatory drugs achieve their therapeutic actions at least in part by regulation of cytokine formation. A "cytokine hypothesis" of depression is supported by the observation that depressed individuals have elevated plasma levels of certain cytokines compared with healthy controls. Here the authors investigated a possible interaction between antidepressant agents and antiinflammatory agents on antidepressant-induced behaviors and on p11, a biochemical marker of depressive-like states and antidepressant responses. They found that widely used antiinflammatory drugs antagonize both biochemical and behavioral responses to selective serotonin reuptake inhibitors (SSRIs). In contrast to the levels detected in serum, they found that frontal cortical levels of certain cytokines (e.g., TNFα and IFNγ) were increased by serotonergic antidepressants and that these effects were inhibited by antiinflammatory agents. The antagonistic effect of antiinflammatory agents on antidepressant-induced behaviors was confirmed by analysis of a dataset from a large-scale real-world human study, "sequenced treatment alternatives to relieve depression" (STAR*D), underscoring the clinical significance of these findings. These data indicate that clinicians should carefully balance the therapeutic benefits of antiinflammatory agents versus the potentially negative consequences of antagonizing the therapeutic efficacy of antidepressant agents in patients suffering from depression. Warner-Schmidt JL, Vanover KE, Chen EY, Marshall JJ, Greengard P. Antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) are attenuated by antiinflammatory drugs in mice and humans. Proc Natl Acad Sci U S A. 2011 May 31; 108(22): 9262-9267. Epub 2011 Apr 25.

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. The authors 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. Neuron. 2011; Jul 28; 71(2):278-290.

BASIC BEHAVIORAL RESEARCH

Adolescent Nicotine Sensitizes Relapse to Cocaine Seeking in Adulthood: Influence of Selective Breeding for Reward Sensitivity in a Rodent Model Environmental factors such as early drug exposure influence drug abuse vulnerability, and evidence also suggests that drug abuse is highly heritable. The purpose of the present study was to determine whether environmental and genetic factors interact to produce additive drug abuse vulnerability. An animal model of relapse was used to examine the effects of adolescent nicotine exposure on adult cocaine seeking in rats bred for high (HiS) and low (LoS) saccharin intake. Rats from HiS and LoS progenitor lines received s.c. injections of nicotine for 10 days (postnatal days 22–31). Rats were then allowed to reach adulthood and were trained to lever press for cocaine infusions. During each self-administration session, the house light (HL) was illuminated and each lever press activated a set of lights adjacent to the lever (LL). Following cocaine self-administration, the HL and LL were deactivated, cocaine solutions were replaced with saline, and rats extinguished lever pressing. Subsequently, rats were tested under a multi-component reinstatement procedure consisting of: (1) cue-induced reinstatement with LL alone and the HL presented alone, (2) cocaine-induced reinstatement without LL and HL present, (3) and cocaine-induced reinstatement with LL present. The results indicated that adolescent nicotine exposure sensitized the reinstatement of cocaine seeking during adulthood in HiS (but not LoS) rats when lever pressing resulted in LL cue presentations. In addition, following administration of the cocaine priming injection, rats exposed to nicotine (vs. saline) during adolescence (LoS and HiS) engaged in more cocaine seeking under the cocaine-primed reinstatement condition when lever pressing illuminated the LL. These results suggest that drug abuse vulnerability may be a function of early life exposure to drugs of abuse in addition to genetic influences. Anker JJ, Carroll ME. Adolescent nicotine exposure sensitizes cue-induced reinstatement of cocaine seeking in rats bred for high and low saccharin intake. Drug and Alcohol Dependence. 2011 March 23 [Epub ahead of print].

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. The authors 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. Linking context with reward: a functional circuit from hippocampal CA3 to ventral tegmental area. Science. 2011 Jul 15; 333(6040): 353-357.

Chronic Administration of THC Prevents Behavioral Effects of Adolescent MDMA in Rats Most recreational users of 3, 4-methylenedioxymethamphetamine (MDMA or "ecstasy") also take cannabis, in part because cannabis can reduce the dysphoric symptoms of the ecstasy come-down such as agitation and insomnia. Although previous animal studies have examined the acute effects of co-administering MDMA and Δ9-tetrahydrocannabinol (THC), which is the major psychoactive ingredient in cannabis, research on chronic exposure to this drug combination is lacking. Therefore, the present study was conducted to investigate the effects of chronic adolescent administration of both THC and MDMA on behavior and on regional serotonin transporter (SERT) binding and serotonin (5-HT) concentrations as indices of serotonergic system integrity. Male Sprague-Dawley rats were divided into four drug administration groups: (1) MDMA alone, (2) THC alone, (3) MDMA plus THC, and (4) vehicle controls. MDMA (2 × 10 mg/kg × 4 h) was administered every fifth day from postnatal day (PD) 35 to 60 to simulate intermittent recreational ecstasy use, whereas THC (5 mg/kg) was given once daily over the same time period to simulate heavy cannabis use. THC unexpectedly produced a modest hyperthermic effect when administered alone, but in animals co-treated with both THC and MDMA, there was an attenuation of MDMA-induced hyperthermia on dosing days. Subsequent testing conducted after a drug washout period revealed that THC reduced MDMA-related behavioral changes in the emergence and social interaction tests of anxiety-like behavior and also blunted the MDMA-induced decrease in exploratory behavior in the hole-board test. THC additionally attenuated MDMA -induced decreases in 5-HT levels and in SERT binding in the frontal cortex, parietal cortex, and striatum, but not in the hippocampus. These results suggest that chronic co-administration of THC during adolescence can provide some protection against various adverse physiological, behavioral, and neurochemical effects produced by MDMA. Shen EY, Ali SF, Meyer JS. Chronic administration of THC prevents thebehavioral effects of intermittent adolescent MDMA administration and attenuates MDMA-induced hyperthermia and neurotoxicity in rats. Neuropharmacology. 2011 Jul 13. [Epub ahead of print].

Impairments of Cognitive Flexibility in Adult Rhesus Monkeys Prenatally Exposed to Cocaine In utero cocaine exposure has been associated with alterations in the dopamine (DA) system in monkeys. However, the behavioral outcomes of prenatal cocaine exposure in adulthood are poorly understood. The objectives of the present study were to assess several behavioral measures in 14-year-old rhesus monkeys exposed to cocaine in utero and controls (n = 10 per group). For these studies, two unconditioned behavioral tasks, novel object reactivity and locomotor activity, and two conditioned behavioral tasks, response extinction and delay discounting, were examined. In addition, cerebrospinal fluid (CSF) samples were analyzed for concentrations of the monoamine metabolites homovanillic acid (HVA) and 5-hydroxyindole acetic acid (5-HIAA). No differences in CSF concentrations of 5-HIAA and HVA, latencies to touch a novel object or locomotor activity measures were observed between groups or sexes. However, prenatally cocaine-exposed monkeys required a significantly greater number of sessions to reach criteria for extinction of food-reinforced behavior than control monkeys. On the delay-discounting task, male prenatally cocaine-exposed monkeys switched preference from the larger reinforcer to the smaller one at shorter delay values than male control monkeys; no differences were observed in females. These findings suggest that prenatal cocaine exposure results in long-term neurobehavioral deficits that are influenced by sex of the individual. Hamilton LR, Czoty PW, Nader MA. Behavioral characterization of adult male and female

rhesus monkeys exposed to cocaine throughout gestation. Psychopharmacology. 2011 Feb; 213(4): 799-808.

Individual Variation in the Motivational Properties of Cocaine Cues in the environment associated with drug use draw the attention of addicts, elicit approach, and motivate drug-seeking and drug-taking behavior, making abstinence difficult. However, preclinical studies have identified large individual differences in the extent to which reward cues acquire these incentive motivational properties. For example, only in some rats does a spatially discrete food cue become attractive, eliciting approach and engagement with it, and acts as an effective conditioned reinforcer. Moreover, a discrete cocaine cue also acquires greater motivational control over behavior in rats prone to attribute incentive salience to a food cue. In this study, the authors asked whether there is similar individual variation in the extent to which interoceptive cues produced by cocaine itself instigate cocaine-seeking behavior. After quantifying individual variation in the propensity to attribute incentive salience to a food cue, rats were trained to self-administer cocaine in the absence of an explicit conditional stimulus. The authors then assessed motivation for cocaine by: (1) performance on a progressive ratio schedule, and (2) the degree to which a cocaine 'prime' reinstated cocaine-seeking following extinction of self-administration behavior. They found that rats prone to attribute incentive salience to a food cue worked harder for cocaine, and showed more robust cocaine-induced reinstatement. They conclude that there is considerable individual variation in the motivational properties of cocaine itself, and this can be predicted by the propensity to attribute incentive salience to reward cues. Saunders BT, Robinson TE. Individual variation in the motivational properties of cocaine. Neuropsychopharmacology. 2011 Jul; 36(8): 1668-1676.

Rats Prone to Attribute Incentive Salience and Prone to Impulsive Action Animals vary considerably in the degree to which they attribute incentive salience to cues predictive of reward. When a discrete cue (conditional stimulus) is repeatedly paired with delivery of a food reward (unconditional stimulus) only some rats ("sign-trackers"; STs) come to find the cue itself an attractive and desirable incentive stimulus. For other rats ("goal-trackers"; GTs) the cue is an effective conditional stimulus – it evokes a conditional response – but it is less attractive and less desirable. Given that STs have particular difficulty resisting reward cues, and are thought to have poor inhibitory control over their behavior, the authors hypothesized that they may also be more impulsive. There are, however, multiple forms of impulsivity; therefore, they compared STs and GTs on two tests of so-called impulsive action – a 2-choice serial reaction time task and a differential reinforcement of low rates of responding task, and one test of impulsive choice – a delay discounting choice procedure. They found that relative to GTs, STs were more impulsive on the two tests of impulsive action, but not on the test of impulsive choice. They speculate that when these two traits combine, that is, when an individual is not only prone to attribute incentive salience to reward cues but also prone to impulsive action, they may be especially susceptible to impulse control disorders, including addiction. Lovic, V, Saunders, BT, Yager, LM, and Robinson, TE. Rats prone to attribute incentive salience to reward cues are also prone to impulsive action. Behavioural Brain Research, 2011; 223(2): 255-261.

Changes in Glutamatergic Synapses after Prolonged Withdrawal from Cocaine Self-Administration but not Experimenter-Administered Cocaine Repeated non-contingent cocaine injections, which lead to behavioral sensitization, increase AMPA receptor (AMPAR) transmission in the rodent nucleus accumbens (NAc) in a withdrawal-dependent manner. On withdrawal days (WD) 10-21, this is attributable to upregulation of GluA1A2-containing AMPARs. However, synaptic incorporation of GluA2-lacking/Ca(2+)-permeable AMPARs (CP-AMPARs) was observed after longer withdrawal (WD35) from repeated non-contingent cocaine injections in young mice (Mameli et al., 2009). CP-AMPARs had previously been observed iNAc synapses only after prolonged (WD30-WD47) withdrawal from extended-access cocaine self-administration. The authors' goal was to determine whether rats receiving repeated non-contingent cocaine injections during adulthood similarly exhibit CP-AMPARs in the NAc after prolonged withdrawal. For comparison, they began by evaluating CP-AMPARs on WD35-WD49 after extended-access cocaine self-administration. Confirming our previous results, whole-cell recordings revealed inwardly rectifying AMPAR EPSCs, a hallmark of CP-AMPARs. This was observed in both core and shell. Next, they conducted the same analysis in adult rats treated with eight daily non-contingent cocaine injections and recorded on WD35-WD49. AMPAR EPSCs in core and shell did not show inward rectification and were insensitive to 1-naphthylacetylspermine (a selective antagonist of CP-AMPARs). Locomotor sensitization could still be demonstrated after this long withdrawal period, although the upregulation of GluA1A2-containing AMPARs observed at earlier withdrawal times was no longer detected. In conclusion, in adult rats, accumulation of synaptic CP-AMPARs in the NAc occurs after prolonged withdrawal from extended-access cocaine self-administration but not after prolonged withdrawal from non-contingent cocaine injections. McCutcheon JE, Wang X, Tseng KY, Wolf ME, Marinelli M. Calcium-permeable AMPA receptors are present in nucleus accumbens synapsesafter prolonged withdrawal from cocaine self-administration but not experimenter-administered cocaine. J Neurosci. 2011 Apr 13; 31(15): 5737-5743.

Projection-Specific Modulation of Dopamine Neuron Synapses by Aversive and Rewarding Stimuli Midbrain dopamine (DA) neurons are not homogeneous but differ in their molecular properties and responses to external stimuli. The authors examined whether the modulation of excitatory synapses on DA neurons by rewarding or aversive stimuli depends on the brain area to which these DA neurons project. They identified DA neuron subpopulations in slices after injection of "Retrobeads" into single target areas of adult mice and found differences in basal synaptic properties. Administration of cocaine selectively modified excitatory synapses on DA cells projecting to nucleus accumbens (NAc) medial shell while an aversive stimulus selectively modified synapses on DA cells projecting to medial prefrontal cortex. In contrast, synapses on DA neurons projecting to NAc lateral shell were modified by both rewarding and aversive stimuli, which presumably reflects saliency. These results suggest that the mesocorticolimbic DA system may be comprised of three anatomically distinct circuits, each modified by distinct aspects of motivationally relevant stimuli. Lammel S, Ion DI, Roeper J, Malenka RC. Projection-specific modulation of dopamine neuron synapses by aversive and rewarding stimuli. Neuron. 2011; Jun 9; 70(5): 855-862.

Social Bonding Decreases the Rewarding Properties of Amphetamine through a Dopamine D1 Receptor-Mediated Mechanism Although the protective effects of social bonds on drug use/abuse have been well documented, little is known about the underlying neural mechanisms. Using the prairie vole (Microtus ochrogaster)-a socially monogamous rodent that forms long-term pair bonds after mating-the authors demonstrate that amphetamine (AMPH) conditioning induced a conditioned place preference (CPP) in sexually naive (SN), but not pair-bonded (PB), males. Although AMPH treatment induced a similar magnitude of dopamine release in the nucleus accumbens (NAcc) of SN and PB males, it had differential effects on NAcc D1 receptor (D1R) binding. Specifically, AMPH treatment increased D1R binding in SN, but decreased D1R binding in PB males. NAcc D1R, but not D2 receptor, antagonism blocked AMPH-induced CPP in SN males and NAcc D1R activation before AMPH conditioning enabled AMPH-induced CPP in PB males. Together, our data demonstrate that pair-bonding experience decreases the rewarding properties of AMPH through a D1R-mediated mechanism. Liu Y, Young KA, Curtis JT, Aragona BJ, Wang Z. Social Bonding Decreases the Rewarding Properties of Amphetamine through a Dopamine D1 Receptor-Mediated Mechanism. J Neurosci. 2011 Jun1; 31(22): 7960-7966.

Loss of Alternative Non-drug Reinforcement Induces Relapse of Cocaine-seeking in Rats Animal models of relapse to drug seeking have focused primarily on relapse induced by exposure to drugs, drug-associated cues or contexts, and foot-shock stress. However, relapse in human drug abusers is often precipitated by loss of alternative non-drug reinforcement. The present experiment used a novel 'resurgence' paradigm to examine relapse to cocaine seeking of rats as a result of loss of an alternative source of non-drug reinforcement. Rats were first trained to press a lever for intravenous infusions of cocaine. Next, cocaine deliveries were omitted and food pellets were provided for an alternative nose-poke response. Once cocaine seeking was reducedto low levels, food pellets for the alternative response were also omitted. Cocaine seeking increased with the loss of the alternative non-drug reinforcer (ie, resurgence occurred) despite continued extinction conditions. The increase in cocaine seeking did not occur in another group of rats injected with SCH 23390 before the loss of the alternative reinforcer. These results suggest that removal of an alternative source of reinforcement may induce relapse of cocaine seeking and that the dopamine D(1) receptor may have a role in this effect. Quick SL, Pyszczynski AD, Colston KA, Shahan TA. Loss of alternative non-drug reinforcement induces relapse of cocaine-seeking in rats: role of dopamine D(1) receptors. Neuropsychopharmacology. 2011 Apr; 36(5): 1015-1020.

BEHAVIORAL AND BRAIN DEVELOPMENT RESEARCH

Neural Correlates of Verbal Learning in Adolescent Alcohol and Marijuana Users Alcohol and marijuana are the most widely used intoxicants among adolescents, yet their potential unique and interactive influences on the developing brain are not well established. Brain regions subserving learning and memory undergo continued maturation during adolescence, and may be particularly susceptible to substance-related neurotoxic damage. In this study, the authors characterize brain response during verbal learning among adolescent users of alcohol and marijuana. Participants performed a verbal paired associates encoding task during functional magnetic resonance imaging (fMRI) scanning. Adolescent subjects were recruited from local public schools and imaged at a university-based fMRI center. Participants were 74 16-18-year-olds, divided into four groups: 22 controls with limited alcohol and marijuana experience, 16 binge drinkers, eight marijuana users and 28 binge drinking marijuana users. Diagnostic interview ensured that all teens were free from neurological or psychiatric disorders; urine toxicology and breathalyzer verified abstinence for 22-28 days before scanning; a verbal paired associates task was administered during fMRI. Groups demonstrated no differences in performance on the verbal encoding task, yet exhibited different brain response patterns. A main effect of drinking pointed to decreased inferior frontal but increased dorsal frontal and parietal fMRI response among binge drinkers (corrected $P < 0.05$). There was no main effect of marijuana use. Binge drinking × marijuana interactions were found in bilateral frontal regions (corrected $P < 0.05$), where users of either alcohol or marijuana showed greater response than non-users, but users of both substances resembled non-users. Adolescent substance users demonstrated altered fMRI response relative to non-using controls, yet binge drinking appeared to be associated with more differences in activation than marijuana use. Schweinsburg AD, Schweinsburg BC, Nagel BJ, Eyler LT, Tapert SF. Alcohol and marijuana may have interactive effects that alter these differences, particularly in prefrontal brain regions. Dev Sci. 2011 Mar; 14(2): 1-10.

Peers Increase Adolescent Risk Taking by Enhancing Activity in the Brain's Reward Circuitry The presence of peers increases risk taking among adolescents but not adults. The authors posited that the presence of peers may promote adolescent risk taking by sensitizing brain regions associated with the anticipation of potential rewards. Using fMRI, they measured brain activity in adolescents, young adults, and adults as they made decisions in a simulated driving task. Participants completed one task block while alone, and one block while their performance was observed by peers in an adjacent room. During peer observation blocks, adolescents selectively demonstrated greater activation in reward-related brain regions, including the ventral striatum and orbitofrontal cortex, and activity in these regions predicted subsequent risk taking. Brain areas associated with cognitive control were less strongly recruited by adolescents than adults, but activity in the cognitive control system did not vary with social context. Results suggest that the presence of peers increases adolescent risk taking by heightening sensitivity to the potential reward value of risky decisions. Chein J, Albert D, O'Brien L, Uckert K, Steinberg L. Peers increase adolescent risk taking by enhancing activity in the brain's reward circuitry. Psychiatry Res. 2011 Mar 31; 191(3): 201-211.

Neural Systems of Threat Processing in Adolescents: Role of Pubertal Maturation and Relation to Measures of Negative Affect Adolescence ushers in dramatic social and affective changes and increased vulnerability for affective disorders. Yet, little is known about the effects of pubertal maturation on neural systems of social threat processing. The authors examined adolescents' brain function to social stimuli in relation to pubertal maturation, depressive symptoms, and real-world subjective negative affect. Compared with pre/early adolescents, mid/late adolescents exhibited less amygdala reactivity to emotionally neutral faces relative to non-face stimuli; less ventrolateral prefrontal cortex (VLPFC) reactivity to fearful faces relative to non-face stimuli, neutral faces, or angry faces; and more VLPFC reactivity to angry relative to neutral faces. Amygdala and VLPFC reactivity were correlated with negative affect and depressive symptoms. Threat-processing changes during puberty may facilitate changes in social behavior and negative affect. Forbes EE, Phillips ML, Silk JS, Ryan ND, Dahl RE. Neural systems of threat processing in adolescents: role of pubertal maturation and relation to measures of negative affect. Dev Neuropsychol. 2011 May; 36(4): 429-452.

Puberty Influences Medial Temporal Lobe and Cortical Gray Matter Maturation differently in Boys than Girls Matched for Sexual Maturity Sex differences in age- and puberty-related maturation of human brain structure have been observed in typically developing age-matched boys and girls. Because girls mature 1-2 years earlier than boys, the present study aimed at assessing sex differences in brain structure by studying 80 adolescent boys and girls matched on sexual maturity, rather than age. The authors have evaluated pubertal influences on medial temporal lobe (MTL), thalamic, caudate, and cortical gray matter volumes utilizing structural magnetic resonance imaging and 2 measures of pubertal status: physical sexual maturity and circulating testosterone. As predicted, significant interactions between sex and the effect of puberty were observed in regions with high sex steroid hormone receptor densities; sex differences in the right hippocampus, bilateral amygdala, and cortical gray matter were greater in more sexually mature adolescents. Within sex, the authors found larger volumes in MTL structures in more sexually mature boys, whereas smaller volumes were observed in more sexually mature girls. These results demonstrate puberty-related maturation of the hippocampus, amygdala, and cortical gray matter that is not confounded by age, and is different for girls and boys, which may contribute to differences in social and cognitive development during adolescence, and lasting sexual dimorphisms in the adult brain. Bramen JE, Hranilovich JA, Dahl RE, Forbes EE, Chen J, Toga AW, Dinov ID, Worthman CM, Sowell ER. Puberty influences medial temporal lobe and cortical gray matter maturation differently in boys than girls matched for sexual maturity. Cereb Cortex. 2011 Mar; 21(3): 636-646.

Preliminary Evidence for White Matter Metabolite Differences in Marijuana-Dependent Young Men Using 2D J-Resolved Magnetic Resonance Spectroscopic Imaging at 4 Tesla Chronic marijuana (MRJ) use is associated with altered cognition and mood state, altered brain metabolites, and functional and structural brain changes. The objective of this study was to apply proton magnetic resonance spectroscopic imaging (MRSI) to compare proton metabolite levels in 15 young men with MRJ dependence and 11 healthy non-using (NU) young men. Spectra were acquired at 4.0 Tesla using 2D J-resolved MRSI to resolve coupled resonances in J-space and to quantify the entire J-coupled spectral surface of metabolites from voxels containing basal ganglia and thalamus, temporal and parietal lobes, and occipital white and gray matter. This method permitted investigation of high-quality spectra for regression analyses to examine

metabolites relative to tissue type. Distribution of myo-inositol (mI)/creatine (Cr) was altered in the MRJ group whereas the NU group exhibited higher mI/Cr in WM than GM, this pattern was not observed in MRJ subjects. Significant relationships observed between global mI/Cr and distribution in WM, and self-reported impulsivity and mood symptoms were also unique between MRJ and NU groups. These preliminary findings suggest that mI, and distribution of this glial metabolite in WM, is altered by MRJ use and is associated with behavioral and affective features reported by young MRJ-dependent men. Silveri MM, Jensen JE, Rosso IM, Sneider JT, Yurgelun-Todd DA. Preliminary evidence for white matter metabolite differences in marijuana-dependent young men using 2D J-resolved magnetic resonance spectroscopic imaging at 4 tesla. Psychiatry Res. 2011 Mar 31; 191(3): 201-211.

Associations Between Cortical Thickness and Verbal Fluency in Childhood, Adolescence, and Young Adulthood Neuroimaging studies of normative human brain development indicate that the brain matures at differing rates across time and brain regions, with some areas maturing into young adulthood. In particular, changes in cortical thickness may index maturational progressions from an overabundance of neuropil toward efficiently pruned neural networks. Developmental changes in structural MRI measures have rarely been examined in relation to discrete neuropsychological functions. In this study, healthy right-handed adolescents completed MRI scanning and the Controlled Oral Word Association Test (COWAT). Associations of task performance and cortical thickness were assessed with cortical-surface-based analyses. Significant correlations between increasing COWAT performances and decreasing cortical thickness were found in left hemisphere language regions, including perisylvian regions surrounding Wernicke's and Broca's areas. Task performance was also correlated with regions associated with effortful verbal processing, working memory, and performance monitoring. Structure-function associations were not significantly different between older and younger subjects. Decreases in cortical thicknesses in regions that comprise the language network likely reflect maturation toward adult-like cortical organization and processing efficiency. The changes in cortical thicknesses that support verbal fluency are apparent by middle childhood, but with regionally separate developmental trajectories for males and females, consistent with other studies of adolescent development. Porter JN, Collins PF, Muetzel RL, Lim KO, Luciana MA associations between cortical thickness and verbal fluency in childhood, adolescence, and young adulthood. Neuroimage. 2011 Apr 15; 55(4):1865-1877.

Maternal Substance Use during Pregnancy and Environmental Adversity: Stress Hormone Levels of Preadolescent Children in the Maternal Lifestyle Study (MLS) 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 CL, 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 Drug Exposure and Early Adversity and Neurobehavioral Disinhibition in Childhood and Adolescence in MLS 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.

Increased "Default Mode" Activity in Adolescents Prenatally Exposed to Cocaine
Prenatal cocaine exposure (PCE) is associated with attention/arousal dysregulation and possible inefficiencies in some cognitive functions. However, the neurobiological bases of these teratogenic effects have not been well characterized. Because activities in the default mode network (DMN) reflect intrinsic brain functions that are closely associated with arousal regulation and cognition, alterations in the DMN could underlie cognitive effects related to PCE. With resting-state and task activation functional magnetic resonance imaging (fMRI), this study investigated the possible PCE related changes in functional brain connectivity and brain activation in the DMN. In the resting state, the PCE group was found to have stronger functional connectivity in the DMN, as compared to the nonexposed controls. During a working memory task with emotional distracters, the PCE group exhibited less deactivation in the DMN and their fMRI signal was more increased by emotional arousal. These data revealed additional neural effects related to PCE, and consistent with previous findings, indicate that PCE may affect behavior and functioning by increasing baseline arousal and altering the excitatory/inhibitory balancing mechanisms involved in cognitive resource allocation. Li Z, Santhanam P, Coles CD,

Lynch ME, Hamann S, Peltier S, Hu X. Increased "default mode" activity in adolescents prenatally exposed to cocaine. Hum Brain Mapp. 2011 May; 32(5): 759-770.

Early Adolescent Executive Functioning, Intrauterine Exposures and Drug Use
Individual differences in adolescents' executive functioning are often attributed either to intrauterine substance exposure or to adolescents' own substance use, but both predictors typically have not been evaluated simultaneously in the same study. This prospective study evaluated whether intrauterine drug exposures, the adolescents' own substance use, and/or their potential interactions are related to poorer executive functioning after controlling for important contextual variables. Analyses were based on data collected on a sample of 137 predominantly African-American/African Caribbean adolescents from low-income urban backgrounds who were followed since their term birth. Intrauterine substance exposures (cocaine, marijuana, alcohol, and cigarettes) and adolescents' substance use were documented using a combination of biological assays and maternal and adolescent self-report. At 12-14 years of age, examiners masked to intrauterine exposures and current substance use assessed the adolescents using the Delis-Kaplan Executive Function System (D-KEFS), an age-referenced instrument evaluating multiple dimensions of executive functioning (EF). Results of covariate-controlled analyses in this study suggest that when intrauterine substance exposures and young adolescents' substance use variables were in the same analysis models, subtle differences in specific EF outcomes were identifiable in this non-referred sample. While further study with larger samples is indicated, these findings suggest that 1) research on adolescent substance use and intrauterine exposure research should evaluate both predictors simultaneously, 2) subtle neurocognitive effects associated with specific intrauterine drug exposures can be identified during early adolescence, and 3) intrauterine substance exposure effects may differ from those associated with adolescents' own drug use. Rose-Jacobs R, Soenksen S, Appugliese DP, Cabral HJ, Richardson MA, Beeghly M, Heeren TC, Frank DA. Early adolescent executive functioning, intrauterine exposures and own drug use. Neurotoxicol Teratol. 2011 May-Jun; 33(3): 379-432.

Prenatal Cocaine Exposure and Language Development at Age 10 The objective of this study was to examine the long term effects of prenatal cocaine exposure (PCE) on the language development of 10-year-old children utilizing a prospective design, controlling for confounding drug and environmental factors. Children exposed to cocaine in utero (PCE; n=175) and non-exposed children (NCE; n=175) were followed prospectively to 10 years of age and were compared on language subscales of the Test of Language Development-Intermediate 3rd Edition (TOLD-I:3) and phonological processing as measured by the Comprehensive Test of Phonological Processing (CTOPP). Multivariate analysis of covariance (MANCOVA), linear regression, and logistic regressions were used to evaluate the relationship of prenatal cocaine exposure to language development, while controlling for confounders. After controlling for confounding variables, prenatal cocaine effects were observed for specific aspects of language including syntax (Sentence Combining subtest of the TOLD-I:3, p=0.001), semantics (Malopropism subtest of the TOLD-I:3, p=0.05) and phonological processing (Phonological Awareness subscale, p=0.01). The caregiver factors of vocabulary, HOME, and psychological symptoms also had consistent effects on language subtests and phonological processing scores. Children with PCE who experienced foster or adoptive care had enhanced language development compared to those living with birth mothers or in relative care. Cocaine exposed girls had lower scores on the phonological awareness subscale of the CTOPP than non-exposed girls. The

authors conclude that PCE has subtle effects on specific aspects of language development and phonological processing at age 10, even after controlling for confounding variables. Environmental factors (i.e., postnatal lead exposure, home environment, and caregiver vocabulary and psychological symptoms) also impact language skills at 10 years. Adoptive or foster care appears to enrich PCE children's linguistic environment and protects children against language delay in the PCE sample. Lewis BA, Minnes S, Short EJ, Weishampel P, Satayathum S, Min MO, Nelson S, Singer LT. The effects of prenatal cocaine on language development at 10 years of age. Neurotoxicol Teratol. 2011 Jan-Feb; 33(1): 17-24.

Preadolescent Behavior Problems after Prenatal Cocaine Exposure from the Maternal Lifestyle Study The authors previously reported an association between prenatal cocaine exposure (PCE) and childhood behavior problems as observed by the parent or caretaker. However, these behavior problems may not manifest in a structured environment, such as a school setting. They determined whether there is an association between PCE and school behavior problems and whether ratings of behavior problems from the teacher differ from those noted by the parent or caretaker. The Maternal Lifestyle Study, a multicenter study, enrolled 1388 children with and without PCE at one month of age for longitudinal assessment. Teachers masked to prenatal drug exposure status completed the Teacher Report Form (TRF/6-18) when children were 7, 9, and 11 years old. The authors also administered the Child Behavior Checklist-parent report (CBCL) to the parent/caretaker at same ages and then at 13 years. They performed latent growth curve modeling to determine whether high PCE will predict externalizing, internalizing, total behavior, and attention problems at 7 years of age and whether changes in problems' scores over time differ between those exposed and non-exposed from both teacher and parent report. Besides levels of PCE as predictors, the authors controlled for the following covariates, namely: site, child characteristics (gender and other prenatal drug exposures), family level influences (maternal age, depression and psychological symptomatology, continuing drug use, exposure to domestic violence, home environment, and socioeconomic status), and community level factors (neighborhood and community violence). The mean behavior problem T scores from the teacher report were significantly higher than ratings by the parent or caretaker. Latent growth curve modeling revealed a significant relationship between intercepts of problem T scores from teacher and parent ratings; i.e., children that were rated poorly by teachers were also rated poorly by their parent/caretaker or vice versa. After controlling for covariates, we found high PCE to be a significant predictor of higher externalizing behavior problem T scores from both parent and teacher report at 7 years ($p=0.034$ and $p=0.021$, respectively) in comparison to non-PCE children. These differences in scores from either teacher or caregiver were stable through subsequent years or did not change significantly over time. Boys had higher T scores than girls on internalizing and total problems by caretaker report; they also had significantly higher T scores for internalizing, total, and attention problems by teacher ratings; the difference was marginally significant for externalizing behavior ($p=0.070$). Caretaker postnatal use of tobacco, depression, and community violence were significant predictors of all behavior problems rated by parent/caretaker, while lower scores on the home environment predicted all behavior outcomes by the teacher report. The authors concluded that children with high PCE are likely to manifest externalizing behavior problems; their behavior problem scores at 7 years from either report of teacher or parent remained higher than scores of non-exposed children on subsequent years. Screening and identification of behavior problems at earlier ages could make possible initiation of intervention, while

considering the likely effects of other confounders. Bada HS, Bann CM, Bauer CR, Shankaran S, Lester B, LaGasse L, Hammond J, Whitaker T, Das A, Tan S, Higgins R. Preadolescent behavior problems after prenatal cocaine exposure: Relationship between teacher and caretaker ratings (Maternal Lifestyle Study). Neurotoxicol Teratol. 2011 Jan-Feb; 33(1): 78-87.

Fetal Neurobehavioral Effects of Exposure to Methadone or Buprenorphine As part of a double-blind study of medication treatment for opioid dependence during pregnancy, 17 opioid-dependent pregnant women maintained on either buprenorphine or methadone underwent fetal monitoring at 24, 28, 32, and 36 weeks gestation. Maternal demographic information and infant outcomes did not significantly differ by medication group. Earlier in gestation (24 and 28 weeks), buprenorphine-exposed fetuses had higher levels of fetal heart rate variability, more accelerations in fetal heart rate and greater coupling between fetal heart rate and fetal movement than the methadone-exposed group (all ps < .05). Later in gestation (32 and 36 weeks), buprenorphine-exposed fetuses displayed less suppression of motor activity and longer duration of movements than the methadone-exposed group (all ps < .05). These results may have implications for the optimal treatment of the opioid-dependent pregnant woman. Jansson LM, Dipietro JA, Velez M, Elko A, Williams E, Milio L, O'Grady K, Jones HE. Fetal neurobehavioral effects of exposure to methadone or buprenorphine. Neurotoxicol Teratol. 2011 Mar-Apr; 33(2): 240-243.

Infant Temperament and High Risk Environment and not Prenatal Methamphetamine Exposure Relate to Behavior Problems and Language in Toddlers This study examined the role that easy infant temperament and cumulative environmental risk play in predicting cognitive, language, and behavioral outcomes in 3-year-old children at high social risk. Subjects were 412 mother-infant dyads, recruited at birth, participating in a longitudinal study examining the effects of prenatal methamphetamine on child development. This analysis includes a subsample (n = 290) of the study with a completed 3-year visit. Temperament was assessed by the Infant Behavior Questionnaire at 12 months. Factor analysis from well-validated measures generated "easy" and "difficult" temperament profiles and a profile for high-risk environment. Caretaker receptive vocabulary served as a proxy for intelligence quotient. Outcomes at 3 years included motor and mental development, behavior problems, and language. Linear regression and hierarchical linear modeling examined the effects of temperament, high-risk environment, and caregiver receptive language on outcomes adjusting for maternal drug use and demographic and socioeconomic covariates. Internalizing and externalizing behaviors were lower in children with easy temperament and higher with increased environmental risk. Easy temperament attenuated behavioral problems only in the setting of lower environmental risk. Caregiver receptive language was associated with lower internalizing scores. High-risk environment and temperament factors were not related to cognitive or motor outcomes. Prenatal methamphetamine exposure was not associated with 3-year-old outcomes, nor did it alter the protective effects of an easier temperament on child behavior. Children growing up in adverse social environments had increased behavioral problems and compromised language development. Conversely, an easy temperament acts as a protective factor for social-emotional development and could be related to resilience. Derauf C, LaGasse L, Smith L, Newman E, Shah R, Arria A, Huestis M, Haning W, Strauss A, Della Grotta S, Dansereau L, Lin H, Lester B. Infant temperament and high-risk environment relate to behavior problems and language in toddlers. J Dev Behav Pediatr. 2011 Feb-Mar; 32(2): 125-135.

Maternal Cocaine Use and Mother-Toddler Aggression This study examined the direct and indirect associations between maternal cocaine use during pregnancy and mother-toddler aggression in an interactive context at 2 years of child age. The authors hypothesized that in addition to direct effects of cocaine exposure on maternal and child aggression, the association between maternal cocaine use and mother-toddler aggression may be indirect via higher maternal psychiatric symptoms, negative affect, or poor infant autonomic regulation at 13 months. Participants consisted of 220 (119 cocaine exposed, 101 non-cocaine exposed) mother-toddler dyads participating in an ongoing longitudinal study of prenatal cocaine exposure. Results indicated that mothers who used cocaine during pregnancy displayed higher levels of aggression toward their toddlers compared to mothers in the control group. Results from model testing indicated significant indirect associations between maternal cocaine use and maternal aggression via higher maternal negative affect as well as lower infant autonomic regulation at 13 months. Although there were no direct associations between cocaine exposure and toddler aggression, there was a significant indirect effect via lower infant autonomic regulation at 13 months. Results highlight the importance of including maternal aggression in predictive models of prenatal cocaine exposure examining child aggression. Results also emphasize the important role of infant regulation as a mechanism partially explaining associations between cocaine exposure and mother-toddler aggression. Eiden RD, Schuetze P, Colder CR, Veira Y. Maternal cocaine use and mother-toddler aggression. Neurotoxicol Teratol. 2011 May-Jun; 33(3): 360-369.

Longitudinal Pathways From Marital Hostility to Toddler's Anger: Genetic Susceptibility and Harsh Parenting The authors examined direct and indirect pathways from marital hostility to toddler anger/frustration via harsh parenting and parental depressive symptoms, with an additional focus on the moderating role of genetic influences as inferred from birth parent anger/frustration. Participants were 361 linked triads of birth mothers, adoptive parents, and adopted children who were 9 (T1) and 18 (T2) months old across the study period. Results indicated an indirect effect from T1 marital hostility to T2 toddler anger/frustration via T2 parental harsh discipline. Results also indicated that the association between marital hostility and toddler anger was moderated by birth mother anger/frustration. For children whose birth mothers reported high levels of anger/frustration, adoptive parents' marital hostility at T1 predicted toddler anger/frustration at T2. This relation did not hold for children whose birth mothers reported low levels of anger/frustration. The results suggest that children whose birth mothers report elevated frustration might inherit an emotional lability that makes them more sensitive to the effects of marital hostility. Rhoades KA, Leve LD, Harold GT, Neiderhiser JM, Shaw DS, Reiss D. Longitudinal pathways from marital hostility to child anger during toddlerhood: Genetic susceptibility and indirect effects via harsh parenting. J Fam Psychol. 2011 Apr; 25(2): 282-291.

Emotional Abuse and Childhood Borderline Personality Features: Findings from a Study on the Development of HIV Risk Behaviors Most of the extant literature on borderline personality disorder has focused on the course, consequences, and correlates of this disorder among adults. However, little is known about childhood borderline personality (BP) features, or the factors associated with the emergence of BP pathology in childhood. A greater understanding of childhood BP features and associated risk factors has important implications for the development of primary and secondary prevention programs. The goal of the present study was to examine the interrelationships among two BP-relevant traits (affective dysfunction and

impulsivity), a BP-relevant environmental stressor (emotional abuse), and BP features in a sample of 225 children aged 11 to 14 years. Results provide support for the role of both trait vulnerabilities and environmental stressors in childhood BP features. Further, findings highlight the moderating role of affective dysfunction in the relationship between emotional abuse and childhood BP features. Gratz KL, Latman RD, Tull MT, Reynolds EK, Lejuez CW. Exploring the association between emotional abuse and childhood borderline personality features: The moderating role of personality traits. Behav Ther. 2011 Sep; 42(3): 493-508.

Microbicide to Prevent HIV in Young Women: Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) Collaboration with the Microbicides Trials Network (MTN) The study was designed to assess the safety, adherence, acceptability, and effect on vaginal microflora of 3% SPL7013 Gel (VivaGel), a novel dendrimer topical microbicide that inhibits HIV, herpes simplex virus-2, and human papillomavirus in vitro and in animal models. The design was a Phase 1, randomized, double-blind, placebo-controlled study on sexually active women. Sixty-one sexually active women aged 18-24 years were recruited from three sites in the United States. Participants were randomized 1: 1: 1 to receive VivaGel, VivaGel placebo, or a hydroxyethylcellulose (HEC) placebo twice daily for 14 consecutive days. Safety endpoints included genitourinary and/or other adverse events. Changes in vaginal flora were determined from Gram-stained vaginal smears and quantitative vaginal culture. No serious adverse events or withdrawals due to adverse events were reported. Genitourinary symptoms were reported as follows: VivaGel (n = 17/22; 77.3%), VivaGel placebo (n = 14/21; 66.7%), and HEC (n = eight of 18; 44.4%; not significant, P = 0.1). The incidence of abnormal pelvic examination findings was similar across all gel arms of the study. Using pairwise comparison, women in the VivaGel arm had a significantly higher incidence of related genitourinary adverse events compared with women in the HEC gel arm (0.297 versus 0.111 per 100 person-years, respectively; P = 0.003). Exposure to VivaGel and VivaGel placebo resulted in minor shifts in the vaginal microflora, but there was no overall impact on incidence of bacterial vaginosis as assessed by Nugent score. VivaGel was generally well tolerated and comparable with the VivaGel placebo, although there was a higher incidence of low-grade related genial adverse events compared to the HEC placebo gel. McGowan I, Gomez K, Bruder K, Febo I, Chen BA, Richardson BA, Husnik M, Livant E, Price C, Jacobson C and MTN 004 Protocol Team. Phase 1 randomized trial of the vaginal safety and acceptability of SPL7013 gel (VivaGel) in sexually active young women (MTN-004). AIDS. 2011 May 15; 25(8): 1057-1064.

Hepatitis B Vaccination in HIV-Infected Youth in the ATN HIV-infected youth are at risk of hepatitis B infection and should be vaccinated. Previous reports suggest reduced response to standard hepatitis B vaccine regimens. HIV-infected youth, aged 12 to younger than 25 years, were randomly assigned to one of three treatment arms: Arm 1: Engerix B, 20 µg HBsAg; Arm 2: Engerix B (GlaxoSmithKline, Rixensart, Belgium), 40 µg; and Arm 3: Twinrix (GlaxoSmithKline, Rixensart, Belgium), 20 µg HBsAg combined with 720 ELU hepatitis A antigen. Vaccines were administered at Weeks 0, 4, and 24. Characteristics of evaluable patients (n = 336) at entry were similar in the study arms. At enrollment, median CD4+ T-cell count was 460 cells/mm3 (interquartile range, 305-668); 13% were less than 200 cells/mm3. Among Engerix B, 20-µg recipients, 60.4% responded to vaccine (HBsAb 10 IU/mL or greater at Week 28). Improved vaccine response was seen in recipients of Engerix B, 40 µg (73.2% versus Arm 1, P = 0.04) and Twinrix (75.4% versus Arm 1,P = 0.02). In multivariate analysis, only baseline

CD4+ T-cell count and study arm were independent predictors of vaccine response. In HIV-infected youth, a three-dose vaccination regimen with Engerix B, 40 µg, or Twinrix and higher baseline CD4+ T-cell counts were independently associated with improved vaccine response. Flynn PM, Cunningham CK, Rudy B, Wilson CM, Kapogiannis B, Worrell C, Bethel J, Monte D, Bojan K and the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). Hepatitis B vaccination in HIV-infected youth: A randomized trial of three regimens. J Acquir Immune Defic Syndr. 2011 Apr; 56(4): 325-332.

Project Accept: An Intervention for Youth Newly Diagnosed with HIV Given the potential for negative psychosocial and medical outcomes following an HIV diagnosis, Project ACCEPT, a 12-session behavioral intervention, was developed and pilot-tested for youth (aged 16-24) newly diagnosed with HIV. Fifty participants recently diagnosed with HIV were enrolled from 4 sites selected through the Adolescent Medicine Trials Network (ATN). The majority of participants identified as African American (78%). Feasibility and acceptability data demonstrated high rates of participation and high levels of satisfaction with the intervention program from both participants and staff. Exploratory outcome data demonstrated improved levels of HIV knowledge that were sustained over time (Cohen's effect [d] d = .52) and improvements in peer (d = .35) and formal (d = .20) social support immediately postintervention. Gender differences emerged over time in the areas of depressive symptoms, family social support, self-efficacy for sexual discussion, and personalized stigma. Project ACCEPT appears to be an acceptable and feasible intervention to implement in clinical settings for youth newly diagnosed with HIV. Hosek SG, Lemos D, Harper GW, Telander K. Evaluating the acceptability and feasibility of Project ACCEPT: An intervention for youth newly diagnosed with HIV/AIDS Educ Prev. 2011 Apr; 23(2): 128-144.

HIV Medication Adherence in High-Risk Youth in the ATN This study explored the role of situational temptation, a component of self-efficacy, in adolescent and young adult (ages 16-24) HIV medication adherence by assessing participants' perceptions of their temptation to miss medications in various situations (e.g., when edication causes physical side effects, when there is fear of disclosure of HIV status). Youth (n = 186; 83% African American) were participants in a multisite clinical trial examining the efficacy of a motivational intervention. Data were collected using computer-assisted personal interviewing. Youth believed the most tempting reasons or situations that might lead them to miss their HIV medications to be symptoms (if the medicine caused you to have other physical symptoms) and sick (if the medicine made you sick to your stomach or made you throw up or if it tasted bad), but these were not significantly associated with nonadherence. This suggests disconnection between youths' expectations of temptation and actual tempting situations associated with nonadherence. Situational temptations associated with nonadherence included lack of social support, needing a break from medications, and not seeing a need for medications. Interventions to improve adherence should consider perceptions of HIV medications, particularly the benefits of taking medications and expectations of physical symptoms. Interventionists and clinicians should consider situations that may tempt youth to miss doses of medication and help youth gain insight into these temptations. Emerging methods, such as Ecological Momentary Assessment (e.g., daily diaries, cell phone text messaging), may be useful in gaining insight into the day-to-day experience of youth living with HIV. MacDonell KE, Naar-King S, Murphy D, Parsons JT, Hszti H. Situational temptation for HIV medication adherence in high risk youth. AIDS Patient Care STDS. 2011 Jan; 25(1): 47-52.

CLINICAL NEUROSCIENCE RESEARCH

Value-Driven Attentional Capture Attention selects which aspects of sensory input are brought to awareness. To promote survival and well-being, attention prioritizes stimuli both voluntarily, according to context-specific goals (e.g., searching for car keys), and involuntarily, through attentional capture driven by physical salience (e.g., looking toward a sudden noise). Valuable stimuli strongly modulate voluntary attention allocation, but there is little evidence that high-value but contextually irrelevant stimuli capture attention as a consequence of reward learning. Here the authors show that visual search for a salient target is slowed by the presence of an inconspicuous, task-irrelevant item that was previously associated with monetary reward during a brief training session. Thus, arbitrary and otherwise neutral stimuli imbued with value via associative learning capture attention powerfully and persistently during extinction, independently of goals and salience. Vulnerability to such value-driven attentional capture covaries across individuals with working memory capacity and trait impulsivity. This unique form of attentional capture may provide a useful model for investigating failures of cognitive control in clinical syndromes in which value assigned to stimuli conflicts with behavioral goals (e.g., addiction, obesity). Anderson BA, Laurent PA, Yantis S. Value-driven attentional capture. Proc. Natl. Acad. Sci. U.S.A 2011 Jun; 108(25): 10367-10371.

Frontal Hyperconnectivity Related to Discounting and Reversal Learning in Cocaine Subjects Functional neuroimaging studies suggest that chronic cocaine use is associated with frontal lobe abnormalities. Functional connectivity (FC) alterations of cocaine-dependent individuals (CD), however, are not yet clear. This is the first study to the authors' knowledge that examines resting FC of anterior cingulate cortex (ACC) in CD. Because ACC is known to integrate inputs from different brain regions to regulate behavior, they hypothesized that CD will have connectivity abnormalities in ACC networks. In addition, they hypothesized that abnormalities would be associated with poor performance in delayed discounting and reversal learning tasks. Resting functional magnetic resonance imaging data were collected to look for FC differences between 27 CD (5 women, age: M = 39.73, SD = 6.14 years) and 24 control subjects (5 women, age: M = 39.76, SD = 7.09 years). Participants were assessed with delayed discounting and reversal learning tasks. With seed-based FC measures, the authors examined FC in CD and control subjects within five ACC connectivity networks with seeds in subgenual, caudal, dorsal, rostral, and perigenual ACC. The CD showed increased FC within the perigenual ACC network in left middle frontal gyrus, ACC, and middle temporal gyrus when compared with control subjects. The FC abnormalities were significantly positively correlated with task performance in delayed discounting and reversal learning tasks in CD. The present study shows that participants with chronic cocaine-dependency have hyperconnectivity within an ACC network known to be involved in social processing and "mentalizing." In addition, FC abnormalities found in CD were associated with difficulties with delay rewards and slower adaptive learning. Camchong J, MacDonald III AW, Bell C, Mueller BA, Specker S, Lim KO. Frontal hyperconnectivity related to discounting and reversal learning in cocaine subjects. Biol Psychiat 2011; 69(11): 1117-1123.

Reduced Interhemispheric Resting State Functional Connectivity in Cocaine Addiction Models of cocaine addiction emphasize the role of disrupted frontal circuitry supporting cognitive control processes. However, addiction-related alterations in functional interactions among brain regions, especially between the cerebral hemispheres, are rarely examined directly. Resting-state functional magnetic resonance imaging (fMRI) approaches, which reveal patterns of coherent spontaneous fluctuations in the fMRI signal, offer a means to quantify directly functional interactions between the hemispheres. The authors examined interhemispheric resting-state functional connectivity (RSFC) in cocaine dependence using a recently validated approach, voxel-mirrored homotopic connectivity. They compared interhemispheric RSFC between 25 adults (aged 35.0 ± 8.8) meeting DSM-IV criteria for cocaine dependence within the past 12 months but currently abstaining (>2 weeks) from cocaine and 24 healthy comparisons (35.1 ± 7.5), group-matched on age, sex, education, and employment status. They observed reduced prefrontal interhemispheric RSFC in cocaine-dependent participants relative to control subjects. Further analyses demonstrated a striking cocaine-dependence-related reduction in interhemispheric RSFC among nodes of the dorsal attention network, comprising bilateral lateral frontal, medial premotor, and posterior parietal areas. Further, within the cocaine-dependent group, RSFC within the dorsal attention network was associated with self-reported attentional lapses. These findings provide further evidence of an association between chronic exposure to cocaine and disruptions within large-scale brain circuitry supporting cognitive control. The authors did not detect group differences in diffusion tensor imaging measures, suggesting that alterations in the brain's functional architecture associated with cocaine exposure can be observed in the absence of detectable abnormalities in the white matter microstructure supporting that architecture. Kelly C, Zuo X-N, Gotimer K, Cox CL, Lynch L, Brock D, Imperati D, Garavan H, Rotrosen J, Castellanos FX, Milham MP. Reduced interhemispheric resting state functional connectivity in cocaine addiction. Biological Psychiatry. 2011 Apr; 69(7): 684-692.

Modafinil Increases Frontocortical Activation and Normalizes Cognitive Deficits in Methamphetamine-Dependent Subjects Methamphetamine (MA)-dependent individuals exhibit deficits in cognition and prefrontal cortical function. Therefore, medications that improve cognition in these subjects may improve the success of therapy for their addiction, especially when cognitive behavioral therapies are used. Modafinil has been shown to improve cognitive performance in neuropsychiatric patients and healthy volunteers. The authors therefore conducted a randomized, double-blind, placebo-controlled, cross-over study, using functional magnetic resonance imaging, to examine the effects of modafinil on learning and neural activity related to cognitive function in abstinent, MA-dependent, and healthy control participants. Modafinil (200mg) and placebo were administered orally (one single dose each), in counterbalanced fashion, 2h before each of two testing sessions. Under placebo conditions, MA-dependent participants showed worse learning performance than control participants. Modafinil boosted learning in MA-dependent participants, bringing them to the same performance level as control subjects; the control group did not show changes in performance with modafinil. After controlling for performance differences, MA-dependent participants showed a greater effect of modafinil on brain activation in bilateral insula/ventrolateral prefrontal cortex and anterior cingulate cortices than control participants. The findings suggest that modafinil improves learning in MA-dependent participants, possibly by enhancing neural function in regions important for learning and cognitive control. These results suggest that modafinil may be a suitable pharmacological adjunct for enhancing the efficiency of cognitive-based therapies for

MA dependence. Ghahremani DG, Tabibnia G, Monterosso J, Hellemann G, Poldrack RA, London ED. Effect of modafinil on learning and task-related brain activity in methamphetamine-dependent and healthy individuals. Neuropsychopharmacology. 2011 Apr; 36(5): 950-959.

Genetic Variability of Smoking Persistence in African Americans To date, most genetic association analyses of smoking behaviors have been conducted in populations of European ancestry and many of these studies focused on the phenotype that measures smoking quantity, i.e. cigarettes per day. Additional association studies in diverse populations with different linkage disequilibrium (LD) patterns and an alternate phenotype, such as total tobacco exposure which accounts for intermittent periods of smoking cessation within a larger smoking period as measured in large cardiovascular risk studies, can aid the search for variants relevant to smoking behavior. For these reasons, the authors undertook an association analysis using a genotyping array that includes 2100 genes to analyze smoking persistence in unrelated African-American participants from The Atherosclerosis Risk in Communities (ARIC) study. A locus located ~ 4 Kb downstream from the 3' UTR of the Brain-Derived Neurotrophic Factor (BDNF) significantly influenced smoking persistence. In addition, independent variants rs12915366 and rs12914385 in the cluster of genes encoding nicotinic acetylcholine receptor subunits (CHRNA5-CHRNA3-CHRNB4) on 15q25.1 were also associated with the phenotype in this sample of African American subjects. To the authors' knowledge, this is the first study to more extensively evaluate the genome in the African American population as a limited number of previous studies of smoking behavior in this population included evaluations of only single genomic regions. Hamidovic A, Kasberger J, Young TR, Goodloe RJ, Redline S, Buxbaum SG, Benowitz NL, Bergen AW, Butler KR Jr., Franceschini N, Gharib SA, Hitsman B, Levy D, Men G Y, Papanicolaou GJ, Preiss SR, Spring BJ, Styn MA, Elisa K. Tong EK, White W, Wiggins KL, Jorgenson E. Genetic variability of smoking persistence in African Americans. Cancer Prev Res. March 24, 2011. [Epub ahead of print].

OPRM1 Gene Variants Modulate Amphetamine-Induced Euphoria in Humans The μ-opioid receptor is involved in the rewarding effects of not only opioids like morphine but also psychostimulants like amphetamine. This study aimed to investigate associations between subjective response to amphetamine and genetic polymorphisms and haplotypes in the μ-opioid receptor including the exonic variant rs1799971 (Asp40Asn). One hundred and sixty-two Caucasian volunteers participated in three sessions receiving either placebo or d-amphetamine (10 and 20 mg). Associations between levels of self-reported Euphoria, Energy and Stimulation [Addiction Research Center Inventory 49-item questionnaire (ARCI-49)] after d-amphetamine ingestion and polymorphisms in OPRM1 were investigated. The intronic single nucleotide polymorphisms (SNPs) rs510769 and rs2281617 were associated with significantly higher ratings of Euphoria, Energy and Stimulation after 10 mg amphetamine. Feelings of Euphoria, Energy and Stimulation were also found to be associated with a two-SNP haplotype formed with rs1799971 and rs510769 and a three-SNP haplotype formed with rs1918760, rs2281617 and rs1998220. These results support the hypothesis that genetic variability in the μ-opioid receptor gene influences the subjective effects of amphetamine and may suggest new strategies for prevention and treatment of psychostimulant abuse. Dlugos AM, Hamidovic A, Hodgkinson C, Shen PH, Goldman D, Palmer AA, de Wit H. OPRM1 gene variants modulate amphetamine-induced euphoria in humans. Genes Brain Behav. 2011 Mar; 10(2): 199-209.

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 between sleep and pain measures were identified, but differences in sleep between the two groups were not found to mediate altered pain perception in MDMA users. 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, Edward RR, Smith MT, Kelley K, Wilson M, Sgambati F, Ricaurte G. Altered pain responses in abstinent (±)3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users. Psychopharm. 2011 May 21. [Epub ahead of print].

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. 2011 June 22. [Epub ahead of print].

A Multistudy Analysis of the Effects of Early Cocaine Abstinence on Sleep The objective of this study was to describe the sleep patterns of early cocaine abstinence in chronic users by polysomnographic and subjective measures. 28 cocaine-dependent participants (ages 24–55) underwent polysomnographic sleep (PSG) recording on the 1st, 2nd and 3rd weeks of abstinence on a research dedicated inpatient facility. Objective measures of total sleep time, total REM time, slow wave sleep, sleep efficiency and a subjective measure (sleep quality) along with demographic data were collected from three different long term research studies over a five year period. Data were reanalysed to allow greater statistical power for comparisons. Progressive weeks of abstinence had main effects on all assessed PSG sleep measures showing decreased total sleep time, REM sleep, stages 1 and 2 sleep, and sleep efficiency; increases in sleep onset and REM latencies and a slight increase in slow-wave sleep time were also present. Total sleep time and slow wave sleep were negatively associated with years of cocaine use. Total sleep time was positively associated with the amount of current ethanol use. Sex differences were found with females having more total REM time and an increase at a near significance level in slow wave sleep. Subjective measures were reported as improving with increasing abstinence over the same time period. Chronic cocaine users show a general deterioration in objective sleep measures over a three-week period despite an increase in subjective overall sleep quality providing further evidence for "occult insomnia" during early cocaine abstinence. Matuskey D, Pittman B, Forselius E, Malison RT, Morgan PT. A multistudy analysis of the effects of early cocaine abstinence on sleep. Drug Alcohol Depend. 2011; 115(1-2): 62-66.

Acoustic Startle Reduction in Cocaine Dependence Persists for 1 Year of Abstinence
Chronic cocaine use results in long-lasting neurochemical changes that persist beyond the acute withdrawal period. Previous work from the authors' group reported a profound reduction in the acoustic startle response (ASR) in chronic cocaine-dependent subjects in early abstinence compared to healthy controls that may be related to long-lasting neuroadaptations following withdrawal from chronic cocaine use. This study aims to investigate the persistence and time course of the decrements in the ASR of cocaine-dependent subjects during prolonged abstinence. Seventy-six cocaine-dependent (COC) subjects and 30 controls (CONT) were tested, the former after a period of heavy cocaine dependence. COC subjects were retested sequentially for 1 year of abstinence or until relapse. ASR testing was conducted at 3-dB levels and the eye-blink component of the startle response was quantified with electromyographic recording of the orbicularis oculi muscle. While there was no difference in startle magnitude between CONT and COC in early abstinence, by day 40 of abstinence COC subjects exhibited a statistically significant decline (p=0.0057) in ASR magnitude as compared with CONT and this decrement persisted for up to 1 year of abstinence (p=0.0165). In addition, startle latency was slower in COC subjects as compared with CONT at all stages of abstinence. These results replicate and expand upon the earlier finding that chronic cocaine use impairs the ASR in a manner that persists beyond the acute withdrawal period. This phenomenon may represent a biological measure of long-term neural changes accompanying cocaine dependence and subsequent withdrawal. Corcoran S, Norrholm SD, Cuthbert B, Sternberg M, Hollis J, Duncan E. Acoustic startle in cocaine dependence persists for 1 year abstinence. Psychopharm. 2011; 215(1): 93-103.

Brain Reactivity to Emotional, Neutral and Cigarette-related Stimuli in Smokers Addiction has been described as the pathological usurpation of the neural mechanisms normally involved in emotional processing. Event-related potentials (ERPs) can provide a non-invasive index of neural responses associated with the processing of emotionally relevant stimuli and serve as a tool for examining temporal and spatial commonalities between the processing of intrinsically motivating stimuli and drug cues. Before beginning a smoking cessation program, 116 smokers participated in a laboratory session in which dense-array ERPs (129 sensors) were recorded during the presentation of pictures with emotional (pleasant and unpleasant), neutral and cigarette-related content. ERP differences among categories were analyzed with use of randomization tests on time regions of interest identified by temporal principal component analysis. Both emotional and cigarette-related pictures prompted significantly more positivity than did neutral pictures over central, parietal, and frontal sites in the 452–508 ms time window. During the 212–316 ms time window, both pleasant and cigarette-related pictures prompted less positivity than neutral images did. Cigarette-related pictures enhanced the amplitude of the P1 component (136–144 ms) above the levels measured in the emotional and neutral conditions. These results support the hypothesis that for smokers, cigarette-related cues are motivationally relevant stimuli that capture attentional resources early during visual processing and engage brain circuits normally involved in the processing of intrinsically emotional stimuli. Versace F, Minnix JA, Robinson JD, Lam CY, Brown VL, Cinciripini PM. Brain reactivity to emotional, neutral and cigarette-related stimuli in smokers. Addiction Biol. 2011 Apr; 16(2): 296-307.

Young Smokers Show Reduced Advantageous Risk-Taking Cigarette smoking has been linked to real-world risky behavior, but this association has been based largely on retrospective self-reports. Limitations of self-report data can be avoided by using laboratory, performance-based measures, such as the Balloon Analogue Risk Task (BART; Lejuez et al., J Exp Psychol Appl 8:75-84, 2002). Initial studies have suggested that smokers display greater risk-taking on this task than nonsmokers, but these studies did not account for drug abuse and psychiatric comorbidities, which are commonplace among smokers. The authors sought to examine the performance of smokers and nonsmokers on the BART after excluding drug abuse and psychiatric comorbidities. They conducted a study of late adolescent/young adult (age 18 to 21) smokers (n=26) and nonsmokers (n=38) performing the BART and excluded individuals with positive drug or alcohol toxicology screens, substance abuse or dependence diagnoses, and/or current psychiatric conditions. Contrary to previous findings, smokers did not display greater risk-taking on the BART than nonsmokers. In fact, when performance was examined trial-by-trial, the nonsmokers displayed progressively greater pumping relative to smokers over time ($p<0.001$), earning them a nonsignificantly greater amount of money than the smokers. Controlling for smoking status, additional analyses revealed that pumping on the BART was positively associated with years of education, nonverbal IQ, and employment. The results suggest that in young adults, smoking may be associated with a failure to take risks in situations where risk-taking is adaptive. Dean AC, Sugar CA, Hellemann G, London ED. Is all risk bad? Young adult cigarette smokers fail to take adaptive risk in a laboratory decision-making test. Psychopharmacology (Berl). 2011 Jun; 215(4): 801-811.

Smokers Show Blunted Ventral Striatal Sensitivity to Delayed Reward Prospects Brain regions that track value (including the ventral striatum) respond more during the anticipation of immediate than delayed rewards, even when the delayed rewards are larger and equally preferred to the immediate. The anticipatory response to immediate vs. delayed rewards has not previously been examined in association with cigarette smoking. Smokers (n=35) and nonsmokers (n=36) performed a modified monetary incentive functional Magnetic Resonance Imaging (fMRI) task (Knutson et al., 2000) that included opportunities to win either immediate or delayed rewards. The delayed rewards were larger and equally preferred to the immediate rewards. Across groups, greater activation was observed in regions previously shown to track value including bilateral ventral/dorsal striatum during the anticipation of immediate relative to delayed rewards. This effect was significantly greater among smokers than nonsmokers within the right ventral striatum. This group difference was driven particularly by low striatal activation among smokers during delayed reward trials. The general tendency for striatal reward anticipatory activity to be attenuated when rewards are delayed is exaggerated among smokers relative to comparison participants. Among possible explanations of this relationship are that (1) low anticipatory response to delayed rewards is a phenotypic risk factor for smoking and (2) smoking-related neuroadaptations result in reduced recruitment during the anticipation of delayed rewards. Luo S, Ainslie G, Giragosian L, Monterosso JR. Striatal hyposensitivity to delayed rewards among cigarette smokers. Drug Alcohol Depend. 2011 Jul 1; 116(1-3): 18-23.

Humans Can Utilize Contextual Information to Bolster Cortical Inhibitors of a Prepotent Behavior While most research on stopping action examines how an initiated response is stopped when a signal occurs (i.e., reactively), everyday life also calls for a mechanism to prepare to stop a particular response tendency (i.e., proactively and selectively). The authors hypothesized that human subjects can prepare to stop a particular response by proactively suppressing that response representation in the brain. They tested this by using single-pulse transcranial magnetic stimulation and concurrent electromyography. This allowed us to interrogate the corticomotor excitability of specific response representations even before action ensued. They found that the motor evoked potential of the effector that might need to be stopped in the future was significantly reduced compared with when that effector was at rest. Further, this neural index of proactive and selective suppression predicted the subsequent selectivity with which the behavioral response was stopped. These results go further than earlier reports of reduced motor excitability when responses are stopped. They show that the control can be applied in advance (proactively) and also targeted at a particular response channel (selectively). This provides novel evidence for an active mechanism of suppression in the brain that is setup according to the subject's goals and even before action ensues. Cai W, Oldenkamp CL, Aron AR. A proactive mechanism for selective suppression of response tendencies. J Neurosci. 2011 Apr 20; 31(16): 5965-5969.

Ventromedial Cortex Damage Impairs Ability for Subjective Valuation to Guide Choices Recent work in neuroeconomics has shown that regions in orbitofrontal and medial prefrontal cortex encode the subjective value of different options during choice. However, these electrophysiological and neuroimaging studies cannot demonstrate whether such signals are necessary for value-maximizing choices. Here the authors used a paradigm developed in experimental economics to empirically measure and quantify violations of utility theory in humans with damage to the ventromedial frontal lobe (VMF). They show that people with such

damage are more likely to make choices that violate the generalized axiom of revealed preference, which is the one necessary and sufficient condition for choices to be consistent with value maximization. These results demonstrate that the VMF plays a critical role in value-maximizing choice. Camille N, Griffiths CA, Vo K, Fellows LK, Kable JW. Ventromedial frontal lobe damage disrupts value maximization in humans. J Neurosci. 2011 May 18; 31(20): 7527-7532.

Novel Application of Real-Time Functional MRI Using Pseudo-Continuous Arterial Spin Labeling The first implementation of real-time acquisition and analysis of arterial spin labeling-based functional magnetic resonance imaging time series is presented in this article. The implementation uses a pseudo-continuous labeling scheme followed by a spiral k-space acquisition trajectory. Real-time reconstruction of the images, preprocessing, and regression analysis of the functional magnetic resonance imaging data were implemented on a laptop computer interfaced with the MRI scanner. The method allows the user to track the current raw data, subtraction images, and the cumulative t-statistic map overlaid on a cumulative subtraction image. The user is also able to track the time course of individual time courses and interactively selects a region of interest as a nuisance covariate. The pulse sequence allows the user to adjust acquisition and labeling parameters while observing their effect on the image within two successive pulse repetition times. This method is demonstrated by two functional imaging experiments: a simultaneous finger-tapping and visual stimulation paradigm, and a bimanual finger-tapping task. Hernandez-Garcia L, Jahanian H, Greenwald MK, Zubieta JK, Peltier SJ. Real-time functional MRI using pseudo-continuous arterial spin labeling. Magn Reson Med. 2011 Jun; 65(6): 1570-1577.

Advances in Real-Time fMRI Brain State Classification and Application to Neurofeedback This article reviews a technological advance that originates from two areas of ongoing neuroimaging innovation-(1) the use of multivariate supervised learning to decode brain states and (2) real-time functional magnetic resonance imaging (rtfMRI). The approach uses multivariate methods to train a model capable of decoding a subject's brain state from fMRI images. The decoded brain states can be used as a control signal for a brain computer interface (BCI) or to provide neurofeedback to the subject. The ability to adapt the stimulus during the fMRI experiment adds a new level of flexibility for task paradigms and has potential applications in a number of areas, including performance enhancement, rehabilitation, and therapy. Multivariate approaches to real-time fMRI are complementary to region-of-interest (ROI)-based methods and provide a principled method for dealing with distributed patterns of brain responses. Specifically, a multivariate approach is advantageous when network activity is expected, when mental strategies could vary from individual to individual, or when one or a few ROIs are not unequivocally the most appropriate for the investigation. Beyond highlighting important developments in rtfMRI and supervised learning, the article discusses important practical issues, including implementation considerations, existing resources, and future challenges and opportunities. Some possible future directions are described, calling for advances arising from increased experimental flexibility, improvements in predictive modeling, better comparisons across rtfMRI and other BCI implementations, and further investigation of the types of feedback and degree to which interface modulation is obtainable for various tasks. LaConte SM. Decoding fMRI brain states in real-time. Neuroimage. 2011 May 15; 56(2): 440-454.

Bupropion Reduces Neurophysiological and Behavioral Indices of Craving in Smokers Nicotine-dependent smokers exhibit craving and brain activation in the prefrontal and limbic regions when presented with cigarette-related cues. Bupropion hydrochloride treatment reduces cue-induced craving in cigarette smokers; however, the mechanism by which bupropion exerts this effect has not yet been described. The objective of this study was to assess changes in regional brain activation in response to cigarette-related cues from before to after treatment with bupropion (vs placebo). The design was a randomized, double-blind, before-after controlled trial. The setting was an academic brain imaging center. Participants comprised 30 nicotine-dependent smokers (paid volunteers). Participants were randomly assigned to receive 8 weeks of treatment with either bupropion or a matching placebo pill (double-blind). Main outcome measures included subjective cigarette craving ratings and regional brain activations (blood oxygen level-dependent response) in response to viewing cue videos. Bupropion-treated participants reported less craving and exhibited reduced activation in the left ventral striatum, right medial orbitofrontal cortex, and bilateral anterior cingulate cortex from before to after treatment when actively resisting craving compared with placebo-treated participants. When resisting craving, reduction in self-reported craving correlated with reduced regional brain activation in the bilateral medial orbitofrontal and left anterior cingulate cortices in all participants. Treatment with bupropion is associated with improved ability to resist cue-induced craving and a reduction in cue-induced activation of limbic and prefrontal brain regions, while a reduction in craving, regardless of treatment type, is associated with reduced activation in prefrontal brain regions. Culbertson CS, Bramen J, Cohen MS, London ED, Olmstead RE, Gan JJ, Costello MR, Shulenberger S, Mandelkern MA, Brody AL. Effect of bupropion treatment on brain activation induced by cigarette-related cues in smokers. Arch Gen Psychiatry. 2011 May; 68(5): 505-515.

Machine Learning with fMRI Data Reveals Patterns Indicative of Whether We Believe or Not Machine learning (ML) has become a popular tool for mining functional neuroimaging data, and there are now hopes of performing such analyses efficiently in real-time. Towards this goal, the authors compared accuracy of six different ML algorithms applied to neuroimaging data of persons engaged in a bivariate task, asserting their belief or disbelief of a variety of propositional statements. They performed unsupervised dimension reduction and automated feature extraction using independent component (IC) analysis and extracted IC time courses. Optimization of classification hyperparameters across each classifier occurred prior to assessment. Maximum accuracy was achieved at 92% for Random Forest, followed by 91% for AdaBoost, 89% for Naïve Bayes, 87% for a J48 decision tree, 86% for K*, and 84% for support vector machine. For real-time decoding applications, finding a parsimonious subset of diagnostic ICs might be useful. The authors used a forward search technique to sequentially add ranked ICs to the feature subspace. For the current data set, they determined that approximately six ICs represented a meaningful basis set for classification. They then projected these six IC spatial maps forward onto a later scanning session within subject. They then applied the optimized ML algorithms to these new data instances, and found that classification accuracy results were reproducible. Additionally, they compared their classification method to their previously published general linear model results on this same data set. The highest ranked IC spatial maps show similarity to brain regions associated with contrasts for belief > disbelief, and disbelief < belief. Douglas PK, Harris S, Yuille A, Cohen MS. Performance comparison of machine learning

algorithms and number of independent components used in fMRI decoding of belief vs. disbelief. Neuroimage. 2011 May 15; 56(2): 544-553.

Spatio-Temporal Activity in Real Time (STAR): Optimization of Regional fMRI Feedback The use of real-time feedback has expanded fMRI from a brain probe to include potential brain interventions with significant therapeutic promise. However, whereas time-averaged blood oxygenation level-dependent (BOLD) signal measurement is usually sufficient for probing a brain state, the real-time (frame-to-frame) BOLD signal is noisy, compromising feedback accuracy. The authors have developed a new real-time processing technique (STAR) that combines noise-reduction properties of multi-voxel (e.g., whole-brain) techniques with the regional specificity critical for therapeutics. Nineteen subjects were given real-time feedback in a cognitive control task (imagining repetitive motor activity vs. spatial navigation), and were all able to control a visual feedback cursor based on whole-brain neural activity. The STAR technique was evaluated, retrospectively, for five a priori regions of interest in these data, and was shown to provide significantly better (frame-by-frame) classification accuracy than a regional BOLD technique. In addition to regional feedback signals, the output of the STAR technique includes spatio-temporal activity maps (movies) providing insight into brain dynamics. The STAR approach offers an appealing optimization for real-time fMRI applications requiring an anatomically-localized feedback signal. Magland JF, Tjoa CW, Childress AR. Spatio-temporal activity in real time (STAR): optimization of regional fMRI feedback. Neuroimage. 2011 Apr 1; 55(3): 1044-1053.

Aversion-Related Circuitry in the Cerebellum: Responses to Noxious Heat and Unpleasant Images The cerebellum is reliably activated during both acute and chronic pain conditions, but it is unclear whether the response to aversive painful stimuli can be generalized to other aversive stimuli. The authors hypothesized that cerebellar activation during pain reflects higher-level encoding of aversive stimuli. They used functional magnetic resonance imaging (fMRI) to compare cerebellar responses in 11 healthy volunteers to noxious heat (46 °C) applied to the hand and to the passive viewing of images selected from the International Affective Picture System. Aversive stimuli in the form of noxious heat and unpleasant pictures (unpleasant vs neutral) activated overlapping areas in the posterior cerebellum, specifically in hemispheric lobule VI, Crus I, and VIIb. Pleasant pictures (pleasant vs neutral) did not share the same pattern of activation as observed with the aversive stimuli. Cerebellar areas that showed functional overlap with both heat pain and unpleasant picture viewing were significantly inversely correlated with fMRI signals measured in limbic system structures, including the anterior hypothalamus, subgenual anterior cingulate cortex, and the parahippocampal gyrus. Heat-specific functional connectivity was detected in many regions including primary motor cortex, secondary somatosensory cortex, anterior insula, and the periaqueductal gray. The overlap between cerebellar lobuli reactive to noxious heat and passive viewing of unpleasant images suggest that the cerebellum may contain specific regions involved in encoding generalized aversive processing. The separate cortical networks suggest that noxious heat-evoked responses in the cerebellum can be divided into sensorimotor and emotional networks. Moulton EA, Elman I, Pendse G, Schmahmann J, Becerra L, Borsook D. Aversion-related circuitry in the cerebellum: responses to noxious heat and unpleasant images. J Neurosci. 2011 Mar 9; 31(10): 3795-3804.

Brain Activity and Correlates of Placebo Analgesia Recent studies have identified brain correlates of placebo analgesia, but none have assessed how accurately patterns of brain activity can predict individual differences in placebo responses. The authors reanalyzed data from two fMRI studies of placebo analgesia (N = 47), using patterns of fMRI activity during the anticipation and experience of pain to predict new subjects' scores on placebo analgesia and placebo-induced changes in pain processing. They used a cross-validated regression procedure, LASSO-PCR, which provided both unbiased estimates of predictive accuracy and interpretable maps of which regions are most important for prediction. Increased anticipatory activity in a frontoparietal network and decreases in a posterior insular/temporal network predicted placebo analgesia. Patterns of anticipatory activity across the cortex predicted a moderate amount of variance in the placebo response (~12% overall, ~40% for study 2 alone), which is substantial considering the multiple likely contributing factors. The most predictive regions were those associated with emotional appraisal, rather than cognitive control or pain processing. During pain, decreases in limbic and paralimbic regions most strongly predicted placebo analgesia. Responses within canonical pain-processing regions explained significant variance in placebo analgesia, but the pattern of effects was inconsistent with widespread decreases in nociceptive processing. Together, the findings suggest that engagement of emotional appraisal circuits drives individual variation in placebo analgesia, rather than early suppression of nociceptive processing. This approach provides a framework that will allow prediction accuracy to increase as new studies provide more precise information for future predictive models. Wager TD, Atlas LY, Leotti LA, Rilling JK. Predicting individual differences in placebo analgesia: contributions of brain activity during anticipation and pain experience. J Neurosci. 2011 Jan 12; 31(2): 439-452.

Meta Analysis of Functional Neuroimaging Data via Bayesian Spatial Point Processes As the discipline of functional neuroimaging grows there is an increasing interest in meta analysis of brain imaging studies. A typical neuroimaging meta analysis collects peak activation coordinates (foci) from several studies and identifies areas of consistent activation. Most imaging meta analysis methods only produce null hypothesis inferences and do not provide an interpretable fitted model. To overcome these limitations, the authors propose a Bayesian spatial hierarchical model using a marked independent cluster process. They model the foci as offspring of a latent study center process, and the study centers are in turn offspring of a latent population center process. The posterior intensity function of the population center process provides inference onthe location of population centers, as well as the inter-study variability of foci about the population centers. They illustrate their model with a meta analysis consisting of 437 studies from 164 publications, show how two subpopulations of studies can be compared and assess our model via sensitivity analyses and simulation studies. Kang J, Johnson TD, Nichols TE, Wager TD. Meta-analysis of functional neuroimaging data via Bayesian spatial point processes. J Am Stat Assoc. 2011 Mar 1; 106(493): 124-134.

Social Rejection Shares Somatosensory Representations with Physical Pain How similar are the experiences of social rejection and physical pain? Extant research suggests that a network of brain regions that support the affective but not the sensory components of physical pain underlie both experiences. Here the authors demonstrate that when rejection is powerfully elicited--by having people who recently experienced an unwanted break-up view a photograph of their ex-partner as they think about being rejected--areas that support the sensory components of physical pain (secondary somatosensory cortex; dorsal posterior insula) become active. The authors

demonstrate the overlap between social rejection and physical pain in these areas by comparing both conditions in the same individuals using functional MRI. They further demonstrate the specificity of the secondary somatosensory cortex and dorsal posterior insula activity to physical pin by comparing activated locations in their study with a database of over 500 published studies. Activation in these regions was highly diagnostic of physical pain, with positive predictive values up to 88%. These results give new meaning to the idea that rejection "hurts." They demonstrate that rejection and physical pain are similar not only in that they are both distressing--they share a common somatosensory representation as well. Kross E, Berman MG, Mischel W, Smith EE, Wager TD. Social rejection shares somatosensory representations with physical pain. Proc Natl Acad Sci U S A. 2011 Apr 12; 108(15): 6270-6275.

Multi-Contrast Human Neonatal Brain Atlas: Application to Normal Neonate Development Analysis MRI is a sensitive method for detecting subtle anatomic abnormalities in the neonatal brain. To optimize the usefulness for neonatal and pediatric care, systematic research, based on quantitative image analysis and functional correlation, is required. Normalization-based image analysis is one of the most effective methods for image quantification and statistical comparison. However, the application of this methodology to neonatal brain MRI scans is rare. Some of the difficulties are the rapid changes in T1 and T2 contrasts and the lack of contrast between brain structures, which prohibits accurate cross-subject image registration. Diffusion tensor imaging (DTI), which provides rich and quantitative anatomical contrast in neonate brains, is an ideal technology for normalization-based neonatal brain analysis. In this paper, the authors report the development of neonatal brain atlases with detailed anatomic information derived from DTI and co-registered anatomical MRI. Combined with a diffeo-morphic transformation, they were able to normalize neonatal brain images to the atlas space and three-dimensionally parcellate images into 122 regions. The accuracy of the normalization was comparable to the reliability of human raters. This method was then applied to babies of 37-53 post-conception weeks to characterize developmental changes of the white matter, which indicated a posterior-to-anterior and a central-to-peripheral direction of maturation. The authors expect that future applications of this atlas will include investigations of the effect of prenatal events and the effects of preterm birth or low birth weights, as well as clinical applications, such as determining imaging biomarkers for various neurological disorders. Oishi K, Mori S, Donohue PK, Ernst T, Anderson L, Buchthal S, Faria A, Jiang H, Li X, Miller I, van Zijl PC, Chang L. Multi-contrast human neonatal brain atlas: application to normal neonate development analysis. Neuroimage. 2011 May 1; 56(1): 8-20.

Mitogen-Activated Protein Kinase p38 in HIV Infection and Associated Brain Injury Infection with human immunodeficiency virus-1 (HIV-1) often leads to HIV-associated neurocognitive disorders (HAND) prior to the progression to acquired immunodeficiency syndrome (AIDS). At the cellular level, mitogen-activated protein kinases (MAPK) provide a family of signal transducers that regulate many processes in response to extracellular stimuli and environmental stress, such as viral infection. Recently, evidence has accumulated suggesting that p38 MAPK plays crucial roles in various pathological processes associated with HIV infection, ranging from macrophage activation to neurotoxicity and impairment of neurogenesis to lymphocyte apoptosis. Thus, p38 MAPK, which has generally been linked to stress-related signal transduction, may be an important mediator in the development of AIDS and HAND. Medders

KE, Kaul M. Mitogen-activated protein kinase p38 in HIV infection and associated brain injury. J Neuroimmune Pharmacol. 2011 Jun; 6(2): 202-215.

Evidence of Dopamine D3 Receptor SNP Associated with Cognitive Impairment Frequency in HIV$^+$/METH$^+$ Males Macrophages are one of HIV-1's principal targets and chiefly responsible for translocating HIV into the central nervous system (CNS). Previous research suggested an increase in macrophages being infected by HIV in the presence of methamphetamine (METH) or increased extracellular dopamine (DA). Experimental studies indicate that this is mediated by DA receptors, including DA receptor D3 (DRD3), which is expressed in macrophages. A single nucleotide polymorphism (SNP) of the DRD3 gene (rs6280TC) modulates its dopamine binding affinity, resulting in the possibility that inheriting a variant of this SNP increases macrophage susceptibility to HIV infection in the presence of METH and DA, particularly in the CNS where METH is sequestered, leading to cognitive impairment (CI). Thus, the authors conducted a retrospective clinical investigation to evaluate whether rs6280TC is associated with CI among HIV-positive METH users. They stratified 310 males by HIV serostatus (HIV-positive, -negative) and METH dependence (METH-positive, -negative) and then by rs6280TC genotype (CC, CT, and TT). Genotypic groups within each of four IV/METH groups were compared for rates of CI. They hypothesized that only HIV-positive/METH-positive carriers of the C allele, which increases the DRD3's binding to DA, would be more likely to develop CI. Cochran-Armitage test for trends in proportions yielded significant ($p < 0.05$) association between three genotypes and impairment rates in the hypothesized order, but only among HIV-positive/METH-positive subjects. The results also confirmed that C allele carriers (CC and CT, 53.3%) in this group had higher impairment rates ($p = 0.05$) than TT carriers (33.3%). These findings support the theory that rs6280TC influences the frequency of CI in HIV-positive/METH-positive males. Gupta S, Bousman CA, Chana G, Cherner M, Heaton RK, Deutsch R, Ellis RJ, Grant I, Everall IP. Dopamine receptor D3 genetic polymorphism (rs6280TC) is associated with rates of cognitive impairment in methamphetamine-dependent men with HIV: preliminary findings. J Neurovirol. 2011 Jun; 17(3): 239-247.

Misremembering Future Intentions in Methamphetamine-Dependent Individuals Methamphetamine (MA) dependence is associated with neural abnormalities (e.g., frontalsystems neurotoxicity) and corresponding cognitive deficits, including impairment in episodic memory and executive functions. This study evaluated the hypothesis that MA use is associated with impairment in memory for intentions, or prospective memory (ProM), which is an ecologically relevant aspect of episodic memory that involves the execution of a previously encoded intention at an appropriate moment in the future and is known to rely on frontal systems integrity. A total of 39 MA-dependent individuals and 26 demographically similar non-MA-using comparison participants were administered the Memory for Intentions Screening Test (MIST). The MA group performed significantly lower than the comparison participants on overall ProM, an effect that could not be better explained by demographics, psychiatric factors, infectious disease comorbidity, or other substance use disorders. The ProM impairment observed in the MA group was comparable on time- and event-based tasks and was marked by an increased rate of task substitution (i.e., intrusions) and loss of time (e.g., early responding) errors. Within the MA cohort, ProM impairment was associated with executive dysfunction and earlier age at first MA use. Findings suggest that individuals with MA dependence experience difficulty

in the strategic components involved in the retrieval of future intentions and are discussed with regard to their implications for everyday functioning. Iudicello JE, Weber E, Grant I, Weinborn M, Woods SP; HIV Neurobehavioral Research Center (HNRC) Group. Mis-remembering future intentions in methamphetamine-dependent individuals. Clin Neuropsychol. 2011 Feb; 25(2): 269-286.

Are Time- and Event-based Prospective Memory Comparably Affected in HIV Infection? According to the multi-process theory of prospective memory (ProM), time-based tasks rely more heavily on strategic processes dependent on prefrontal systems than do event-based tasks. Given the prominent frontostriatal pathophysiology of HIV infection, one would expect HIV-infected individuals to demonstrate greater deficits in time-based versus event-based ProM. However, the two prior studies examining this question have produced variable results. The authors evaluated this hypothesis in 143 individuals with HIV infection and 43 demographically similar seronegative adults (HIV-) who completed the research version of the Memory for Intentions Screening Test, which yields parallel subscales of time- and event-based ProM. Results showed main effects of HIV serostatus and cue type, but no interaction between serostatus and cue. Planned pair-wise comparisons showed a significant effect of HIV on time-based ProM and a trend-level effect on event-based ProM that was driven primarily by the subset of participants with HIV-associated neurocognitive disorders. Nevertheless, time-based ProM was more strongly correlated with measures of executive functions, attention/working memory, and verbal fluency in HIV-infected persons. Although HIV-associated deficits in time- and event-based ProM appear to be of comparable severity, the cognitive architecture of time-based ProM may be more strongly influenced by strategic monitoring and retrieval processes. Zogg JB, Woods SP, Weber E, Doyle K, Grant I; HIV Neurobehavioral Research Programs (HNRP) Group. Are time- and event-based prospective memory comparably affected in HIV infection? Arch Clin Neuropsychol. 2011 Apr; 26(3): 250-259.

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 an abridged 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.

Psychiatric Context of Human Immunodeficiency Virus Infection among Former Plasma Donors in Rural China China's HIV epidemic commenced in its agrarian provinces through contaminated commercial plasma donation centers and is now becoming a public health concern nationwide. Little is known of the psychiatric and substance use disorder characteristics of this population, or their impact on everyday function, employment, and life quality. HIV-infected (HIV^+) former plasma donors (N=203) and HIV-negative (HIV-) donor controls (N=198) completed the World Mental Health Survey Composite International Diagnostic Interview to determine lifetime major depressive disorder (MDD), substance use disorders, and suicidality. Current mood and suicidality were assessed with the Beck Depression Inventory-II. Everyday function was measured by an Activity of Daily Living questionnaire; life quality was evaluated by the Medical Outcomes Study-HIV. HIV^+ participants had known their infected status for 2 years on average. Most were taking antiretroviral treatment and had frank AIDS. Rates of current MDD were similar across groups (1-2%), but HIV^+ had a higher frequency of lifetime MDD (14% vs. 5%, $p<.05$). Its onset preceded date of known infection in one-third of cases. Alcoholism was the only substance use disorder detected; HIV^+ had a higher proportion of lifetime substance use diagnoses (14% vs. 6%, $p<.05$). Depression and AIDS independently predicted worse daily functioning and life quality, and unemployment. The epicenter of China HIV has moved into urban injection drug users, limiting the representativeness of this sample. High rates of MDD and its impact suggest that in China, as elsewhere, comprehensive care requires detection and treatment of mood disorder. Atkinson JH, Jin H, Shi C, Yu X, Duarte NA, Casey CY, Franklin DR Jr, Vigil O, Cysique L, Wolfson T, Riggs PK, Gupta S, Letendre S, Marcotte TD, Grant I, Wu Z, Heaton RK; HIV Neurobehavioral Research Center Group. Psychiatric context of human immunodeficiency virus infection among former plasma donors in rural China. J Affect Disord. 2011 May; 130(3): 421-428.

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.

Neuroimaging Insights into the Role of Cortical GABA Systems and the Influence of Nicotine on the Recovery from Alcohol Dependence This paper reviews evidence suggesting that nicotine and tobacco smoke profoundly modulate the effects of alcohol on γ-aminobutyric acid (GABA) neuronal function, specifically at the GABA(A)-benzodiazepine receptor (GABA(A)-BZR). The focus of this paper is on recent neuroimaging evidence in preclinical models as well as clinical experiments. First, the authors review findings implicating the role of alcohol at the GABA(A)-BZR and discuss the changes in GABA(A)-BZR availability during acute and prolonged alcohol withdrawal. Second, they discuss preclinical evidence that suggests nicotine affects GABA neuronal function indirectly by a primary action at neuronal nicotinic acetylcholine receptors. Third, they show how this evidence converges in studies that examine GABA levels and GABA(A)-BZRs in alcohol-dependent smokers and nonsmokers, suggesting that tobacco smoking attenuates the chemical changes that occur during alcohol withdrawal. Based on a comprehensive review of literature, the authors hypothesize that tobacco smoking minimizes the changes in GABA levels that typically occur during the acute cycles of drinking in alcohol-dependent individuals. Thus, during alcohol withdrawal, the continued tobacco smoking decreases the severity of the withdrawal-related changes in GABA chemistry. Cosgrove KP, Esterlis I, Mason GF, Bois F, O'Malley SS, Krystal JH. Neuroimaging insights into the role of cortical GABA systems and the influence of nicotine on the recovery from alcohol dependence. Neuropharmacology. 2011 Jun; 60(7-8): 1318-1325.

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.

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, Lukas SE. fMRI brain activation during a delay discounting task in HIV-positive adults with and without cocaine dependence. Psychiatry Res. 2011 Jun 30; 192(3): 167-1q75.

A Multimodal Approach to Assessing the Impact of Nicotine Dependence, Nicotine Abstinence, and Craving on Negative Affect in Smokers The authors used multimodal measurement to evaluate whether (a) nicotine dependence is associated with baseline and postquit negative affect and craving, (b) smoking relapse is associated with greater negative affect and craving than abstinence, and (c) craving is associated with negative affect. Treatment-seeking smokers were randomly assigned to either a brief behaviorally based smoking-cessation treatment condition or to a delayed treatment control condition. Participants in the treatment condition attended four assessment sessions, 4-5 days prequit (baseline), 1-2 days postquit, 3-5 days postquit, and 10-14 days postquit, while controls attended four sessions spaced over the same intervals. Retrospective questionnaires were collected at the beginning of each session, and corrugator EMG and in-session ratings were collected during viewing of affective and cigarette-related slides. The multimodal measures indicated that more dependent smokers experienced greater negative affect and craving at baseline and postquit, regardless of abstinence status. The self-report measures indicated that both relapsed and abstinent smokers reported greater negative affect and craving than control smokers. Craving was associated with negative affect across measurement modalities. These results highlight the benefits of using multimodal measures to study the impact of nicotine dependence and withdrawal on negative affect and craving. Robinson JD, Lam CY, Carter BL, Minnix JA, Cui Y, Versace F, Wetter DW, Cinciripini PM. A multimodal approach to assessing the impact of nicotine dependence, nicotine abstinence, and craving on negative affect in smokers. Exp Clin Psychopharmacol. 2011 Feb; 19(1): 40-52.

Decoding Task-Based Attentional Modulation During Face Categorization Attention is a neurocognitive mechanism that selects task-relevant sensory or mnemonic information to achieve current behavioral goals. Attentional modulation of cortical activity has been observed when attention is directed to specific locations, features, or objects. However, little is known about how high-level categorization task set modulates perceptual representations. In the current study, observers categorized faces by gender (male vs. female) or race (Asian vs. White). Each face was perceptually ambiguous in both dimensions, such that categorization of one dimension demanded selective attention to task-relevant information within the face. The authors used multivoxel pattern classification to show that task-specific modulations evoke reliably distinct spatial patterns of activity within three face-selective cortical regions (right fusiform face area and bilateral occipital face areas). This result suggests that patterns of activity in these regions reflect not only stimulus-specific (i.e., faces vs. houses) responses but also task-specific (i.e., race vs. gender) attentional modulation. Furthermore, exploratory whole-brain multivoxel pattern classification (using a searchlight procedure) revealed a network of dorsal fronto-parietal regions (left middle frontal gyrus and left inferior and superior parietal lobule) that also exhibit distinct patterns for the two task sets, suggesting that these regions may represent abstract goals during high-level categorization tasks. Chiu Y-C, Esterman M, Han Y, Rosen H, Yantis S. Decoding task-based attentional modulation during face categorization. J Cogn Neurosci. 2011 May; 23(5): 1198-1204.

Brain B2*-Nicotinic Acetylcholine Receptor Occupancy After Use of a Nicotine Inhaler The Nicotrol® (Pfizer, USA) nicotine inhaler reduces craving by mimicking the behavioral component of cigarettes and delivering controlled doses of nicotine, which binds to the beta-2 subunit-containing nicotinic acetylcholine receptors (β2*-nAChRs). Previous studies examined β2*-nAChR occupancy after administration of regular and low-nicotine cigarettes. Here, the authors measured occupancy of β2*-nAChRs after administration of nicotine via inhaler, and the relationship between occupancy and changes in craving for tobacco smoking and withdrawal symptoms. Tobacco smokers participated in [123I]5-IA-85380 SPECT studies with either a nicotine inhaler (n=9) or tobacco cigarette (n=4) challenge. [123I]5-IA was administered as a bolus plus constant infusion. After equilibrium was achieved, three 30-min baseline scans were collected, and subjects either used the nicotine inhaler or a regular cigarette, and up to six additional scans were obtained. Receptor occupancy was determined based on the Lassen plot method. Craving for tobacco smoking and withdrawal symptoms were evaluated pre- and postchallenge. Use of the nicotine inhaler produced an average 55.9±6.4% occupancy of β2*-nAChRs 2-5 h post-challenge, whereas use of a cigarette produced significantly higher receptor occupancy ($F=10.6$, $p=0.009$) with an average 67.6±14.1% occupancy 1.5-5 h post-challenge. There was a significant decrease in withdrawal symptoms post-nicotine inhaler use ($F=6.13$, $p=0.04$). These results demonstrate significant differences in occupancy of β2*-nAChRs by nicotine after use of the inhaler vs. a cigarette and confirm the ability of the nicotine inhaler to relieve withdrawal symptoms. Esterlis I, Mitsis EM, Batis JC, Bois F, Picciotto MR, Stiklus SM, Kloczynski T, Perry E, Seibyl JP, McKee S, Staley JK, Cosgrove KP. Brain β2*-nicotinic acetylcholine receptor occupancy after use of a nicotine inhaler. Int. J. Neuropsychopharmacol. 2011 Apr; 14(3): 389-398.

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. The authors provide significance levels without correction for multiple comparisons. The setting was a Field study. Participants comprised 52 illicit ecstasy users and 59 non-users, aged 18-45 years. Measurement taken included a battery of 15 neuropsychological tests tapping a range of cognitive functions. The authors 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.

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

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.

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. The authors' 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 [Epub ahead of print].

The Role of Antipsychotics in Smoking and Smoking Cessation Persons with severe and persistent mental illnesses, e.g. schizophrenia spectrum disorders and bipolar disorder, smoke at a much higher rate than the general population. Treatment options for schizophrenia spectrum disorders and bipolar disorder often include the first-generation (typical) and second-generation (atypical) antipsychotics, which have been shown to be effective in treating both psychotic and mood symptoms. This article reviews studies examining the relationship between antipsychotic medication and cigarette smoking. These studies suggest that in persons with schizophrenia and schizoaffective disorder, typical antipsychotics may increase basal smoking and decrease people's ability to stop smoking, whereas atypical antipsychotics decrease basal smoking and promote smoking cessation. However, the authors found that the data available were generally of moderate quality and from small studies, and that there were conflicting findings. The review also critically assesses a number of potential mechanisms for this effect: the use of smoking as a form of self-medication for the side effects of antipsychotics, the effect of antipsychotics on smoking-related cues and the effect of antipsychotics on the appreciation of the economic cost of smoking behaviour. Gaps in the research are noted and recommendations for further study are included. More study of this important issue is needed to clarify the effect of antipsychotics on smoking behaviours. Matthews AM, Wilson VB, Mitchell SH. The role of antipsychotics in smoking and smoking cessation. CNS Drugs. 2011 Apr; 25(4): 299-315.

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; 57(1): 69-75.

Spatial Inhibition and the Visual Cortex: A Magnetic Resonance Spectroscopy Imaging Study Deficits in processing spatial information have been observed in clinical populations who have abnormalities within the dopamine (DA) system. As psychostimulants such as methamphetamine (MA) are particularly neurotoxic to the dopaminergic system it was of interest to examine the performance of MA-dependent individuals on a task of spatial attention. 51 MA-dependent subjects and 22 age-matched non-substance abusing control subjects were tested on a Spatial Stroop attention test. MR Spectroscopy (MRS) imaging data were analyzed from 32 MA abusers and 13 controls. No group differences in response time or accuracy emerged on the behavioral task with both groups exhibiting equivalent slowing when the word meaning and the spatial location of the word were in conflict. MRS imaging data from the MA abusers revealed a strong inverse correlation between NAA/Cr ratios in the Primary Visual Cortex (PVC) and spatial interference ($p=0.0001$). Moderate inverse correlations were also seen in the Anterior Cingulate Cortex (ACC) ($p=0.02$). No significant correlations were observed in the controls, perhaps due to the small sample of imaging data available ($n=13$). The strong correlation between spatial conflict suppression and NAA/Cr levels within the PVC in the MA-dependent individuals suggests that preserved neuronal integrity within the PVC of stimulant abusers may modulate cognitive mechanisms that process implicit spatial information. Salo R, Nordahl TE, Buonocore MH, Natsuaki YT, Moore CD, Waters C, Leamon MH. Spatial inhibition and the visual cortex: a magnetic resonance spectroscopy imaging study. Neuropsychologia. 2011 Apr; 49(5): 830-838.

Connectivity-Based Segmentation of Human Amygdala Nuclei Using Probabilistic Tractography The amygdala plays an important role in emotional and social functions, and amygdala dysfunction has been associated with multiple neuropsychiatric disorders, including autism, anxiety, and depression. Although the amygdala is composed of multiple anatomically and functionally distinct nuclei, typical structural magnetic resonance imaging (MRI) sequences are unable to discern them. Thus, functional MRI (fMRI) studies typically average the BOLD response over the entire structure, which reveals some aspects of amygdala function as a whole but does not distinguish the separate roles of specific nuclei in humans. The authors developed a method to segment the human amygdala into its four major nuclei using only diffusion-weighted imaging and connectivity patterns derived mainly from animal studies. They refer to this new method as Tractography-based Segmentation, or TractSeg. The segmentations derived from TractSeg were topographically similar to their corresponding amygdaloid nuclei, and were validated against a high-resolution scan in which the nucleic boundaries were visible. In addition, nuclei topography was consistent across subjects. TractSeg relies on short scan acquisitions and widely accessible software packages, making it attractive for use in healthy populations to explore normal amygdala nucleus function, as well as in clinical and pediatric populations. Finally, it paves the way for implementing this method in other anatomical regions which are also composed of functional subunits that are difficult to distinguish with standard structural MRI. Saygin ZM, Osher DE, Augustinack J, Fischl B, Gabrieli JDE. Connectivity-based segmentation of human amygdala nuclei using probabilistic tractography. Neuroimage. 2011 Jun; 56(3): 1353-1361.

Endogenous Dopamine (DA) Competes with the Binding of a Radiolabeled D_3 Receptor Partial Agonist In Vivo: A Positron Emission Tomography Study A series of microPET imaging studies were conducted in anesthetized rhesus monkeys using the dopamine D_3-selective partial agonist, [^{18}F]5. There was variable uptake in regions of brain known to express a high density of D_3 receptors under baseline conditions. Pretreatment with lorazepam (1 mg/kg, i.v. 30 min) to reduce endogenous dopamine activity before tracer injection resulted in a dramatic increase in uptake in the caudate, putamen, and thalamus, and an increase in the binding potential (BP) values, a measure of D_3 receptor binding in vivo. These data indicate that there is a high level of competition between [^{18}F]5 and endogenous dopamine for D_3 receptors in vivo. Mach RH, Tu Z, Xu J, Li S, Jones LA, Taylor M, Luedtke RR, Derdeyn CP, Perlmutter JS, Mintun MA. Endogenous dopamine (DA) competes with the binding of a radiolabeled D_3 receptor partial agonist in vivo: a positron emission tomography study. Synapse. 2011 Aug; 65(8): 724-732.

EPIDEMIOLOGY AND ETIOLOGY RESEARCH

Probability and Predictors of Remission From Life-Time Nicotine, Alcohol, Cannabis or Cocaine Dependence: Results From The National Epidemiologic Survey On Alcohol And Related Conditions To estimate the general, and racial/ethnic specific cumulative probability of remission from nicotine, alcohol, cannabis, or cocaine dependence, and to identify predictors of remission across substances. Data were collected from structured diagnostic interviews using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV version. The 2001-2002 National Epidemiological Survey of Alcohol and Related Conditions (NESARC) surveyed a nationally representative sample from US adults (n = 43,093) selected in a three-stage sampling design. The subsamples of individuals with life-time DSM-IV diagnosis of dependence on nicotine (n = 6937), alcohol (n = 4781), cannabis (n = 530) and cocaine (n = 408). Cumulative probability estimates of dependence remission for the general population and across racial/ethnic groups. Hazard ratios for remission from dependence. Life-time cumulative probability estimates of dependence remission were 83.7% for nicotine, 90.6% for alcohol, 97.2% for cannabis and 99.2% for cocaine. Half of the cases of nicotine, alcohol, cannabis and cocaine dependence remitted approximately 26, 14, 6 and 5 years after dependence onset, respectively. Males, Blacks and individuals with diagnosis of personality disorders and history of substance use comorbidity exhibited lower hazards of remission for at least two substances. A significant proportion of individuals with dependence on nicotine, alcohol, cannabis or cocaine achieve remission at some point in their life-time, although the probability and time to remission varies by substance and racial/ethnic group. Several predictors of remission are shared by at least two substances, suggesting that the processes of remission overlap. The lower rates of remission of individuals with comorbid personality or substance use disorders highlight the need for providing coordinated psychiatric and substance abuse interventions. Lopez-Quintero C, Hasin D, de Los Cobos J, Pines A, Wang S, Grant B, Blanco C. Probability And Predictors Of Remission From Life-Time Nicotine, Alcohol, Cannabis Or Cocaine Dependence: Results From The National Epidemiologic Survey On Alcohol And Related Conditions. Addiction. 2011; 106 (3): 657-669.

Enhancing Response Inhibition By Incentive: Comparison of Adolescents With and Without Substance Use Disorder Effective response inhibition is a key component of recovery from addiction. Some research suggests that response inhibition can be enhanced through reward contingencies. The authors examined the effect of monetary incentive on response inhibition among adolescents with and without substance use disorder (SUD) using a fast event-related fMRI anti-saccade reward task. The fMRI task permits investigation of how reward (monetary incentive) might modulate inhibitory control during three task phases: cue presentation (reward or neutral trial), response preparation, and response execution. Adolescents with lifetime SUD (n=12; 100% marijuana use disorder) were gender and age-matched to healthy controls (n=12). Monetary incentive facilitated inhibitory control for SUD adolescents; for healthy controls, the difference in error rate for neutral and reward trials was not significant. There were no significant differences in behavioral performance between groups across reward and neutral trials, however, group differences in regional brain activation were identified. During the response preparation phase of reward trials, SUD adolescents, compared to controls, showed increased activation of prefrontal and oculomotor control (e.g., frontal eye field) areas, brain regions that have been associated with effective response inhibition. Results indicate differences in brain activation between SUD and control youth when preparing to inhibit a pre-potent response in the context of

reward, and support a possible role for incentives in enhancing response inhibition among youth with SUD. Chung T, Geier C, Luna B, Pajtek S, Terwilliger R, Thatcher D, Clark D. Enhancing Response Inhibition By Incentive: Comparison Of Adolescents With And Without Substance Use Disorder. Drug Alcohol Depend. 2011; 115 (1-2): 43-50.

Female Gender Predicts Lower Access and Adherence To Antiretroviral Therapy In A Setting of Free Healthcare Barriers to HIV treatment among injection drug users (IDU) are a major public health concern. However, there remain few long-term studies investigating key demographic and behavioral factors--and gender differences in particular--that may pose barriers to antiretroviral therapy (ART), especially in settings with universal healthcare. The authors evaluated access and adherence to ART in a long-term cohort of HIV-positive IDU in a setting where medical care and antiretroviral therapy are provided free of charge through a universal healthcare system. They evaluated baseline antiretroviral use and subsequent adherence to ART among a Canadian cohort of HIV-positive IDU. They used generalized estimating equation logistic regression to evaluate factors associated with 95% adherence to antiretroviral therapy estimated based on prescription refill compliance. Between May 1996 and April 2008, 545 IDU participants were followed for a median of 23.8 months (Inter-quartile range: 8.5-91.6), among whom 341 (63%) were male and 204 (37%) were female. Within the six-month period prior to the baseline interview, 133 (39%) men and 62 (30%) women were on ART (p=0.042). After adjusting for clinical characteristics as well as drug use patterns measured longitudinally throughout follow-up, female gender was independently associated with a lower likelihood of being 95% adherent to ART (Odds Ratio [OR]=0.70; 95% Confidence Interval: 0.53-0.93). Despite universal access to free HIV treatment and medical care, female IDU were less likely to access and adhere to antiretroviral therapy, a finding that was independent of drug use and clinical characteristics. These data suggest that interventions to improve access to HIV treatment among IDU must be tailored to address unique barriers to antiretroviral therapy faced by female IDU. Tapp C, Milloy M, Kerr T, Zhang R, Guillemi S, Hogg R, Montaner J, Wood E. Female Gender Predicts Lower Access And Adherence To Antiretroviral Therapy In A Setting Of Free Healthcare. BMC Infect Dis. 2011; 11: 86-93.

High Rates of Transitions to Injecting Drug Use Among Mexican American Non-Injecting Heroin Users In San Antonio, Texas (Never and Former Injectors) To assess the incidence and rate of transition to injecting among Mexican American non-injecting heroin users. In a prospective cohort study of street-recruited MA-NIU in San Antonio, Texas, 2002-2005, participants were administered structured interviews and tested for Human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). The analysis sample comprised former injection drug users (last injected >6 months ago, n=47) and those who had never injected drugs and tested HCV negative (n=219). A transition to injecting was defined as the first injection of illicit drugs since baseline interview. Transition rates were based on person-years at-risk (PYAR). Proportional hazards regression was used to estimate crude and adjusted (for significant differences between former and never injectors) hazard ratios and 95% confidence intervals of injecting history on transitioning to injecting. Sixty-three (24%) participants transitioned to injecting at a rate of 22.3/100 PYAR (95% CI: 17.2-28.2). Former-injectors were significantly more likely to transition than never injectors (43% or 20/47 vs. 20% or 43/219; p<0.001), and did so at a faster rate (40.4/100 PYAR, 95% CI: 24.6-60.0 vs. 18.5/100 PYAR, 95% CI: 13.4-24.4), with the crude HR=1.931 (95% CI: 1.116, 3.341) and adjusted

HR=2.263 (95% CI: 1.192-4.294). The rate of transitioning to injecting was high and greater among former injectors. Of particular concern is the high rate of injecting initiation among never injectors. Future analyses will examine factors associated with injecting initiation, including individual susceptibility and behaviors, social networks, and the cultural and drug market context. Valdez A, Neaigus A, Kaplan C, Cepeda A. High Rates Of Transitions To Injecting Drug Use Among Mexican American Non-Injecting Heroin Users In San Antonio, Texas (Never And Former Injectors). Drug Alcohol Depend. 2011; 114 (2-3): 233-236.

Incarceration, Sex With an STI- or HIV-Infected Partner, and Infection With an STI or HIV in Bushwick, Brooklyn, NY: A Social Network Perspective The authors examined the link between incarceration and sexually transmitted infection (STI), including HIV, from a social network perspective. They used data collected during a social network study conducted in Brooklyn, NY (n = 343), to measure associations between incarceration and infection with herpes simplex virus-2, chlamydia, gonorrhea, and syphilis or HIV and sex with an infected partner, adjusting for characteristics of respondents and their sex partners. Infection with an STI or HIV was associated with incarceration of less than 1 year (adjusted prevalence ratio [PR] = 1.33; 95% confidence interval [CI] = 1.01, 1.76) and 1 year or longer (adjusted PR = 1.37; 95% CI = 1.08, 1.74). Sex in the past 3 months with an infected partner was associated with sex in the past 3 months with 1 partner (adjusted PR = 1.42; 95% CI = 1.12, 1.79) and with 2 or more partners (adjusted PR = 1.85; 95% CI = 1.43, 2.38) who had ever been incarcerated. The results highlight the need for STI and HIV treatment and prevention for current and former prisoners and provide preliminary evidence to suggest that incarceration may influence STI and HIV, possibly because incarceration increases the risk of sex with infected partners. Khan M, Epperson M, Mateu-Gelabert P, Bolyard M, Sandoval M, Friedman S. Incarceration, Sex With An STI- Or HIV-Infected Partner, And Infection With An STI Or HIV In Bushwick, Brooklyn, NY: A Social Network Perspective. Am J Public Health. 2011; 101 (6): 1110-1117.

Marijuana But Not Alcohol Use During Adolescence Mediates the Association Between Transmissible Risk For Substance Use Disorder and Number of Lifetime Violent Offenses This study determined the extent to which alcohol and marijuana use during adolescence mediates the relation between transmissible risk for substance use disorder (SUD) and lifetime number of different types of violent offenses. The transmissible liability index was administered to 359 10–12 year old youths who were tracked to 22 years of age. Past year frequency of alcohol and marijuana consumption was longitudinally tracked to age 22 at which time lifetime violent offenses was recorded. Rate of increase in marijuana use mediated the association between transmissible risk and lifetime number of different types of violent offenses. No association was found between past year frequency of alcohol use and violent offenses. Prevention directed at lowering the psychological characteristics associated with transmissible risk for SUD may also reduce violent offending. Reynolds MD, Tarter RE, Kirisci L, Clark DB. Marijuana But Not Alcohol Use During Adolescence Mediates The Association Between Transmissible Risk For Substance Use Disorder And Number Of Lifetime Violent Offenses. Journal of Criminal Justice. 2011; 39: 218-223.

Prescription Analgesic Use among Young Adults: Adherence to Physician Instructions and Diversion The purpose of this study was to understand the extent to which medication adherence was related to diversion of prescription analgesics. The design was a cross-sectional analyses of data from the College Life Study, a prospective study of young adults. Participants were originally sampled as incoming first-time first-year college students from one large public university in the Mid-Atlantic United States. One hundred ninety-two young adults aged 21-26 who were prescribed an analgesic to treat acute pain in the past year. The study tested two competing hypotheses: 1) individuals who skip doses (under-users) are at greatest risk for diversion because they have leftover medication; and 2) individuals who over-use their prescriptions (over-users) are at greatest risk for diversion, perhaps because of a general propensity to engage in deviant behavior. Fifty-eight percent followed physician's instructions regarding their prescription analgesic medication; 27% under-used their prescribed medication and 16% over-used their prescribed medication. Twenty-seven percent of the total sample diverted their medication, with over-users being the most likely to divert (63%). Holding constant demographic characteristics and perceived harmfulness of nonmedical use, over-users were almost five times as likely as adherent users to divert analgesic medications ($P<0.05$). Further research is needed to better understand the relationship between adherence and diversion. If these findings are replicated, physicians who are involved in pain management for acute conditions among young adults should take steps to monitor adherence and reduce diversion of prescription analgesics. Arria A, Garnier-Dykstra L, Caldeira K, Vincent K, O 'Grady K. Prescription Analgesic Use Among Young Adults: Adherence To Physician Instructions And Diversion. Pain Med. 2011; 12 (6): 898-903.

Statewide Estimation of Racial/Ethnic Populations of Men Who Have Sex With Men in the U.S. Men who have sex with men (MSM) bear the greatest burden of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) in every state in the U.S., but their populations are poorly defined. The authors estimated and compared populations of MSM in 2007 by region, state, and race/ethnicity. They averaged findings from two statistical models we had previously developed to estimate the total state-specific percentage and number of males who were MSM. The models were based, respectively, on state-specific rural/ suburban/urban characteristics and an index using state-specific household census data on same-sex male unmarried partners. A third model, based on racial/ethnic ratios from a nationally representative behavioral survey, partitioned these statewide numbers by race/ethnicity.Of an estimated 7.1 million MSM residing in the U.S. in 2007, 71.4% (5.1 million) were white, 15.9% (1.1 million) were Hispanic, 8.9% (635,000) were black, 2.7% (191,000) were Asian, 0.4% (26,000) were American Indian/Alaska Native, 0.1% (6,000) were Native Hawaiian/other Pacific Islander, and 0.6% (41,000) were of multiple/unknown race/ethnicity. The overall U.S. percentage of males who were MSM (6.4%) varied from 3.3% in South Dakota to 13.2% in the District of Columbia, which we treated as a state. Estimated numbers of MSM ranged from 9,612 in Wyoming to 1,104,805 in California. Plausible estimates of MSM populations by state and race/ethnicity can inform and guide HIV/AIDS surveillance, allocation of resources, and advocacy. They can help in the planning, implementation, and evaluation of HIV prevention programs and other services. Using MSM numbers as denominators, estimates of population-based MSM HIV incidence, prevalence, and mortality rates could help clarify national and state-level epidemic dynamics. Until corroborated by other modeling and/or empirical research, these estimates should be used with caution. Lieb S, Fallon S, Friedman S, Thompson D, Gates G, Liberti T, Malow R.

Statewide Estimation Of Racial/Ethnic Populations Of Men Who Have Sex With Men In The U.S. Public Health Rep. 2011; 126 (1): 60-72.

HIV Among Drug Users at Beth Israel Medical Center, New York City, the First 25 Years New York City experienced the first and largest HIV epidemic among injecting drug users (IDUs). Using data collected from IDUs entering the Beth Israel drug detoxification program, the authors trace the history of this epidemic from the mid-1970s through the early 2000s. The epidemic can best be described in terms of successive stages: (1) introduction and rapid transmission of HIV in the IDU population; (2) stabilization of HIV prevalence at a high level (over 50%); (3) a decline in incidence and prevalence, following large-scale implementation of syringe exchange programs; and (4) a sexual transmission phase, in which HIV prevalence is approximately equal among injecting and noninjecting heroin and cocaine users, and sexual transmission is more important than injecting-related transmission among IDUs. Given the current spread of HIV among IDUs in many places in the world, New York City provides a very strong example for implementation of large-scale comprehensive syringe exchange programs as early as possible in HIV epidemics among IDUs. Des Jarlais D, Arasteh K, Friedman S. HIV Among Drug Users At Beth Israel Medical Center, New York City, The First 25 Years. Subst Use Misuse. 2011; 46 (2-3): 131-139.

Internet Health Information Seeking Behavior and Antiretroviral Adherence in Persons Living with HIV/AIDS While the Internet has the potential to educate persons living with HIV/AIDS (PLWHA), websites may contain inaccurate information and increase the risk of nonadherence with antiretroviral therapy (ART). The objectives of this study were to determine the extent to which PLWHA engage in Internet health information seeking behavior (IHISB) and to determine whether IHISB is associated with ART adherence. The authors conducted a survey of adult, English-speaking HIV-infected patients at four HIV outpatient clinic sites in the United States (Baltimore, Maryland; Detroit, Michigan; New York, and Portland, Oregon) between December 2004 and January 2006. We assessed IHISB by asking participants how much information they had received from the Internet since acquiring HIV. The main outcome was patient-reported ART adherence over the past three days. Data were available on IHISB for 433 patients, 334 of whom were on ART therapy. Patients had a mean age of 45 (standard error [SE] 0.45) years and were mostly male (66%), African American (58%), and had attained a high school degree (73%). Most (55%) reported no IHISB, 18% reported some, and 27% reported "a fair amount" or "a great deal." Patients who reported higher versus lower levels of IHISB were significantly younger, had achieved a higher level of education, and had higher medication self-efficacy. In unadjusted analyses, higher IHISB was associated with ART adherence (odds ratio [OR], 2.96, 95% confidence interval [CI] 1.27-6.94). This association persisted after adjustment for age, gender, race, education, clinic site, and medication self-efficacy (adjusted odds ratio [AOR] 2.76, 95% CI 1.11-6.87). These findings indicate that IHISB is positively associated with ART adherence even after controlling for potentially confounding variables. Future studies should investigate the ways in which Internet health information may promote medication adherence among PLWHA. Samal L, Saha S, Chander G, Korthuis P, Sharma R, Sharp V, Cohn J, Moore R, Beach M. Internet Health Information Seeking Behavior And Antiretroviral Adherence In Persons Living With Hiv/AIDS. AIDS Patient Care STDS. 2011: e-pub.

Drug Use and Receipt of Highly Active Antiretroviral Therapy Among HIV-Infected Persons In Two U.S. Clinic Cohorts Drug use and receipt of highly active antiretroviral therapy (HAART) were assessed in HIV-infected persons from the Comprehensive Care Center (CCC; Nashville, TN) and Johns Hopkins University HIV Clinic (JHU; Baltimore, MD) between 1999 and 2005. Participants with and without injection drug use (IDU) history in the CCC and JHU cohorts were evaluated. Additional analysis of persons with history of IDU, non-injection drug use (NIDU), and no drug use from CCC were performed. Activity of IDU and NIDU also was assessed for the CCC cohort. HAART use and time on HAART were analyzed according to drug use category and site of care. 1745 persons were included from CCC: 268 (15%) with IDU history and 796 (46%) with NIDU history. 1977 persons were included from JHU: 731 (35%) with IDU history. Overall, the cohorts differed in IDU risk factor rates, age, race, sex, and time in follow-up. In multivariate analyses, IDU was associated with decreased HAART receipt overall (OR = 0.61, 95% CI: [0.45-0.84] and OR = 0.58, 95% CI: [0.46-0.73], respectively for CCC and JHU) and less time on HAART at JHU (0.70, [0.55-0.88]), but not statistically associated with time on HAART at CCC (0.78, [0.56-1.09]). NIDU was independently associated with decreased HAART receipt (0.62, [0.47-0.81]) and less time on HAART (0.66, [0.52-0.85]) at CCC. These associations were not altered significantly whether patients at CCC were categorized according to historical drug use or drug use during the study period. Persons with IDU history from both clinic populations were less likely to receive HAART and tended to have less cumulative time on HAART. Effects of NIDU were similar to IDU at CCC. NIDU without IDU is an important contributor to HAART utilization. McGowan C, Weinstein D, Samenow C, Stinnette S, Barkanic G, Rebeiro P, Sterling T, Moore R, Hulgan T. Drug Use and Receipt Of Highly Active Antiretroviral Therapy Among HIV-Infected Persons In Two U.S. Clinic Cohorts. PLoS One. 2011; 6 (4): e18462-e18470.

The Effect of Neighborhood Deprivation and Residential Relocation on Long-term Injection Cessation among Injection Drug Users (IDUs) in Baltimore, Maryland The objective of this study was to determine the incidence of long-term injection cessation and its association with residential relocation and neighborhood deprivation. ALIVE (AIDS Linked to the Intravenous Experience) is a prospective cohort with semi-annual follow-up since 1988. Multi-level discrete time-to-event models were constructed to investigate individual and neighborhood-level predictors of long-term injection cessation. The study setting was Baltimore, MD, USA Participants were 1,697 active injectors from ALIVE with at least 8 semi-annual study visits. Long-term injection cessation was defined as three consecutive years without self-reported injection drug use. 706 (42%) injectors achieved long-term cessation (incidence = 7.6 per 100 person-years). After adjusting for individual-level factors, long-term injection cessation was 29% less likely in neighborhoods in the third quartile of deprivation (Hazard Ratio [HR]= 0.7, 95% CI:0.53-0.95) and 43% less likely in the highest quartile of deprivation (HR = 0.57, 95% CI:0.43, 0.76) as compared to the first quartile. Residential relocation was associated with increased likelihood of long-term injection cessation (HR = 1.55, 95% CI:1.31, 1.82); however the impact of relocation varied depending on the deprivation in the destination neighborhood. Compared to those who stayed in less deprived neighborhoods, relocation from highly deprived to less deprived neighborhoods had the strongest positive impact on long-term injection cessation (HR = 1.96, 95% CI:1.50, 2.57), while staying in the most deprived neighborhoods was detrimental (HR = 0.76, 95% CI:0.63, 0.93). Long-term cessation of injection of opiates and cocaine occurred frequently following a median of 9 years of injection and contextual factors

appear to be important. These findings suggest that improvements in the socio-economic environment may improve the effectiveness of cessation programs. Genberg B, Gange S, Go V, Celentano D, Kirk G, Latkin C, Mehta S. The Effect Of Neighborhood Deprivation And Residential Relocation On Long-Term Injection Cessation Among Injection Drug Users (IDUs) In Baltimore, Maryland. Addiction. 2011: e-pub.

Prevalence and Risk Factors For Unrecognized Obstructive Lung Disease Among Urban Drug Users Obstructive lung disease (OLD) is frequently unrecognized and undertreated. Urban drug users are at higher risk for OLD due to race, behavioral, and socioeconomic characteristics, yet little data exist on prevalence and risk factors associated with unrecognized OLD in this population. The objective of this study was to determine the prevalence of unrecognized OLD in an urban population and identify the characteristics associated with lack of physician-diagnosed OLD. Cross-sectional analysis from the Acquired Immunodeficiency Syndrome Linked to the Intravenous Experience (ALIVE) study, an observational study of current and former injection drug users in Baltimore, Maryland, USA. All participants with spirometry-defined airflow obstruction were stratified by the presence or absence of physician diagnosis of OLD. Using cross-sectional demographic, clinical, and spirometric measurements, multivariable regression models were generated to identify factors independently associated with unrecognized OLD. Of the 1083 participants evaluated in the ALIVE lung substudy, 176 (16.3%) met spirometric criteria for OLD. Of those, only 88 (50%) had a physician diagnosis of OD. The prevalence of unrecognized OLD decreased as severity of airflow obstruction increased. Factors independently associated with unrecognized OLD were absence of respiratory symptoms (prevalence ratio [PR], 1.70; 95% confidence interval [CI]: 1.29-2.23; $P < 0.01$) and less severe dyspnea (PR, 0.83; 95% CI: 0.72-0.96, per point increase in dyspnea scale; $P = 0.01$). In the subset of human immunodeficiency virus (HIV)-infected participants, the use of antiretroviral therapy (ART) was independently associated with an increased prevalence of unrecognized OLD (PR, 1.93; 95% CI: 1.05-3.56; $P = 0.03$). In a cohort of current and former urban drug users, OLD is substantially underrecognized and associated with lack of respiratory symptoms. Relying on the presence of respiratory symptoms as a trigger to perform spirometry may result in a substantial underdiagnosis of OLD in this population. HIV-infected individuals receiving ART are a population particularly vulnerable to unrecognized OLD. Drummond M, Kirk G, Astemborski J, McCormack M, Marshall M, Mehta S, Wise R, Merlo C. Prevalence And Risk Factors For Unrecognized Obstructive Lung Disease Among Urban Drug Users. Int J Chron Obstruct Pulmon Dis. 2011; 6: 89-95.

Prevalence of Sexually Acquired Antiretroviral Drug Resistance In A Community Sample Of HIV-Positive Men Who Have Sex With Men in New York City To examine antiretroviral (RV) drug resistance, we recruited a community sample (n=347) of sexually active HIV-positive men who have sex with men (MSM) in New York City, each of whom completed a structured interview and donated a blood sample for HIV genotyping. Participants reported high levels of sexual activity, with 94.6% reporting at least one sexual contact in the past month, and an average of 3.13 partners during this time. Anal intercourse was common, with 70.7% reporting at least one act of insertive anal intercourse (21% of whom reported ejaculating inside their partner without a condom) and 62.1% reporting at least one act of receptive anal intercourse during this time (22.6% of whom received ejaculate without a condom). Seventeen percent reported having sex with a woman in the past year. Although 17.4% of participants reported having ever injected

drugs, no association was found between injection and antiretroviral resistance. Average HIV diagnosis was 12.1 years prior to the interview, and 92.1% had taken ARV medication. Sexually transmitted infections (STIs) were widely reported, with 78% having been diagnosed with an STI since being diagnosed with HIV. A genotype was obtained for 188 (54.7%) of the samples and 44.7% revealed mutations conferring resistance to at least one ARV. Resistance to at least one ARV within a given class of medication was most common for nucleoside reverse transcriptase inhibitors (30.3%) and non-nucleoside reverse transcriptase inhibitors (27.7%) and least common for protease inhibitors (18.1%). The combination of high prevalence of antiretroviral resistance and risky sexual practices makes transmission between sex partners a likely mode of acquisition. Goldsamt L, Clatts M, Parker M, Colon V, Hallack R, Messina M. Prevalence Of Sexually Acquired Antiretroviral Drug Resistance In A Community Sample Of HIV-Positive Men Who Have Sex With Men In New York City. AIDS Patient Care STDS. 2011; 25 (5): 287-293.

Adherence and Plasma HIV RNA Response to Antiretroviral Therapy Among HIV-Seropositive Injection Drug Users in a Canadian Setting HIV-positive individuals who use injection drugs (IDU) may have lower rates of adherence to highly active antiretroviral therapy (ART). However, previous studies of factors associated with adherence to ART among IDU have been limited primarily to samples drawn from clinical settings and in areas with financial barriers to healthcare. The authors evaluated patterns of ART adherence and rates of plasma HIV RNA response among a Canadian cohort of community-recruited IDU. Using data from a community recruited cohort of antiretroviral-naive HIV-infected IDU, they investigated ART adherence patterns based on prescription refill compliance and factors associated with time to plasma HIV-1 RNA suppression (<500 copies/mL) using Cox proportional hazards regression in a setting with universal health care, including free ART. Between 1996 and 2008, 267 antiretroviral-naive HIV-infected IDU initiated ART and had a median of 51 months (inter-quartile range: 17-95 months) of follow-up. Overall, 81 (30.3%) were e95% adherent during the first year of HAART and 187 (70.0%) achieved HIV RNA suppression at least once over the study period, for an incidence-density of 34.5 (95% confidence interval [CI]: 29.8-39.9) per 100 person-years. The Kaplan-Meier cumulative plasma HIV RNA suppression rates at 12 months after the initiation of ART were 80.8% (95% CI: 71.2-88.7) for adherent and 28.9% (95% CI: 22.8-36.1) for non-adherent participants. While several socio-demographic characteristics and drug-using behaviours were identified as barriers to successful treatment in unadjusted analyses, the factor most strongly associated with time to HIV RNA suppression in multivariate analysis was adherence to ART of at least 95% (adjusted hazard ratio [AHR]=6.0, 95% CI: 4.2-8.6, p<0.001). These results demonstrate low rates of adherence to ART among a community-recruited cohort of IDU and reinforce the importance of adherence as the key determinant of successful virological response to antiretroviral therapy. Nolan S, Milloy M, Zhang R, Kerr T, Hogg R, Montaner J, Wood E. Adherence And Plasma HIV RNA Response To Antiretroviral Therapy Among HIV-Seropositive Injection Drug Users In A Canadian Setting. AIDS Care. 2011: 1-8.

Associations Between Subtypes of Major Depressive Episodes and Substance Use Disorders The goal of this study was to examine whether certain subtypes of major depressive episodes (MDEs)-defined by their particular constellations of symptoms-were more strongly associated with substance use disorders (SUDs), compared to other subtypes of MDEs. Participants were adults in the National Comorbidity Survey-Replication sample who met DSM criteria for at least one lifetime MDE (n=1829). Diagnostic assessments were conducted using structured

interviews. The following MDE subtypes were examined: atypical, psychomotor agitation, psychomotor retardation, melancholic, and suicidal. The results indicated that: (1) suicidal MDEs were associated with increased risk for all SUDs; (2) melancholic MDEs were associated with increased risk for alcohol use disorders; and (3) psychomotor agitation was associated with increased risk for alcohol dependence. These associations did not differ significantly by gender. Adjusting for age, the severity of the MDE, the age of onset of the first MDE, and psychiatric comorbidity did not substantially change the results. Supplemental analyses examining only diagnoses that occurred in the year prior to the assessment demonstrated a similar pattern (with MDEs characterized by psychomotor agitation being associated with drug use disorders as well). Exploratory order of onset analyses indicated that participants with lifetime MDEs and SUDs tended to report an MDE onset prior to the SUD onset, and those who experienced a suicidal MDE at some time in their lives were particularly likely to have had their first MDE prior to developing a SUD. Therefore, risk for lifetime SUDs differs according to the particular set of symptoms experienced during MDEs. Marmorstein N. Associations Between Subtypes Of Major Depressive Episodes And Substance Use Disorders. Psychiatry Res. 2011; 186 (2-3): 248-253.

A Population-Based Twin Study of the Genetic and Environmental Relationship of Major Depression, Regular Tobacco Use and Nicotine Dependence Numerous epidemiological studies have reported a positive association between major depression (MD) and regular tobacco use (RU) nicotine dependence (ND). However, few have used a genetically informative design to assess whether these traits share a common genetic and/or environmental liability. The authors assessed MD, RU and ND in same-sex twins from the population-based Swedish Twin Registry. In males, they examined both cigarette use and snus (smokeless tobacco) use. They used structural equation modeling to examine the relationship between MD, RU, and ND given RU. The results suggest modest correlations between MD and RU, and between MD and ND. In males, the liability shared between MD and RU is solely genetic for both cigarettes and snus, while MD and ND share both genetic and unique environmental influences. The continuation to ND given RU differed considerably between cigarette and snus users. In females, both MD-RU and MD-ND relationships are partially attributable to genetic and unique environmental correlations. The relationship among MD, RU and ND is at least partially attributable to shared genetic and environmental risk factors. The genetic and environmental correlations between traits are modest. The nature of the shared liability differs by sex, and in males, by the type of tobacco product used. Differences between previous reports and results presented in the current study are suggestive of population differences in how MD and tobacco use inter-relate. Edwards A, Maes H, Pedersen N, Kendler K. A Population-Based Twin Study of the Genetic and Environmental Relationship Of Major Depression, Regular Tobacco Use and Nicotine Dependnce. Psychol Med. 2011; 41 (2): 395-405.

The AVPR1A Gene and Substance Use Disorders: Association, Replication, and Functional Evidence The liability to addiction has been shown to be highly genetically correlated across drug classes, suggesting nondrug-specific mechanisms. In 757 subjects, the authors performed association analysis between 1536 single nucleotide polymorphisms (SNPs) in 106 candidate genes and a drug use disorder diagnosis (DUD). Associations (p d .0008) were detected with three SNPs in the arginine vasopressin 1A receptor gene, AVPR1A, with a gene-wise p value of 3 × 10(-5). Bioinformatic evidence points to a role for rs11174811 (microRNA binding site disruption) in AVPR1A function. Based on literature implicating AVPR1A in social bonding,

they tested spousal as a mediator of the association of rs11174811 with the DUD. Spousal satisfaction was significantly associated with DUD in males ($p < .0001$). The functional AVPR1A SNP, rs11174811, was associated with spousal satisfaction in males ($p = .007$). Spousal satisfaction was a significant mediator of the relationship between rs11174811 and DUD. We also present replication of the association in males between rs11174811 and substance use in one clinically ascertained ($n = 1399$) and one epidemiologic ($n = 2231$). The direction of the association is consistent across the clinically-ascertained samples but reversed in the epidemiologic sample. Lastly, we found a significant impact of rs11174811 genotype on AVPR1A expression in a postmortem brain sample. The findings of this study call for expansion of research into the role of the arginine vasopressin and other neuropeptide system variation in DUD liability. Maher B, Vladimirov V, Latendresse S, Thiselton D, McNamee R, Kang M, Bigdeli T, Chen X, Riley B, Hettema J, Chilcoat H, Heidbreder C, Muglia P, Murrelle E, Dick D, Aliev F, Agrawal A, Edenberg H, Kramer J, Nurnberger J, Tischfield J, Devlin B, Ferrell R, Kirillova G, Tarter R, Kendler K, Vanyukov M. The AVPR1A Gene and Substance Use Disorders: Association, Replication, and Functional Evidence. Biol Psychiatry. 2011: 1-9.

Patterns of Exchange Sex and HIV Infection in High-Risk Heterosexual Men and Women Heterosexual partnerships involving the trade of money or goods for sex are a well-described HIV risk factor in Africa and Southeast Asia, but less research has been conducted on exchange partnerships and their impact on HIV infection in the United States. In this study, men and women were recruited from high-risk risk neighborhoods in New York City through respondent-driven sampling in 2006-2007. The authors examined the factors associated with having an exchange partner in the past year, the relationship between exchange partnerships and HIV infection, and the risk characteristics of those with exchange partners by the directionality of payment. Overall, 28% of men and 41% of women had a past-year exchange partner. For men, factors independently associated with exchange partnerships were older age, more total sexual partners, male partners, and frequent non-injection drug use. For women, factors were homelessness, more total sexual partners, more unprotected sex partners, and frequent non-injection drug use. Exchange partnerships were associated with HIV infection for both men and women, although the relationships were substantially confounded by other behavioral risks. Those who both bought and sold sex exhibited the highest levels of risk with their exchange and non-exchange partners. Exchange partnerships may be an HIV risk both directly and indirectly, given the overlap of this phenomenon with other risk factors that occur with both exchange and non-exchange partners. Jenness SM, Kobrak P, Wendel T, Neaigus A, Murrill CS, Hagan H. Patterns Of Exchange Sex And HIV Infection In High-Risk Heterosexual Men And Women. J Urban Health. 2011; 88 (2): 329-341.

How Trajectories of Reasons For Alcohol Use Relate To Trajectories of Binge Drinking: National Panel Data Spanning Late Adolescence To Early Adulthood Developmental changes in both alcohol use behaviors and self-reported reasons for alcohol use were investigated. Participants were surveyed every 2 years from ages 18 to 30 as part of the Monitoring the Future national study (analytic weighted sample size N = 9,308; 53% women, 40% college attendee's). Latent growth models were used to examine correlations between trajectories of binge drinking and trajectories of self-reported reasons for alcohol use across young adulthood. Results revealed developmental changes in reasons for use and correlations between the patterns of within-person change in frequency of binge drinking and within-person

change in reasons for use. In particular, an increase in binge drinking between ages 18 and 22 was most positively correlated with slopes of using alcohol to get high and because of boredom. Continued binge drinking between ages 22 and 30 was most strongly correlated with using alcohol to get away from problems. Almost no moderation by gender, race, college attendance, employment, or marital status was found. Binge drinking and reasons for alcohol use traveled together, illustrating the ongoing and dynamic connections between changes in binge drinking and changes in reasons for use across late adolescence and early adulthood. Patrick ME, Schulenberg JE. How Trajectories Of Reasons For Alcohol Use Relate To Trajectories Of Binge Drinking: National Panel Data Spanning Late Adolescence To Early Adulthood. Dev Psychol. 2011.

Substance Use and the Risk For Sexual Intercourse With and Without a History of Teenage Pregnancy Among Adolescent Females The present study examined the associations between initiation and intensity of substance use and with sexual experience with and without a history of teenage pregnancy. Participants were high school females (weighted n = 3,451) who participated in the 1999-2003 Youth Risk Behavior Surveillance System, a cross-sectional, nationally representative survey. Multinomial multivariable logistic regression was used to assess the likelihood of being sexually experienced (but never pregnant) and teenage pregnancy (reference group: never had sexual intercourse) as a function of age at substance use initiation (i.e., age 12 or younger, 13-14 years of age, and age 15 or older) and intensity of substance use (i.e., nonuser, experimental/ new or nondaily, non-experimental/daily user) for alcohol, cigarettes, and marijuana, while controlling for race/ethnicity, metropolitan location, symptoms of depression, and illegal drug availability at school. A major finding of this study is that substance use behaviors across each substance (alcohol, cigarettes, and marijuana) independently contributed to an increased risk in sexual intercourse experience with and without a history of teenage pregnancy (vs. non-sexually experienced females). A dose-response relationship was also observed between an increased likelihood of a teenage pregnancy and marijuana behaviors. Furthermore, the risk for teenage pregnancy was compounded for daily cigarette smokers who initiated use at age 12 or younger. Screening substance use behaviors can help to identify girls who may benefit from pregnancy prevention strategies. Targeting cigarette and marijuana behaviors as early as age 12 or younger may provide an added benefit. Prevention strategies should also consider the role of race above and beyond substance use behaviors. Cavazos-Rehg P, Krauss M, Spitznagel E, Schootman M, Cottler L, Bierut L. Substance Use and the Risk For Sexual Intercourse With And Without A History Of Teenage Pregnancy Among Adolescent Females. J Stud Alcohol Drugs. 2011; 72 (2): 194-198.

A Gradient of Childhood Self-Control Predicts Health, Wealth, and Public Safety Policy-makers are considering large-scale programs aimed at self-control to improve citizens ' health and wealth and reduce crime. Experimental and economic studies suggest such programs could reap benefits. Yet, is self-control important for the health, wealth, and public safety of the population? Following a cohort of 1,000 children from birth to the age of 32 y, the authors show that childhood self-control predicts physical health, substance dependence, personal finances, and criminal offending outcomes, following a gradient of self-control. Effects of children's self-control could be disentangled from their intelligence and social class as well as from mistakes they made as adolescents. In another cohort of 500 sibling-pairs, the sibling with lower self-control had poorer outcomes, despite shared family background. Interventions addressing self-

control might reduce a panoply of societal costs, save taxpayers money, and promote prosperity. Moffitt T, Arseneault L, Belsky D, Dickson N, Hancox R, Harrington H, Houts R, Poulton R, Roberts B, Ross S, Sears M, Thomson W, Caspi A. A Gradient Of Childhood Self-Control Predicts Health, Wealth, And Public Safety. Proc Natl Acad Sci U S A. 2011; 108 (7): 2693-2698.

Developmental Trajectories of Marijuana Use From Adolescence To Adulthood: Personal Predictors The purpose of this study was to investigate the relationship between early adolescent personal characteristics and the developmental trajectories of marijuana use extending from early adolescence to adulthood. This study used a longitudinal design. Data were obtained using structured questionnaires administered by trained interviewers. Interviews were conducted in the participants ' homes in upstate New York. Participants were drawn from a randomly selected cohort and were studied prospectively since 1975 (T1) at a mean age of 6 years. The follow-up data used for this study were collected at 6 time points when the participants were aged between 14 and 37 years in 1983 (T2), 1985-1986 (T3), 1992 (T4), 1997 (T5), 2002 (T6), and 2005-2006 (T7). The outcomes were developmental trajectories of marijuana use. Semiparametric group-based modeling and logistic regression analyses were used to analyze the data. The following 5 distinct trajectories of marijuana use were identified: nonusers or experimenters, occasional users, quitters or decreasers, increasing users, and chronic users. Chronic users compared with other groups studied (nonusers or experimenters, occasional users, quitters or decreasers, and increasing users) reported low self-control, externalizing behavior, and an orientation to sensation seeking. Personal attributes of low self-control, externalizing behavior, and an orientation to sensation seeking have long-term predictive power for distinct trajectories of marijuana use over time. The importance of these findings for prevention and treatment programs is discussed. Brook J, Zhang C, Brook D. Developmental Trajectories Of Marijuana Use From Adolescence To Adulthood: Personal Predictors. Arch Pediatr Adolesc Med. 2011; 165 (1): 55-60.

Early Adolescent Cognitions As Predictors of Heavy Alcohol Use In High School The present study predicts heavy alcohol use across the high school years (aged 14 through 18) from cognitions regarding the use of alcohol assessed in middle school. Using Latent Growth Modeling, the authors examined a structural model using data from 1011 participants in the Oregon Youth Substance Use Project. In this model, social images and descriptive norms regarding alcohol use in grade 7 were related to willingness and intention to drink alcohol in grade 8 and these variables were subsequently related to the intercept and slope of extent of heavy drinking across the high school years (grades 9 through 12). Across the sample, both descriptive norms and social images influenced the intercept of heavy drinking (in the 9th grade) through willingness to drink alcohol. Multiple sample analyses showed that social images also were directly related to the intercept of heavy drinking, for girls only. Results suggest that cognitions regarding alcohol use in middle school predict subsequent heavy drinking in high school. These findings emphasize the need for prevention programs targeting changing students ' social images and encouraging a more accurate perception of peers ' use when students are in middle school. Andrews J, Hampson S, Peterson M. Early Adolescent Cognitions As Predictors Of Heavy Alcohol Use In High School. Addict Behav. 2011; 36 (5): 448-455.

Intergenerational Continuity In Child Maltreatment: Mediating Mechanisms and Implications For Prevention In the interest of improving child maltreatment prevention, this prospective, longitudinal, community-based study of 499 mothers and their infants examined (a) direct associations between mothers' experiences of childhood maltreatment and their offspring 's maltreatment, and (b) mothers' mental health problems, social isolation, and social information processing patterns (hostile attributions and aggressive response biases) as mediators of these associations. Mothers' childhood physical abuse--but not neglect--directly predicted offspring victimization. This association was mediated by mothers' social isolation and aggressive response biases. Findings are discussed in terms of specific implications for child maltreatment prevention. Berlin L, Appleyard K, Dodge K. Intergenerational Continuity In Child Maltreatment: Mediating Mechanisms And Implications For Prevention. Child Dev. 2011; 82 (1): 162-176.

Sensitive Periods For Adolescent Alcohol Use Initiation: Predicting the Lifetime Occurrence and Chronicity of Alcohol Problems In Adulthood This study examined the association between age at alcohol use onset and adult alcohol misuse and dependence by testing the sensitive-period hypothesis that early adolescence (11-14) is a vulnerable period of development during which initiating alcohol use is particularly harmful. Data came from a longitudinal panel of 808 participants recruited in 1981. Participants were followed through age 33 in 2008 with 92% retention. Onset of alcohol use before age 11 (late childhood), when compared with initiation during early adolescence, was related to an increased chronicity of adult alcohol dependence, even after accounting for sociodemographic controls and other substance use in adolescence. The present study finds no evidence that early adolescence is a particularly sensitive period for the onset of alcohol use. Findings related to the onset of regular alcohol use and the chronicity of alcohol dependence suggest that the onset of regular drinking before age 21 is problematic, but no one adolescent period is more sensitive than others. Specifically, although all age groups that started drinking regularly before age 21 had a greater rate of alcohol dependence in adulthood, initiation of regular use of alcohol at or before age 14 was not related to greater chronicity of alcohol dependence than the initiation of regular use of alcohol in middle or late adolescence. The findings suggest the importance of delaying the onset of alcohol use through prevention efforts as early as the elementary grades. In addition, prevention efforts should focus on preventing the onset of regular drinking before age 21. Guttmannova K, Bailey J, Hill K, Lee J, Hawkins J, Woods M, Catalano R. Sensitive Periods For Adolescent AlcoholUse Initiation: Predicting The Lifetime Occurrence And Chronicity Of Alcohol Problems In Adulthood. J Stud Alcohol Drugs. 2011; 72 (2): 221-331.

Symbiotic Goals and the Prevention Of Blood-Borne Viruses Among Injection Drug Users A positive-deviance control-case life history study of injection drug users (IDUs) in New York City who had injected drugs for 8-15 years compared 21 IDUs who were antibody negative for both HIV and hepatitis C with 3 infected with both viruses and 11 infected with hepatitis C virus but not HIV. Eligible subjects were referred from other research studies and from community organizations that conduct testing for HIV and hepatitis C virus. Data were collected during 2005-2008 and were analyzed using life history and grounded theory approaches. They support grounded hypotheses that IDUs who are able to attain symbiotic goals like avoiding withdrawal and maintaining social support are assisted thereby in remaining uninfected with HIV or hepatitis C. These hypotheses should be tested using cohort studies and prevention trials to see if helping

IDUs attain symbiotic goals reduces infection risk. The study's limitations are noted. Friedman S, Sandoval M, Mateu-Gelabert P, Meylakhs P, Des Jarlais D. Symbiotic Goals And The Prevention Of Blood-Borne Viruses Among Injection Drug Users. Subst Use Misuse. 2011; 46 (2-3): 307-315.

HIV Risk Behaviors Among Young Drug Using Women Who Have Sex With Women (WSWs) in New York City Previous research has suggested that multiple stressors may work in tandem to affect the health of women who have sex with women (WSWs). WSWs have been a part of the HIV epidemic in New York City since the beginning, making it an ideal setting to further explore these women's risk. Among a sample of 375 heroin, crack and/or cocaine using women recruited from economically disadvantaged communities in New York City, the authors examined HIV seroprevalence and risk behaviors among WSWs as compared to women who have sex with men only (WSMOs). They also explore differences between WSWs and WSMOs with respect to potential stressors (i.e., decreased access to resources and health care utilization and violence victimization) that might contribute overall HIV risk. The study's limitations are noted. Ompad D, Friedman S, Hwahng S, Nandi V, Fuller C, Vlahov D. HIV Risk Behaviors Among Young Drug Using Women Who Have Sex With Women (WSWS) In New York City. Subst Use Misuse. 2011; 46 (2-3): 274-284.

Changes in Time-Use and Drug Use By Young Adults In Poor Neighbourhoods of Greater Buenos Aires, Argentina, After The Political Transitions of 2001-2002: Results of a Survey In some countries, "Big Events" like crises and transitions have been followed by large increases in drug use, drug injection and HIV/AIDS. Argentina experienced an economic crisis and political transition in 2001/2002 that affected how people use their time. This paper studies how time use changes between years 2001 and 2004, subsequent to these events, were associated with drug consumption in poor neighbourhoods of Greater Buenos Aires. In 2003-2004, 68 current injecting drug users (IDUs) and 235 young non-IDUs, aged 21-35, who lived in impoverished drug-impacted neighbourhoods in Greater Buenos Aires, were asked about time use then and in 2001. Data on weekly hours spent working or looking for work, doing housework/childcare, consuming drugs, being with friends, and hanging out in the neighbourhood, were studied in relation to time spent using drugs. Field observations and focus groups were also conducted. After 2001, among both IDUs and non-IDUs, mean weekly time spent working declined significantly (especially among IDUs); time spent looking for work increased, and time spent with friends an hanging out in the neighbourhood decreased. The authors found no increase in injecting or non-injecting drug consumption after 2001. Subjects most affected by the way the crises led to decreased work time and/or to increased time looking for work--and by the associated increase in time spent in one's neighbourhood--were most likely to increase their time using drugs. Time use methods are useful to study changes in drug use and their relationships to everyday life activities. In these previously-drug-impacted neighbourhoods, the Argentinean crisis did not lead to an increase in drug use, which somewhat contradicts our initial expectations. Nevertheless, those for whom the crises led to decreased work time, increased time looking for work, and increased time spent in indoor or outdoor neighbourhood environments, were likely to spend more time using drugs. These data suggest that young adults in traditionally less-impoverished neighbourhoods may be more vulnerable to Big Events than those in previously drug-impacted impoverished neighbourhoods. Since Big Events will continue to occur, research on the pathways that determine their sequelae is needed. Rossi D, Zunino Singh

D, Pawlowicz M, Touzé G, Bolyard M, Mateu-Gelabert P, Sandoval M, Friedman S. Changes In Time-Use And Drug Use By Young Adults In Poor Neighbourhoods Of Greater Buenos Aires, Argentina, After The Political Transitions Of 2001-2002: Results Of A Survey. Harm Reduct J. 2011; 8 (1): 2-11.

Past Year Treatment Status and Alcohol Abuse Symptoms Among US Adults with Alcohol Dependence The authors tested whether the number and type of alcohol abuse symptoms were associated with an increased likelihood of treatment seeking among respondents with alcohol dependence. Data from 4027 adult respondents from 2006 and 2007 National Survey on Drug Use and Health (NSDUH) who met DSM-IV criteria for the past year alcohol dependence were used. Respondents were classified according to the number of past year alcohol abuse symptoms endorsed, as well as type of abuse symptom. Associations were estimated using weighted multivariate logistic regressions that controlled for severity of alcohol dependence, other drug use disorders and other characteristics. Twenty-eight percent of individuals with alcohol dependence had one alcohol abuse symptom, 20% had two and 19% had three or four. Individuals with more alcohol abuse symptoms differed from those without alcohol abuse symptoms in a number of sociodemographic characteristics and severity of alcohol and drug dependence. Even after adjusting for these factors, individuals with three or four alcohol abuse symptoms had 2.67 times increased odds of treatment seeking, as compared to those without alcohol abuse symptoms [95% CI=1.65-4.30]. However, individuals with one or two alcohol abuse symptoms were no more likely to seek treatment than those without alcohol abuse symptoms. A majority of those with one or two alcohol abuse symptoms endorsed the hazardous abuse symptom. Alcohol abuse symptoms are important factors for treatment seeking in individuals with alcohol dependence, but only among certain subset of individuals with three or four alcohol abuse symptoms. Examining structural and psychosocial differences across these subgroups may help inform and reduce barriers to treatment seeking among this population. Kuramoto S, Martins S, Ko J, Chilcoat H. Past Year Treatment Status And Alcohol Abuse Symptoms Among US Adults With Alcohol Dependence. Addict Behav. 2011; 36 (6): 648-653.

The Tobacco Dependence Dimension in Colombia This epidemiological study of a sample of smokers from the general population of Colombia examined the population distribution and dimensionality of eight hypothesized inter-correlated clinical features (CFs) associated with tobacco dependence syndrome (TDS). Data were drawn from interviews of 4,426 smokers conducted in a national survey in Colombia as part of the World Mental Health Survey Initiative. Daily smokers completed a Spanish-language TDS module, and the 237 smokers who had begun smoking during the five years prior to the assessment were selected. Confirmatory factor analysis (CFA) for a unidimensional TDS provided discrimination and difficulty parameter estimates. Two CFs that were reported very infrequently among the study sample were dropped from the CFA. Among the six remaining CFs, discrimination (D1) estimates ranged from 1.1 to 6.0 and difficulty (D2) estimates ranged from 1.1 to 2.2, providing evidentiary support for a unidimensional tobacco dependence construct. The Spanish-language TDS module used in this study could serve as a valuable tool in future studies for evaluating public health outreach and early intervention programs directed toward community residents who have begun smoking tobacco. Posada-Villa J, Cheng H, Martins S, Storr C, Aguilar-Gaxiola S, Anthony J. The Tobacco Dependence Dimension In Colombia. Rev Panam Salud Publica. 2011; 29 (1): 52-56.

Stability and Change in Self-Reported Sexual Orientation Identity in Young People: Application of Mobility Metrics This study investigated stability and change in self-reported sexual orientation identity over time in youth. The authors describe gender- and age-related changes in sexual orientation identity from early adolescence through emerging adulthood in 13,840 youth ages 12-25 employing mobility measure M, a measure the authors modified from its original application for econometrics. Using prospective data from a large, ongoing cohort of U.S. adolescents, the authors examined mobility in sexual orientation identity in youth with up to four waves of data. Ten percent of males and 20% of females at some point described themselves as a sexual minority, while 2% of both males and females reported ever being "unsure" of their orientation. Two novel findings emerged regarding gender and mobility: (1) Although mobility scores were quite low for the full cohort, females reported significantly higher mobility than did males. (2) As expected, for sexual minorities, mobility scores were appreciably higher than for the full cohort; however, the gender difference appeared to be eliminated, indicating that changing reported sexual orientation identity throughout adolescence occurred at a similar rate in female and male sexual minorities. In addition, the authors found that, of those who described themselves as "unsure" of their orientation identity at any point, 66% identified as completely heterosexual at other reports and never went on to describe themselves as a sexual minority. Age was positively associated with endorsing a sexual-minority orientation identity. The authors discuss substantive and methodological implications of theser findings for understanding development of sexual orientation identity in young people. Ott M, Corliss H, Wypij D, Rosario M, Austin S. Stability And Change In Self-Reported Sexual Orientation Identity In Young People: Application Of Mobility Metrics. Arch Sex Behav. 2011; 40 (3): 519-532.

Epidemiology of HIV Infection in the United States: Implications for Linkage to Care The epidemiology of human immunodeficiency virus (HIV) infection in the United States has changed significantly over the past 30 years. HIV/acquired immune deficiency syndrome (HIV/AIDS) is currently a disease of greater demographic diversity, affecting all ages, sexes, and races, and involving multiple transmission risk behaviors. At least 50,000 new HIV infections will continue to be added each year; however, one-fifth of persons with new infections may not know they are infected, and a substantial proportion of those who know they are infected are not engaged in HIV care. Barriers to early engagement in care may be specific to a demographic group. In this paper, the current epidemiology of HIV/AIDS in the United States is reviewed in order to understand the challenges, successes, and best practices for removing the barriers to effective diagnosis and receipt of HIV care within specific demographic groups. Moore R. Epidemiology Of HIV Infection In The United States: Implications For Linkage To Care. Clin Infect Dis. 2011; 52 (Suppl 2): S208-S213.

HIV Infection in the Etiology of Lung Cancer: Confounding, Causality, and Consequences Persons infected with HIV have an elevated risk of lung cancer, but whether the increase simply reflects a higher smoking prevalence continues to be debated. This review summarizes existing data on the association of HIV infection and lung cancer, with particular attention to study design and adjustment for cigarette smoking. Potential mechanisms by which HIV infection may lead to lung cancer are discussed. Finally, irrespective of causality and mechanisms, lung cancer represents an important and growing problem confronting HIV-infected patients and their providers. Substantial efforts are needed to promote smoking cessation and to control lung cancer among HIV-infected populations. Kirk G, Merlo C, Merlo C. HIV Infection In The

Etiology Of Lung Cancer: Confounding, Causality, And Consequences. Proc Am Thorac Soc. 2011; 8 (3): 326-332.

Middle-Aged and Older Men Who Have Sex With Men Exhibit Multiple Trajectories With Respect to the Number of Sexual Partners This study aimed to examine trajectories with respect to the number of sexual partners among older men who have sex with men and to determine characteristics associated with trajectory groups. Nagin's group-based modeling was used to identify trajectories for 237 men from the Pitt Men's Study with respect to the number of male intercourse partners from age 50.0 to 59.5. Three distinct trajectory groups were identified. Most men (69.2%) had a median of two sexual partners in the past 6 months across the age range of the study. A smaller group (19.4%) had low or no sex partners. The smallest group (11.4%) had 30 or more sexual partners in the past 6 months at age 50. The groups were statistically different with respect to race, HIV status, drug use (marijuana, poppers, crack cocaine, and Viagra), the number of unprotected anal sex partners, and personal attitudes towards sex. Lim S, Christen C, Marshal M, Stall R, Markovic N, Kim K, Silvestre A. Middle-Aged And Older Men Who Have Sex With Men Exhibit Multiple Trajectories With Respect To The Number Of Sexual Partners. AIDS Behav. 2011: e-pub.

HIV Seroadaptation Among Individuals, Within Sexual Dyads, and By Sexual Episodes, Men Who Have Sex With Men, San Francisco, 2008 "Seroadaptation" comprises sexual behaviors to reduce the risk of HIV acquisition and transmission based on knowing one's own and one's sexual partners' serostatus. The authors measured the prevalence of seroadaptive behaviors among men who have sex with men (MSM) recruited through time-location sampling (TLS) across three perspectives: by individuals (N = 1207 MSM), among sexual dyads (N = 3746 partnerships), and for sexual episodes (N = 63,789 episodes) in the preceding six months. Seroadaptation was more common than 100% condom use when considering the consistent behavioral pattern of individuals (adopted by 39.1% vs. 25.0% of men, respectively). Among sexual dyads 100% condom use was more common than seroadaptation (33.1% vs. 26.4%, respectively). Considering episodes of sex, not having anal intercourse (65.0%) and condom use (16.0%) were the most common risk reduction behaviors. Sex of highest acquisition and transmission risks (unprotected anal intercourse with a HIV serodiscordant or unknown status partner in the riskier position) occurred in only 1.6% of sexual episodes. In aggregate, MSM achieve a high level of sexual harm reduction through multiple strategies. Detailed measures of seroadaptive behaviors are needed to effectively target HIV risk and gauge the potential of serosorting and related sexual harm reduction strategies on the HIV epidemic. McFarland W, Chen Y, Raymond H, Nguyen B, Colfax G, Mehrtens J, Robertson T, Stall R, Levine D, Truong H. HIV Seroadaptation Among Individuals, Within Sexual Dyads, And By Sexual Episodes, Men Who Have Sex With Men, San Francisco, 2008. AIDS Care. 2011; 23 (3): 261-268.

Resilience As An Untapped Resource In Behavioral Intervention Design For Gay Men Men who have sex with men experience high rates of psychosocial health problems such as depression, substance use, and victimization that may be in part the result of adverse life experiences related to cultural marginalization and homophobia. These psychosocial health conditions interact to form a syndemic which may be driving HIV risk within this population. However, MSM also evidence great resilience to both the effects of adversity and the effects of syndemics. Investigating and harnessing these natural strengths and resiliencies may enhance

HIV prevention and intervention programs thereby providing the additional effectiveness needed to reverse the trends in HIV infection among MSM. Herrick A, Lim S, Wei C, Smith H, Guadamuz T, Friedman M, Stall R. Resilience As An Untapped Resource In Behavioral Intervention Design For Gay Men. AIDS Behav. 2011; 15 Suppl 1: S25-S29.

Sex While Intoxicated: A Meta-Analysis Comparing Heterosexual and Sexual Minority Youth The social marginalization and victimization experienced by sexual minority youth (SMY) may lead to increased risk behaviors and higher rates of negative health outcomes compared with their heterosexual peers. The authors conducted a meta-analysis to examine whether SMY reported higher rates of sex while intoxicated. Studies that report rates of substance use during sex in both SMY and heterosexual youth and had a mean participant age of 18 or less were included in our meta-analysis. Effect sizes were extracted from six studies (nine independent data sets and 24 effect sizes) that met study criteria and had high inter-rater reliability (.98). Results indicated that SMY were almost twice as likely to report sex while intoxicated as compared with heterosexual peers. A random-effects meta-analysis showed a moderate ([overall weighted effect OR] = 1.91, $p < .0001$) weighted effect size for the relationship between sexual orientation and the use of drugs at the time of sexual intercourse, with the mean effect size for each study ranging from 1.21 to 3.50 and individual effect sizes ranging from .35 to 9.86. These findings highlight the need for healthcare providers to screen SMY for participation in substance use during sexual intercourse and to offer risk reduction counseling during office visits. Herrick A, Marshal M, Smith H, Sucato G, Stall R. Sex While Intoxicated: A Meta-Analysis Comparing Heterosexual And Sexual Minority Youth. J Adolesc Health. 2011; 48 (3): 306-309.

Accelerated Transition to Injection Among Male Heroin Initiates in Hanoi, Vietnam: Implications for Early Harm Reduction Interventions This paper examines changes in the interval between first heroin smoking and onset of injection in a large, out-treatment sample of male heroin users in Hanoi, Vietnam (n = 1,115). Mean age at initiation of heroin use (smoking) was 18.4 and mean age of onset of heroin injection was 20.9 years. Full multivariate analysis indicates that the interval between first heroin use (smoking) and first heroin injection has been significantly attenuated among more recent heroin initiates ($P = 0.0043$), suggesting that heroin users in Vietnam may be at increased risk for exposure to HIV relatively soon after onset of heroin use, highlighting the need for behavioral interventions that target heroin smokers. Critical intervention goals include delaying the onset of injection and improved education about safer drug sharing and drug injection practices. Clatts M, Goldsamt L, Minh Giang L, Colón-López V. Accelerated Transition To Injection Among Male Heroin Initiates In Hanoi, Vietnam: Implications For Early Harm Reduction Interventions. J Community Health. 2011: e-pub.

A Random Effects Branch-Site Model For Detecting Episodic Diversifying Selection Adaptive evolution frequently occurs in episodic bursts, localized to a few sites in a gene, and to a small number of lineages in a phylogenetic tree. A popular class of "branch-site" evolutionary models provides a statistical framework to search for evidence of such episodic selection. For computational tractability current branch-site models unrealistically assume that all branches in the tree can be partitioned a priori into two rigid classes - "foreground" branches which are allowed to undergo diversifying selective bursts, and "background" branches which are negatively selected or neutral. The authors demonstrate that this assumption leads to

unacceptably high rates of false positives or false negatives when the evolutionary process along background branches strongly deviates from modeling assumptions. To address this problem, they extend Felsenstein's pruning algorithm to allow efficient likelihood computations for models in which variation over branches (and not just sites) is described in the random effects likelihood (REL) framework. This enables the authors to model the process at every branch-site combination as a mixture of three Markov substitution models - our model treats the selective class of every branch at a particular site as an unobserved state that is chosen independently of that at any other branch. When benchmarked on a previously published set of simulated sequences, our method consistently matched or outperformed existing branch-site tests in terms of power and error rates. Using three empirical datasets, previously analyzed for episodic selection, the authors discuss how modeling assumptions can influence inference in practical situations. Kosakovsky Pond S, Murrell B, Fourment M, Frost S, Delport W, Scheffler K. A Random Effects Branch-Site Model For Detecting Episodic Diversifying Selection. Mol Biol Evol. 2011: e-pub.

Subgroups Analysis when Treatment and Moderators are Time-varying Prevention scientists are often interested in understanding characteristics of participants that are predictive of treatment effects because these characteristics can be used to inform the types of individuals who benefit more or less from treatment or prevention programs. Often, effect moderation questions are examined using subgroups analysis or, equivalently, using covariate × treatment interactions in the context of regression analysis. This article focuses on conceptualizing and examining causal effect moderation in longitudinal settings in which both treatment and the putative moderators are time-varying. Studying effect moderation in the time-varying setting helps identify which individuals will benefit more or less from additional treatment services on the basis of both individual characteristics and their evolving outcomes, symptoms, severity, and need. Examining effect moderation in these longitudinal settings, however, is difficult because moderators of future treatment may themselves be affected by prior treatment (for example, future moderators may be mediators of prior treatment). This article introduces moderated intermediate causal effects in the time-varying setting, describes how they are part of Robins' Structural Nested Mean Model, discusses two problems with using a traditional regression approach to estimate these effects, and describes a new approach (a two-stage regression estimator) to estimate these effects. The methodology is illustrated using longitudinal data to examine the time-varying effects of receiving community-based substance abuse treatment as a function of time-varying severity (or need). Almirall D, McCaffrey D, Ramchand R, Murphy S. Subgroups Analysis When Treatment And Moderators Are Time-Varying. Prev Sci. 2011: e-pub.

Dose-Response Effect Of Incarceration Events On Non-Adherence To HIV Antiretroviral Therapy Among Injection Drug Users Although some studies have identified impressive clinical gains for incarcerated HIV-seropositive injection drug users (IDUs) undergoing antiretroviral therapy (ART), the effect of incarceration on adherence to ART remains undetermined. The authors used data from a long-term community-recruited cohort of HIV-seropositive IDUs, including comprehensive ART dispensation records, in a setting where HIV care is free.They estimated the relationship between the cumulative burden of incarceration, measured longitudinally, and the odds of < 95% adherence to ART, with use of multivariate modeling. From 1996 through 2008, 490 IDUs were recruited and contributed 2220 person-years of follow-up; 271 participants (55.3%) experienced an incarceration episode, with the number of

incarcerations totaling 1156. In a multivariate model, incarceration had a strong dose-dependent effect on the likelihood of nonadherence to ART: 1-2 incarceration events (adjusted odds ratio [AOR], 1.49; 95% confidence interval [95% CI], 1.03-2.05), 3-5 events (AOR, 2.48; 95% CI, 1.62-3.65), and > 5 events (AOR, 3.11; 95% CI, 1.86-4.95). Among HIV-seropositive IDUs receiving ART, an increasing burden of incarceration was associated with poorer adherence in a dose-dependent fashion. These findings support improved adherence support for HIV-seropositive IDUs experiencing incarceration. Milloy M, Kerr T, Buxton J, Rhodes T, Guillemi S, Hogg R, Montaner J, Wood E. Dose-Response Effect Of Incarceration Events On Nonadherence To HIV Antiretroviral Therapy Among Injection Drug Users. J Infect Dis. 2011; 203 (9): 1215-1221.

Racial/Ethnic Differences In the Relationship Between Parental Education and Substance Use Among U.S. 8th-, 10th-, And 12th-Grade Students: Findings From The Monitoring The Future Project Secondary school students' rates of substance use vary significantly by race/ethnicity and by their parents ' level of education (a proxy for socioeconomic status). The relationship between students' substance use and race/ethnicity is, however, potentially confounded because parental education also differs substantially by race/ethnicity. This report disentangles the confounding by examining White, African American, and Hispanic students separately, showing how parental education relates to cigarette smoking, heavy drinking, and illicit drug use. Data are from the 1999-2008 Monitoring the Future nationally representative in-school surveys of more than 360,000 students in Grades 8, 10, and 12. Results were (a) High proportions of Hispanic students have parents with the lowest level of education, and the relatively low levels of substance use by these students complicates total sample data linking parental education and substance use. (b) There are clear interactions: Compared with White students, substance use rates among African American and Hispanic students are less strongly linked with parental education (and are lower overall). (c) Among White students, 8th and 10th graders show strong negative relations between parental education and substance use, whereas by 12th grade their heavy drinking and marijuana use are not correlated with parental education. Low parental education appears to be much more of a risk factor for White students than for Hispanic or African American students. Therefore, in studies of substance use epidemiology, findings based on predominantly White samples are not equally applicable to other racial/ethnic subgroups. Conversely, the large proportions of minority students in the lowest parental education category can mask or weaken findings that are clearer among White students alone. Bachman J, O 'Malley P, Johnston L, Schulenberg J, Wallace J. Racial/Ethnic Differences In The Relationship Between Parental Education And Substance Use Among U.S. 8th-, 10th-, And 12th-Grade Students: Findings From The Monitoring The Future Project. J Stud Alcohol Drugs. 2011; 72 (2): 279-285.

Exercise and Substance Use Among American Youth, 1991-2009 The National Institute on Drug Abuse has called for increased research into the use of physical activity in substance abuse prevention, specifically research into physical activity type and context. This paper examines the relationships between (1) secondary school student substance use and (2) exercise in general and school athletic team participation, and examines such relationships over time. Nationally representative cross-sectional samples of 8th-, 10th-, and 12th-grade students were surveyed each year from 1991 to 2009. Substance use measures included past 2-week binge drinking and past 30-day alcohol, cigarette, smokeless tobacco, marijuana, and steroid use. Analyses were

conducted during 2009-2010. Across grades, higher levels of exercise were associated with lower levels of alcohol, cigarette, and marijuana use. Higher levels of athletic team participation were associated with higher levels of smokeless tobacco use and lower levels of cigarette and marijuana use across grades and to higher levels of high school alcohol and steroid use. Exercise helped suppress the undesired relationship between team participation and alcohol use; exercise and athletic team participation worked synergistically in lowering cigarette and marijuana use. Observed relationships were generally stable across time. There appear to be substantive differences between exercise and team sport participation in relation to adolescent substance use. These findings from cross-sectional data suggest that interventions to improve levels of general physical activity should be evaluated to determine if they help delay or reduce substance use among youth in general as well as among student athletes. Terry-McElrath Y, O 'Malley P, Johnston L. Exercise And Substance Use Among American Youth, 1991-2009. Am J Prev Med. 2011; 40 (5): 530-540.

Applying Experience Sampling Methods to Partner Violence Research: Safety and Feasibility in a 90-Day Study of Community Women An experience sampling method (ESM) rarely has been applied in studies of intimate partner violence (IPV) despite the benefits to be gained. Because ESM approaches and women who experience IPV present unique challenges for data collection, an empirical question exists: Is it safe and feasible to apply ESM to community women who currently are experiencing IPV? A 90-day, design-driven feasibility study examined daily telephone data collection, daily paper diaries, and monthly retrospective semi-structured interview methods among a community sample of 123 women currently experiencing IPV to study within-person relationships between IPV and substance use. Findings suggest that ESM is a promising method for collecting data among this population and can elucidate daily dynamics of victimization as well as associated behaviors and experiences. Lessons learned from the application of ESM to this population are also discussed. Sullivan T, Khondkaryan E, Dos Santos N, Peters E. Applying Experience Sampling Methods To Partner Violence Research: Safety And Feasibility In A 90-Day Study Of Community Women. Violence Against Women. 2011; 17 (2): 251-266.

Prognostic Utility of Serum Potassium in Chronic Digoxin Toxicity: A Case-Control Study In contrast to patients with acute digoxin overdose, the prognostic utility of the serum potassium concentration for patients with chronic digoxin toxicity is unclear. In such patients, the authors aimed to evaluate the relationship between pre-treatment serum potassium and survival. This was a case-control study at an urban Poison Control Center affiliated with a large urban medical center. They compared the serum potassium concentration between patients with chronic digoxin toxicity resulting in fatality (cases) over a 7-year period (2000-2006) versus survivors (controls) over a 1-year period (2007-2008). During the study period, there were 13 fatalities (cases) and 13 survivors (controls), of whom seven cases and five controls received appropriately dosed digoxin-specific antibody Fab fragments (Fab). There were no statistically significant differences between cases and controls with respect to serum digoxin concentration, creatinine, age, or sex. Serum potassium elevation pre-Fab was significantly associated with fatality both in mean difference ($p < 0.03$) and using a dichotomous cutoff of 5.0 mEq/L ($p < 0.001$), which performed with 92% sensitivity (95% CI 67, 99). In 86% of deaths despite appropriate Fab administration, the clinical presentation included the combination of bradycardia plus hyperkalemia. In these patients with chronic digoxin toxicity, elevated serum potassium was associated with fatality.

The combination of bradycardia and hyperkalemia strongly predicted fatality even in cases with appropriate Fab administration. Manini A, Nelson L, Hoffman R. Prognostic Utility Of Serum Potassium In Chronic Digoxin Toxicity: A Case-Control Study. Am J Cardiovasc Drugs. 2011; 11 (3): 173-178.

Understanding Subtypes of Inner-City Drug Users with a Latent Class Approach The authors empirically identified subtypes of inner-city users of heroin and cocaine based on type of drug used and route of administration. The sample was recruited from the communities in Baltimore, MD (SHIELD study) and consisted of 1061 participants who used heroin and or cocaine in the past 6 months on a weekly basis or more. Latent class analysis (LCA) was used to identify subtypes of drug users based on type of drug and route of administration. Logistic regression was used to compare the subtypes on depressive symptoms, injection risk and drug network compositions. Inner-city drug users were classified into five subtypes: three subtypes of injection drug users (IDUs) [heroin injecting (n=134; 13%), polydrug and polyroute (n=88, 8%), and heroin and cocaine injecting (n=404, 38%)], and two subtypes with low proportions of IDUs (LIDUs) [heroin snorting (n=275, 26%) and crack smoking (n=160; 14%)]. The polydrug and polyroute subtype had the highest depressive symptoms risk among all subtypes. Injection risk was lowest in the heroin injecting subtype and significantly differed from heroin and cocaine injecting subtype. The IDU subtypes also varied in the drug network compositions. The LIDU subtypes had similar depressive symptoms risk but vastly differed in the drug network compositions. Subgroups of inner-city cocaine and heroin users based on type and route of administration differed in their depressive symptoms, injection risk and drug network compositions. Future studies should longitudinally examine factors associated with transitioning across these subtypes to better inform prevention and treatment efforts. Kuramoto S, Bohnert A, Latkin C. Understanding Subtypes Of Inner-City Drug Users With A Latent Class Approach. Drug Alcohol Depend. 2011: 1-7.

Childhood Physical Punishment and the Onset of Drinking Problems: Evidence from Metropolitan China Evidence in support of a suspected causal association linking childhood physical punishment (CPP) and later alcoholic beverage-related disturbances has been found in metropolitan China. Here, the focus shifts to the CPP association with the estimated risk of starting to drink, having the first drinking problem, and transitioning from first drink to the first drinking problem. Data are from the World Mental Health Surveys-metropolitan China study, with representative samples of adult household residents living in two metropolitan cities, Beijing and Shanghai. Recalled information was available for early life experiences (including CPP, other childhood adversities, and parental alcohol and drug problems), as well as the onset age of drinking and drinking problems. Survival analyses were used to estimate the Hazard Ratio. A structural equation modeling approach was used to control for other inter-correlated childhood adversities. Cox proportional hazards modeling discloses statistically robust associations linking CPP with drinking and drinking problems, as well as more rapid transitions from first drink to first drinking problem, even after accounting for other childhood adversities and parental drinking problems. These associations cannot be attributed to a more general noxious family environment. These results lay a foundation for future experimental studies on the possible causal relationship linking CPP with the onset of drinking problems and the transition from drinking to drinking problems. Cheng H, Anthony J, Huang Y, Lee S, Liu Z, He

Y. Childhood Physical Punishment And The Onset Of Drinking Problems: Evidence From Metropolitan China. Drug Alcohol Depend. 2011: 1-9.

PREVENTION RESEARCH

When to Intervene: Elementary School, Middle School, or Both? This article presents the findings of a study exploring two questions: What age is most efficacious to expose Mexican heritage youth to drug abuse prevention interventions, and what dosage of the prevention intervention is needed? These issues are relevant to Mexican heritage youth-many from immigrant families-in particular ways due to the acculturation process and other contextual factors. The study utilized growth curve modeling to investigate the trajectory of recent substance use (alcohol, cigarettes, marijuana, inhalants) among Mexican heritage students (N = 1,670) participating in the Keepin it REAL drug prevention program at different developmental periods: the elementary school (5th grade), middle school (7th grade), or both. The findings provide no evidence that intervening only in elementary school was effective in altering substance use trajectories from 5th to 8th grade, neither for licit nor illicit substances. Implementing Keepin it REAL in middle school alone altered the trajectories of use of all four substances for Mexican heritage youth. A double dose of prevention in elementary and middle schools proved to be equally as effective as intervening in 7th grade only, and only for marijuana and inhalants. The decrease in use of marijuana and inhalants among students in the 7th-grade-only or the 5th- and 7th-grade interventions occurred just after students received the curriculum intervention in 7th grade. These results are interpreted from an eco-developmental and culturally specific perspective and recommendations for prevention and future research are discussed. Marsiglia FF, Kulis S, Yabiku ST, Nieri TA, Coleman E. When To Intervene: Elementary School, Middle School Or Both? Effects Of Keepin It REAL On Substance Use Trajectories Of Mexican Heritage Youth. Prev Sci. 2011; 12 (1): 48-62.

Preventing Substance Misuse through Community-University Partnerships: Randomized Controlled Trial Outcomes 4½ Years Past Baseline Substance misuse by adolescents and related health issues constitute a major public health problem. Community-based partnership models designed for sustained, quality implementation of proven preventive interventions have been recommended to address this problem. There is very limited longitudinal study of such models. The purpose of this study was to examine the long-term findings from an RCT of a community-university partnership model designed to prevent substance misuse and related problems. A cohort sequential design included 28 public school districts in rural towns and small cities in Iowa and Pennsylvania that were randomly assigned to community-university partnership or usual-programming conditions. At baseline, 11,960 students participated, across two consecutive cohorts. Data were collected from 2002 to 2008. Partnerships supported community teams that implemented universal, evidence-based interventions selected from a menu. The selected family-focused intervention was implemented with 6th-grade students and their families; school-based interventions were implemented during the 7th grade. Observations demonstrated intervention implementation fidelity. Outcome measures were lifetime, past-month, and past-year use of a range of substances, as well as indices of gateway and illicit substance use; they were administered at baseline and follow-ups, extending to 4.5 years later. Intent-to-treat, multilevel ANCOVAs of point-in-time use at 4.5 years past baseline were conducted, with supplemental analyses of growth in use. Data were analyzed in 2009. Results showed significantly lower substance use in the intervention group for 12 of 15 point-in-time outcomes, with relative reductions of up to 51.8%. Growth trajectory analyses showed significantly slower growth in the intervention group for 14 of 15 outcomes. Partnership-based

implementation of brief universal interventions has potential for public health impact by reducing growth in substance use among youth; a multistate network of partnerships is being developed. Notably, the tested model is suitable for other types of preventive interventions. Spoth R, Redmond C, Clair S, Shin C, Greenberg M, Feinberg M. Preventing Substance Misuse Through Community-University Partnerships: Randomized Controlled Trial Outcomes 4½ Years Past Baseline. Am J Prev Med. 2011; 40 (4): 440-447.

The Effects of the Fast Track Preventive Intervention on the Development of Conduct Disorder across Childhood The impact of the Fast Track intervention on externalizing disorders across childhood was examined. Eight hundred-ninety-one early-starting children (69% male; 51% African American) were randomly assigned by matched sets of schools to intervention or control conditions. The 10-year intervention addressed parent behavior-management, child social cognitive skills, reading, home visiting, mentoring, and classroom curricula. Outcomes included psychiatric diagnoses after grades 3, 6, 9, and 12 for conduct disorder, oppositional defiant disorder, attention deficit hyperactivity disorder, and any externalizing disorder. Significant interaction effects between intervention and initial risk level indicated that the intervention prevented the lifetime prevalence of all diagnoses, but only among those at highest initial risk, suggesting that targeted intervention can prevent externalizing disorders to promote the raising of healthy children. Problems C. The Effects Of The Fast Track Preventive Intervention On The Development Of Conduct Disorder Across Childhood. Child Dev. 2011; 82 (1): 331-345.

Preventing Prescription Drug Misuse: Field Test of the SmartRx Web Program The purpose of the project was to test a Web-based program designed to prevent prescription drug misuse. Study sample consisted of 346 working women randomized into either an experimental or wait-list control condition. Analysis of covariance and logistic regression were used to compare responses. Women receiving the intervention had greater knowledge of drug facts and greater self-efficacy in medication adherence and ability to manage problems with medications compared with controls. Women receiving the intervention also had reduced symptoms reported on the CAGE for prescription medications. Findings suggest that multimedia Web-based programs can be a beneficial addition to substance misuse prevention services. The study's limitations are noted. Deitz D, Cook R, Hendrickson A. Preventing Prescription Drug Misuse: Field Test of the SmartRx Web Program. Subst Use Misuse. 2011; 46 (5): 678-686.

Six-Year Sustainability of Evidence-Based Intervention Implementation Quality by Community-University Partnerships: The PROSPER Study There is a knowledge gap concerning how well community-based teams fare in implementing evidence-based interventions (EBIs) over many years, a gap that is important to fill because sustained high quality EBI implementation is essential to public health impact. The current study addresses this gap by evaluating data from PROSPER, a community-university intervention partnership model, in the context of a randomized-control trial of 28 communities. Specifically, it examines community teams' sustainability of implementation quality on a range of measures, for both family-focused and school-based EBIs. Average adherence ratings approached 90% for family-focused and school-based EBIs, across as many as 6 implementation cohorts. Additional indicators of implementation quality similarly showed consistently positive results. Correlations of the implementation quality outcomes with a number of characteristics of community teams and intervention leaders were calculated to explore their potential relevance to sustained

implementation quality. Though several relationships attained statistical significance at particular points in time, none were stable across cohorts. The role of PROSPER 's continuous, proactive technical assistance in producing the positive results is discussed. Spoth R, Guyll M, Redmond C, Greenberg M, Feinberg M. Six-Year Sustainability Of Evidence-Based Intervention Implementation Quality By Community-University Partnerships: The PROSPER Study. Am J Community Psychol. 2011.

Team Factors that Predict to Sustainability Indicators for Community-Based Prevention Teams Because they often set out with a guarantee of only short-term funding, many community partnerships will face a threat to their sustainability almost as soon as the first money runs out. Research into the factors that enable some coalitions and partnerships to meet the challenge when others fail is limited. This study begins to fill this gap in our understanding by examining influences on the process of sustainability planning in the context of a collaborative partnership focused on youth development. The authors report on a longitudinal examination of the quality of planning and attitudes underpinning the sustainability of PROSPER community prevention teams whose members implement evidence-based programs designed to support positive youth development and reduce early substance use and other problem behaviors. The current research concentrates on a particular dimension of partnership effectiveness to establish whether perceptions about team functioning in play at 6 and 18 months predict the quality of sustainability planning at 36 and 48 months. How well teams functioned in the early stages was found to be strongly related to the quality of their later preparations for sustainability. Recruitment and integration of new team members, and the encouragement they subsequently received were also found to be key factors. The results strengthen the argument for providing technical assistance to meet the needs of those who promote prevention partnerships, and they provide longitudinal empirical data to support the hypotheses of other researchers who have similarly found a correlation between effective sustainability and early planning and support. Perkins D, Feinberg M, Greenberg M, Johnson L, Chilenski S, Mincemoyer C, Spoth R. Team Factors That Predict To Sustainability Indicators For Community-Based Prevention Teams. Eval Program Plan. 2011; 34 (3): 283-291.

Impact Challenges in Community Science-with-Practice: Lessons from PROSPER on Transformative Practitioner-Scientist Partnerships and Prevention Infrastructure Development At present, evidence-based programs (EBPs) to reduce youth violence are failing to translate into widespread community practice, despite their potential for impact on this pervasive public health problem. In this paper the authors address two types of challenges in the achievement of such impact, drawing upon lessons from the implementation of a partnership model called PROSPER. First, they address five key challenges in the achievement of community-level impact through effective community planning and action: readiness and mobilization of community teams; maintaining EBP implementation quality; sustaining community teams and EBPs; demonstrating community-level impact; and continuous, proactive technical assistance. Second, they consider grand challenges in the large-scale translation of EBPs: (1) building, linking and expanding existing infrastructures to support effective EBP delivery systems, and (2) organizing networks of practitioner-scientist partnerships-networks designed to integrate diffusion of EBPs with research that examines effective strategies to do so. The PROSPER partnership model is an evidence-based delivery system for community-based prevention and has evolved through two decades of NIH-funded research, assisted by land grant

universities' Cooperative Extension Systems. Findings and lessons of relevance to each of the challenges are summarized. In this context, we outline how practitioner-scientist partnerships can serve to transform EBP delivery systems, particularly in conjunction with supportive federal policy. Spoth R, Greenberg M. Impact Challenges In Community Science-With-Practice: Lessons From PROSPER On Transformative Practitioner-Scientist Partnerships And Prevention Infrastructure Development. Amer. J Community Psychology. 2011.

Creating Nurturing Environments: A Science-Based Framework for Promoting Child Health and Development within High-Poverty Neighborhoods Living in poverty and living in areas of concentrated poverty pose multiple risks for child development and for overall health and well-being. Poverty is a major risk factor for several mental, emotional, and behavioral disorders, as well as for other developmental challenges and physical health problems. In this paper, the Promise Neighborhoods Research Consortium describes a science-based framework for the promotion of child health and development within distressed high-poverty neighborhoods. The authors lay out a model of child and adolescent developmental outcomes and integrate knowledge of potent and malleable influences to define a comprehensive intervention framework to bring about a significant increase in the proportion of young people in high-poverty neighborhoods who will develop successfully. Based on a synthesis of research from diverse fields, the Creating Nurturing Environments framework was created to guide community-wide efforts to improve child outcomes and reduce health and educational inequalities. Komro K, Flay B, Biglan A. Creating Nurturing Environments: A Science-Based Framework For Promoting Child Health And Development Within High-Poverty Neighborhoods. Clin Child Fam Psychol Rev. 2011; 14 (2): 111-134.

Contextual Stress and Health Risk Behaviors among African American Adolescents This study examined the longitudinal association between contextual stress and health risk behaviors and the role of protective factors in a community epidemiologically-defined sample of urban African American adolescents (N = 500; 46.4% female). Structural equation modeling was used to create a latent variable measuring contextual stress (community violence, neighborhood disorder, and experiences with racial discrimination). Contextual stress in 8th grade was associated with aggressive behavior and substance use 2 years later for boys. For girls, contextual stress predicted later substance use, but not aggressive behavior. High academic competence and self-worth reduced the impact of contextual stress on substance use for boys. Implications for intervention and directions for future research on health risk behaviors among African American adolescents are discussed. Copeland-Linder N, Lambert S, Chen Y, Ialongo N. Contextual Stress And Health Risk Behaviors Among African American Adolescents. J. Youth Adolesc. 2011; 40 (2): 158-173.

Changes in Self-Control Problems and Attention Problems during Middle School Predict Alcohol, Tobacco, and Marijuana Use during High School Although deficits in impulse control have been linked to adolescent use of alcohol and illicit drugs, less attention has been given to variability in change in impulse control across adolescence and whether this variability may be a signal of risk for early substance use. The goals of the current study were to examine growth in two aspects of impulse control, self-control problems and attention problems, across middle adolescence, and to test the prospective effects of level and change in these variables on levels and change over time in substance use. Data are from a community sample of 955

adolescents interviewed (along with their parents and teachers) annually from 6th to 11th grade. Results indicated that greater self-control problems and attentional problems in the 6th grade and increases in these problems over time were associated with higher levels of substance use at 11th grade. These results suggest that modeling change over time enhances the understanding of how impulse control influences the development of substance use. King K, Fleming C, Monahan K, Catalano R. Changes In Self-Control Problems And Attention Problems During Middle School Predict Alcohol, Tobacco, And Marijuana Use During High School. Psychol Addict Behav. 2011; 25 (1): 69-79.

Childhood ADHD Symptoms and Risk for Cigarette Smoking during Adolescence: School Adjustment as a Potential Mediator Although a large body of research suggests that children with attention-deficit/hyperactivity disorder (ADHD) are at increased risk for cigarette smoking during adolescence compared with their non-ADHD peers, much less research has examined why. The current study addressed this gap in the literature by examining middle school adjustment, broadly defined, as a possible mediator of the relation between childhood ADHD symptoms and cigarette smoking during middle adolescence (10th grade). Longitudinal data were collected from a community sample of 754 youth using self-report and parent report along with school records, and a novel statistical technique was used in the process of testing for mediation. Consistent with hypotheses, school adjustment was found to mediate the relation between childhood ADHD symptoms and later cigarette smoking, even after controlling for early externalizing problems. Results have implications for etiological theories of adolescent deviant behavior and suggest that successful smoking prevention programs targeting youth with ADHD should include a school adjustment component. Flory K, Malone P, Lamis D. Childhood ADHD Symptoms And Risk For Cigarette Smoking During Adolescence: School Adjustment As A Potential Mediator. Psychol Addict Behav. 2011; Epub (Mar 14).

Investigating Ethnic Differences in Adolescent Alcohol Use and Peer Norms Using Semi-Continuous Latent Growth Models To investigate whether ethnic differences in vulnerability to peer norms supportive of alcohol use is a viable, partial explanation for the ethnic differences in reported prevalence and amount of alcohol use during high school. Survey data from a sample of 680 adolescents from Project STAR (Students Taught Awareness and Resistance) of the Midwestern Prevention Project were used. Hypotheses were tested using sequential, semi-continuous growth curve models. Relative to Black adolescents, White adolescents reported greater peer alcohol use during middle school and were much more likely to consume alcohol during high school. General peer norms in seventh grade and middle school growth in alcohol use norms among close friends was predictive of a greater propensity to consume alcohol in ninth grade among White adolescents. Lower peer norms for alcohol use among Black adolescents might better account for differences between Black and White adolescents than the possibility that White adolescents are more vulnerable to peer norms. Weaver S, Cheong J, Mackinnon D, Pentz M. Investigating Ethnic Differences in Adolescent Alcohol Use and Peer Norms Using Semi-Continuous Latent Growth Models. Alcohol Alcohol. 2011; Epub (April 9).

Adverse Life Events and Depressive Symptomlogy The association between experiences of adverse life events and adolescent depressive symptoms has been well documented. However, this association is not consistently observed in urban and low income African American youth. In addition, mechanisms linking life event stress and African American adolescents' depressive

symptoms have received little attention. This study examined past year violent and nonviolent life events assessed in 6th grade as predictors of 7th grade depressive symptoms among a community epidemiologically defined sample of 447 (47% girls) urban African American adolescents. Depressive symptoms were assessed twice, at a 1-year interval, and initial depressive symptoms were controlled in the analyses. Control-related beliefs were examined as mediators of the association between life events and depressive symptoms, and gender was examined as a moderator of the association between control-related beliefs and depressive symptoms. Associations among study variables were examined in a series of models, from general to more specific. A model in which nonviolent and violent life events were examined separately and control and contingency beliefs examined as one latent variable was the most informative about the etiology of depressive symptoms in a sample of urban, African American youth. Implications of the findings for preventive interventions and future research are discussed. Sanchez Y, Lambert S, Ialongo N. Adverse Life Events And Depressive Symptoms In African American Youth: The Role Of Control-Related Beliefs. Depress Res Treat. 2011; doi:10.1155/2011/871843.

Self-regulatory Problems, Contextual Stressors, and Unprotected Intercourse Among Rural African American Young Men In this brief report, the hypothesis that self-regulatory problems would mediate the association between contextual stressors and unprotected intercourse among rural African American young adult men was investigated. Family support and religiosity were hypothesized to ameliorate the influence of contextual stressors on self-regulatory problems. Hypotheses were tested on 79 sexually active men from a sample recruited with Respondent Driven Sampling; episodes of unprotected intercourse constituted the criterion variable. Analyses supported the mediating role of self-regulatory problems in linking young adult men's contextual stressors with a heightened likelihood of unprotected intercourse. Religious involvement and family support interacted with contextual stressors to predict diminished associations with self-regulatory problems. Kogan S, Brody G, Chen Y, DiClemente R. Self-Regulatory Problems Mediate The Association Of Contextual Stressors And Unprotected Intercourse Among Rural, African American, Young Adult Men. J Health Psychol. 2011; 16 (1): 50-57.

Effects of Early Adolescent Depressive Symptoms and Impulsivity on Late Adolescent Gambling Depression and impulsivity have been positively correlated to problem gambling, but no study has focused on their combined effects on the onset of problem gambling. This study examined the possible synergistic effect of depressive symptoms and impulsivity in early adolescence on late adolescence gambling behaviors among a longitudinal cohort of 678 students from Baltimore, Maryland. Lee G, Storr C, Ialongo N, Martins S. Compounded Effect Of Early Adolescence Depressive Symptoms And Impulsivity On Late Adolescence Gambling: A Longitudinal Study. J Adolesc Health. 2011; 48 (2): 164-169.

Individual, Familial, Friends-Related and Contextual Predictors of Early Sexual Intercourse This study examined the unique and simultaneous contribution of adolescents' characteristics, parent-child relationship and friends' characteristics on early sexual intercourse, while accounting for family status. A longitudinal multi-sample design was used. The first sample was recruited in a suburban context (n = 265; 62% girls) and the second sample in an urban setting (n = 136; 61% girls). All predictors were measured in Grade 8 and age at first

intercourse was assessed yearly for three years. Being in a non-intact family, low parental control, high antisocial behaviors, low self-disclosure, high proportion of other-sex friends and high substance use were associated with earlier sexual intercourse. When all predictors were considered simultaneously, more antisocial behaviors, high proportion of other-sex friends and non-intact family structure significantly discriminated youth reporting first intercourse at age 13 or less from those who reported first intercourse at age 14, at age 15, or were virgins at age 16 among both samples. Boislard PM, Poulin F. Individual, Familial, Friends-Related And Contextual Predictors Of Early Sexual Intercourse. J Adolesc. 2011; 34 (2): 289-300.

Prevalence and Risk of Psychiatric Disorders as a Function of Variant Rape Histories Rape is an established risk factor for mental health disorders, such as posttraumatic stress disorder (PTSD), major depressive episodes (MDE), and substance use disorders. The majority of studies have not differentiated substance-involved rape or examined comorbid diagnoses among victims. Therefore, the aim of the present study was to estimate the prevalence of common trauma-related psychiatric disorders (and their comorbidity) in a national sample of women, with an emphasis on distinguishing between rape tactics. A secondary objective was to estimate the risk for psychiatric disorders among victims of variant rape tactics, in comparison to non-victims. A nationally representative population-based sample of 3,001 non-institutionalized, civilian, English or Spanish speaking women (aged 18-86 years) participated in a structured telephone interview assessing rape history and DSM-IV criteria for PTSD, MDE, alcohol abuse (AA), and drug abuse (DA). Descriptive statistics and multivariate logistic regression analyses were employed. Women with rape histories involving both substance facilitation and forcible tactics reported the highest current prevalence of PTSD (36%), MDE (36%), and AA (20%). Multivariate models demonstrated that this victim group was also at highest risk for psychiatric disorders, after controlling for demographics and childhood and multiple victimization history. Women with substance-facilitated rapes reported higher prevalence of substance abuse in comparison to women with forcible rape histories. Comorbidity between PTSD and other psychiatric disorders was higher among rape victims in comparison to non-rape victims. Researchers and clinicians should assess substance-facilitated rape tactics and attend to comorbidity among rape victims. Empirically supported treatments are needed to address the complex presentations observed among women with variant rape histories. Zinzow H, Resnick H, McCauley J, Amstadter A, Ruggiero K, Kilpatrick D. Prevalence And Risk Of Psychiatric Disorders As A Function Of Variant Rape Histories: Results From A National Survey Of Women. Soc Psychiatry Psychiatr Epidemiol. 2011.

Drug Assertiveness and Sexual Risk-Taking Behavior in a Sample of HIV-Positive, Methamphetamine-Using Men Who Have Sex with Men Drug assertiveness skills have been demonstrated to be effective in reducing substance use behaviors among patients with alcohol or heroin use disorders. This study examined the association between drug assertiveness and methamphetamine use, psychological factors, and sexual risk behaviors in a sample of 250 HIV-positive men who have sex with men enrolled in a safer sex intervention in San Diego, CA. Less assertiveness in turning down drugs was associated with greater frequency and larger amounts of methamphetamine use, lower self-esteem, higher scores on a measure of sexual sensation seeking, and greater attendance at risky sexual venues. These data suggest that drug assertiveness training should be incorporated into drug abuse treatment programs and other risk reduction interventions for methamphetamine users. Semple S, Strathdee S, Zians J, McQuaid J, Patterson

T. Drug Assertiveness And Sexual Risk-Taking Behavior In A Sample Of HIV-Positive, Methamphetamine-Using Men Who Have Sex With Men. J Subst Abuse Treat. 2011; Epub (May 6).

The Critical Role of Intimacy in the Sexual Risk Behaviors of Gay and Bisexual Men Research indicates that high numbers of gay and bisexual men report infrequent or inconsistent condom use, placing them at risk for HIV and other STDs. The present study examined positive and negative condom-related attitudes along three dimensions-risk reduction, pleasure reduction, and intimacy interference-and examined their relative predictive power in determining condom use among a sample of sexually risky gay and bisexual men in New York City. In a multivariate model, both risk reduction and intimacy interference attitudes emerged as significant predictors of unprotected sex; however, the variance accounted for by a model including intimacy interference was almost three times that accounted for by a model including risk reduction alone. These data suggest a pivotal role for intimacy in shaping condom attitudes and behavior among gay and bisexual men. HIV prevention interventions should consider incorporating intimacy as a motivating factor for sexual behavior and a potential barrier to condom use. Golub S, Starks T, Payton G, Parsons J. The Critical Role Of Intimacy In The Sexual Risk Behaviors Of Gay And Bisexual Men. AIDS Behav. 2011; Epub (Jun 1).

Psychosocial and Behavioral Correlates of Anxiety Symptoms in a Sample of HIV-Positive, Methamphetamine-Using Men Who Have Sex with Men Studies show high rates of psychiatric symptoms among methamphetamine users; however, little information exists regarding methamphetamine use and anxiety. This study investigated psychosocial and behavioral correlates of anxiety symptoms in a sample of 245 HIV-positive men having sex with men (MSM) who were enrolled in a sexual risk-reduction intervention. In a multiple regression analysis, anxiety symptoms were associated with homelessness, recent experience of HIV symptoms, injection drug use, and lifetime sexual abuse, engaging in risky sexual behaviors, and seeking out partners at risky sexual venues when "high" on methamphetamine. These findings can be used to inform and refine sexual risk-reduction interventions and substance-use treatment programs for HIV-positive methamphetamine-using MSM. Semple S, Strathdee S, Zians J, McQuaid J, Patterson T. Psychosocial And Behavioral Correlates Of Anxiety Symptoms In A Sample Of HIV-Positive, Methamphetamine-Using Men Who Have Sex With Men. AIDS Care. 2011; 23 (5): 628-637.

Migration, Neighborhoods, and Networks: Approaches to Understanding How Urban Environmental Conditions Affect Syndemic Adverse Health Outcomes among Gay, Bisexual and Other Men Who Have Sex with Men Adopting socioecological, intersectionality, and lifecourse theoretical frameworks may enhance our understanding of the production of syndemic adverse health outcomes among gay, bisexual and other men who have sex with men (MSM). From this perspective, the authors present preliminary data from three related studies that suggest ways in which social contexts may influence the health of MSM. The first study, using cross-sectional data, looked at migration of MSM to the gay resort area of South Florida, and found that amount of time lived in the area was associated with risk behaviors and HIV infection. The second study, using qualitative interviews, observed complex interactions between neighborhood-level social environments and individual-level racial and sexual identity among MSM in New York City. The third study, using egocentric network

analysis with a sample of African American MSM in Baltimore, found that sexual partners were more likely to be found through face-to-face means than the Internet. They also observed that those who co-resided with a sex partner had larger networks of people to depend on for social and financial support, but had the same size sexual networks as those who did not live with a partner. Overall, these findings suggest the need for further investigation into the role of macro-level social forces on the emotional, behavioral, and physical health of urban MSM. Egan J, Frye V, Kurtz S, Latkin C, Chen M, Tobin K, Yang C, Koblin B. Migration, Neighborhoods, And Networks: Approaches To Understanding How Urban Environmental Conditions Affect Syndemic Adverse Health Outcomes Among Gay, Bisexual and Other Men Who Have Sex With Men. AIDS Behav. 2011; 15 (Siuppl 1): S35-S50.

Prevalence and Correlates of 'Agua Celeste' Use Among Female Sex Workers Who Inject Drugs in Ciudad Juarez, Mexico Agua celeste, or “heavenly water," is the street name for a sky-blue colored solvent reportedly inhaled or ingested to produce an intoxicating effect. Study aims were to (1) describe prevalence of agua celestse (AC) use, and (2) identify correlates of lifetime and recent use of AC use among female sex workers who also inject drugs (FSW-IDUs) in northern Mexico. Between 2008 and 2010, baseline data from FSW-IDUs 18 year olds living in Tijuana or Ciudad Juarez participating in a longitudinal behavioral intervention were analyzed using logistic regression. Among 623 FSW-IDUs (307 from Tijuana and 316 from Ciudad Juarez (CJ)), 166 (26%) reported ever using AC, all of whom lived in CJ. Among the CJ sample, lifetime prevalence of AC use was 53%, median age of first use was 16 years (IQR: 14-23), and 10% reported it as their first abused substance. Ever using AC was independently associated with ever being physically abused and younger age, and was marginally associated with initiating injection drug use and regular sex work at age eighteen or younger. Among those ever using AC, 70/166 (42.2%) reported using it within the last 6 months, which was independently associated with using drugs with clients before or during sex, being on the street more than 8hrs. per day, and younger age. The authors observed considerable geographic variation in the use of AC in northern Mexico. Future studies exploring factors influencing use, its precise formulation(s), and its potential health effects are needed to guide prevention and treatment. Morris M, Case P, Robertson A, Lozada R, Vera A, Clapp J, Medina-Mora M, Strathdee S. Prevalence And Correlates Of 'Agua Celeste' Use Among Female Sex Workers Who Inject Drugs In Ciudad Juarez, Mexico. Drug Alcohol Depend. 2011; Epub (Mar 25).

How Important Are Venue-Based HIV Risks among Male Clients of Female Sex Workers? A Mixed Methods Analysis of the Risk Environment in Nightlife Venues in Tijuana, Mexico In 2008, 400 18 years old males who paid or traded for sex with a female sex worker (FSW) in Tijuana, Mexico in the past 4 months, completed surveys and HIV/STI testing; 30 also completed qualitative interviews. To analyze environmental sources of HIV vulnerability among male clients of FSWs in Tijuana, the authors used mixed methods to investigate correlates of clients who met FSWs in nightlife venues and clients' perspectives on venue-based HIV risk. Logistic regression identified micro-level correlates of meeting FSWs in nightlife venues, which were triangulated with clients' narratives regarding macro-level influences. In a multivariate model, offering increased pay for unprotected sex and binge drinking were micro-level factors that were independently associated with meeting FSWs in nightlife venues versus other places. In qualitative interviews, clients characterized nightlife venues as high risk due to the following macro-level features: social norms dictating heavy alcohol consumption; economic exploitation

by establishment owners; and poor enforcement of sex work regulations. Structural interventions in nightlife venues are needed to address venue-based risks. Goldenberg S, Strathdee S, Gallardo M, Nguyen L, Lozada R, Semple S, Patterson T. How Important Are Venue-Based HIV Risks Among Male Clients Of Female Sex Workers? A Mixed Methods Analysis Of The Risk Environment In Nightlife Venues In Tijuana, Mexico. Health Place. 2011; 17 (3): 748-756.

Social and Structural Factors Associated with HIV Infection among Female Sex Workers Who Inject Drugs in the Mexico-US Border Region FSWs who inject drugs (FSW-IDUs) can acquire HIV through high risk sexual and injection behaviors. The authors studied correlates of HIV infection among FSW-IDUs in northern Mexico, where sex work is quasi-legal and syringes can be legally obtained without a prescription. FSW-IDUs>18 years old who reported injecting drugs and recent unprotected sex with clients in Tijuana and Ciudad Juarez underwent surveys and HIV/STI testing. Logistic regression identified correlates of HIV infection. Of 620 FSW-IDUs, prevalence of HIV, gonorrhea, Chlamydia, trichomonas, syphilis titers e168, or any of these infections was 5.3%, 4%, 13%, 35%, 10% and 72%, respectively. Compared to other FSW-IDUs, HIV-positive women were more likely to: have syphilis titers e168 (36% vs. 9%, $p<0.001$), often/always inject drugs with clients (55% vs. 32%, $p = 0.01$), and experience confiscation of syringes by police (49% vs. 28%, $p = 0.02$). Factors independently associated with HIV infection were syphilis titers, often/always injecting with clients and police confiscation of syringes. Women who obtained syringes from NEPs (needle exchange programs) within the last month had lower odds of HIV infection associated with active syphilis, but among non-NEP attenders, the odds of HIV infection associated with active syphilis was significantly elevated. Factors operating in both the micro-social environment (i.e., injecting drugs with clients) and policy environment (i.e., having syringes confiscated by police, attending NEPs) predominated as factors associated with risk of HIV infection, rather than individual-level risk behaviors. Interventions should target unjustified policing practices, clients; risk behaviors and HIV/STI prevention through NEPs. Strathdee S, Lozada R, Martinez G, Vera A, Rusch M, Nguyen L, Pollini R, Uribe-Salas F, Beletsky L, Patterson T. Social And Structural Factors Associated With HIV Infection Among Female Sex Workers Who Inject Drugs In The Mexico-US Border Region. PloS One. 2011; 6 (4):e19048.

"Over here, it's just drugs, women and all the madness": The HIV Risk Environment of Clients of Female Sex Workers in Tijuana, Mexico HIV vulnerability depends upon social context. Based on broader debates in social epidemiology, political economy, and sociology of health, Rhodes' (2002) "risk environment" framework provides one heuristic for understanding how contextual features influence HIV risk, through different types of environmental factors (social, economic, policy, and physical) which interact at different levels of influence (micro, macro). Few data are available on the "risk environment" of male clients of female sex workers (FSWs); such men represent a potential "bridge" for transmission of HIV and other sexually transmitted infections from high- to low-prevalence populations. Using in-depth interviews ($n = 30$), the authors describe the HIV risk environment of male clients in Tijuana, Mexico, where disproportionately high HIV prevalence has been reported among FSWs and their clients. A number of environmental themes influence risky sex with FSWs and the interplay between individual agency and structural forces: social isolation and the search for intimacy; meanings and identities ascribed to Tijuana's Zona Roja (red light district) as a risky place; social relationships in the Zona Roja; and economic roles. These findings suggest that clients '

behaviors are deeply embedded in the local context. Using the HIV "risk environment" as our analytic lens, we illustrate how clients' HIV risks are shaped by physical, social, economic, and political factors. The linkages between these and the interplay between structural- and individual-level experiences support theories that view structure as both enabling as well as constraining. The authors discuss how the "embeddedness" of clients' experiences warrants the use of environmental interventions that address the circumstances contributing to HIV risk at multiple levels. Goldenberg S, Strathdee S, Gallardo M, Rhodes T, Wagner K, Patterson T. "Over Here, It's Just Drugs, Women And All The Madness": The HIV Risk Environment Of Clients Of Female Sex Workers In Tijuana, Mexico. Soc Sci Med. 2011; 72 (7): 1185-1192.

RMediation: An R Package for Mediation Analysis Confidence Intervals This article describes the RMediation package, which offers various methods for building confidence intervals (CIs) for mediated effects. The mediated effect is the product of two regression coefficients. The distribution-of-the-product method has the best statistical performance of existing methods for building CIs for the mediated effect. RMediation produces CIs using methods based on the distribution of product, Monte Carlo simulations, and an asymptotic normal distribution. Furthermore, RMediation generates percentiles, quantiles, and the plot of the distribution and CI for the mediated effect. An existing program, called PRODCLIN, published in Behavior Research Methods, has been widely cited and used by researchers to build accurate CIs. PRODCLIN has several limitations: The program is somewhat cumbersome to access and yields no result for several cases. RMediation described herein is based on the widely available R software, includes several capabilities not available in PRODCLIN, and provides accurate results that PRODCLIN could not. Tofighi D, Mackinnon D. RMediation: An R Package For Mediation Analysis Confidence Intervals. Behav Res Methods. 2011; Epub (April 13).

BEHAVIORAL & INTEGRATIVE TREATMENT RESEARCH

Employment-based Reinforcement of Abstinence Boosts Adherence to Depot Naltrexone Naltrexone provides excellent opioid blockade, but its clinical utility is limited because opioid-dependent patients typically refuse it. An injectable suspension of naltrexone for extended release (XR-NTX) was recently approved by the FDA for treatment of opioid dependence. XR-NTX treatment may require concurrent behavioral intervention to maximize adherence and effectiveness, thus the authors sought to evaluate employment-based reinforcement as a method of improving adherence to XR-NTX in opiate dependent adults. Opioid-dependent adults (n=38) were detoxified and inducted onto oral naltrexone, then randomly assigned to contingency or prescription conditions. Participants received up to six doses of XR-NTX at four-week intervals. All participants could earn vouchers for attendance and performance at a therapeutic workplace. Contingency participants were required to accept XR-NTX injections to access the workplace and earn vouchers. Prescription participants could earn vouchers independent of their acceptance of XR-NTX injections. Contingency participants accepted significantly more naltrexone injections than prescription participants (87% versus 52%, p=.002), and were more likely to accept all injections (74% versus 26%, p=.004). Participants in the two conditions provided similar percentages of samples negative for opiates (72% versus 65%) and for cocaine (58% versus 54%). Opiate positivity was significantly more likely when samples were also cocaine positive, independent of naltrexone blockade (p=.002). This suggests that contingencies for cocaine use may be necessary in order for participants to fully benefit from naltrexone treatment. Defulio A, Everly JJ, Leoutsakos JM, Umbricht A, Fingerhood M, Bigelow GE, Silverman K. Employment-based reinforcement of adherence to an FDA approved extended release formulation of naltrexone in opioid-dependent adults: A randomized controlled trial. Drug Alcohol Depend. 2011 July. [Epub ahead of print].

Pilot Study of In Session Patient Responses to Screener Predicts Drug Use at 4 Months In a sample of postpartum women (N = 39), several variables elicited during the course of a computerized brief intervention showed promise as predictors of later drug use. A brief index derived from the five best predictors predicted abstinence with a sensitivity of .7 and a specificity of .89. Useful items examined patient ratings of their own states across the treatment session and included items like improved self satisfaction after receiving feedback about drug use and lower self reported likelihood of use after the initial intervention component. Self-reported seriousness of drug use following various intervention components predicted reductions in drug use at follow-up. More research is needed on the utility of dynamic in session predictors but initial results suggest such variables may have utility for predicting change and possibly identifying individuals in need of additional intervention beyond a brief session. Ondersma SJ, Grekin ER, Svikis D. The potential for technology in brief interventions for substance use, and during-session prediction of computer-delivered brief intervention response Subst Use Misuse. 2011; 46(1) :77-86.

Pilot Study in China Suggests Methadone Maintenance Treatment (MMT) Improves with Manual-guided Behavioral Drug and HIV Risk Reduction Counseling (BDRC) Heroin dependent individuals (n=37) enrolling in two MMT clinics in Wuhan, China, received standard MMT services, consisting of daily medication at the clinics and infrequent additional services on demand, and were randomly assigned to MMT only (n=17) or MMT with weekly individual

BDRC (n=20) for 3 months. Participants were followed for six months from the time of enrollment (3 months active counseling phase and 3 months follow-up while treated with standard MMT). Primary outcome measures included reductions of HIV risk behaviors and illicit opiate use and treatment retention. Participants in MMT+BDRC achieved both greater reductions of HIV risk behaviors ($p<0.01$), as indicated by the scores on a short version of the AIDS Risk Inventory, and of illicit opiate use, as indicated by the proportions of opiate negative test results during the active phase of the study and the follow-up ($p<0.001$). 83.3% in the MMT+BDRC group and 76.2% in the standard MMT group were still actively participating in MMT at 6 months. Manual-guided behavioral drug and HIV risk reduction counseling is feasible to deliver by the trained MMT nursing personnel and appears to be a promising approach for improving the efficacy of standard MMT services in China. This is important because MMT in China generally occurs without psychosocial treatment or HIV risk reduction training. More research is needed to conclusively support these results and show they are specific to this treatment and not the result of additional time and attention. Chawarski MC, Zhou W, Schottenfeld RS. Behavioral drug and HIV risk reduction counseling (BDRC) in MMT programs in Wuhan, China: a pilot randomized clinical trial. Drug Alcohol Depend. 2011 Jun 1; 115(3): 237-239.

Using SMS Text Messaging to Assess Moderators of Smoking Reduction: Validating a New Tool for Ecological Measurement of Health Behaviors Understanding the psychological processes that contribute to smoking reduction will yield population health benefits. Negative mood may moderate smoking lapse during cessation, but this relationship has been difficult to measure in ongoing daily experience. The authors used a novel form of ecological momentary assessment to test a self-control model of negative mood and craving leading to smoking lapse. They validated short message service (SMS) text as a user-friendly and low-cost option for ecologically measuring real-time health behaviors. They sent text messages to cigarette smokers attempting to quit eight times daily for the first 21 days of cessation (N-obs = 3,811). Approximately every two hours, the authors assessed cigarette count, mood, and cravings, and examined between- and within-day patterns and time-lagged relationships among these variables. Exhaled carbon monoxide was assessed pre- and posttreatment. Negative mood and craving predicted smoking two hours later, but craving mediated the mood-smoking relationship. Also, this mediation relationship predicted smoking over the next two, but not four, hours. Results clarify conflicting previous findings on the relation between affect and smoking, validate a new low-cost and user-friendly method for collecting fine-grained health behavior assessments, and emphasize the importance of rapid, real-time measurement of smoking moderators. Berkman ET, Dickenson J, Falk EB, Lieberman MD. Using SMS text messaging to assess moderators of smoking reduction: Validating a new tool for ecological measurement of health behaviors. Health Psychol. 2011 Mar; 30(2): 186-194.

In the Trenches of Real-World Self- Control: Neural Correlates of Breaking the Link Between Craving and Smoking Successful goal pursuit involves repeatedly engaging self-control against temptations or distractions that arise along the way. Laboratory studies have identified the brain systems recruited during isolated instances of self-control, and ecological studies have linked self-control capacity to goal outcomes. However, no study has identified the neural systems of everyday self-control during long-term goal pursuit. The present study integrated neuroimaging and experience-sampling methods to investigate the brain systems of successful self-control among smokers attempting to quit. A sample of 27 cigarette smokers

completed a go/no-go task during functional magnetic resonance imaging before they attempted to quit smoking and then reported everyday self-control using experience sampling eight times daily for 3 weeks while they attempted to quit. Increased activation in right inferior frontal gyrus, pre-supplementary motor area, and basal ganglia regions of interest during response inhibition at baseline was associated with an attenuated association between cravings and subsequent smoking. These findings support the ecological validity of neurocognitive tasks as indices of everyday response inhibition. Berkman ET, Falk EB, Lieberman MD. In the trenches of real-world self-control: neural correlates of breaking the link between craving and smoking. Psychol Sci. 2011 Apr; 22(4): 498-506.

Neural Activity during Health Messaging Predicts Reductions in Smoking Above and Beyond Self-Report The current study tested whether neural activity in response to messages designed to help smokers quit could predict smoking reduction, above and beyond self-report. Using neural activity in an a priori region of interest (a subregion of medial prefrontal cortex [MPFC]), in response to ads designed to help smokers quit smoking, the authors prospectively predicted reductions in smoking in a community sample of smokers (N = 28) who were attempting to quit smoking. Smoking was assessed via expired carbon monoxide (CO; a biological measure of recent smoking) at baseline and 1 month following exposure to professionally developed quitting ads. A positive relationship was observed between activity in the MPFC region of interest and successful quitting (increased activity in MPFC was associated with a greater decrease in expired CO). The addition of neural activity to a model predicting changes in CO from self-reported intentions, self-efficacy, and ability to relate to the messages significantly improved model fit, doubling the variance explained (R^2self-report = .15, R^2self-report + neural activity = .35, R^2change = .20). Neural activity is a useful complement to existing self-report measures. In this investigation, the authors extend prior work predicting behavior change based on neural activity in response to persuasive media to an important health domain and discuss potential psychological interpretations of the brain-behavior link. These results support a novel use of neuroimaging technology for understanding the psychology of behavior change and facilitating health promotion. Falk EB, Berkman ET, Whalen D, Lieberman MD. Neural activity during health messaging predicts reductions in smoking above and beyond self-report. Health Psychol. 2011 Mar; 30(2): 177-185.

ADHD Medication Reduces Cotinine Levels and Withdrawal in Smokers with ADHD Individuals with ADHD may self-medicate with nicotine, the main psychoactive ingredient in tobacco smoke, in order to reduce symptoms and negative moods associated with ADHD. ADHD medication (e.g., methylphenidate and atomoxetine) may mimic some of the effects of nicotine and may aid smoking cessation in smokers with ADHD. The present study examined if ADHD medication reduces smoking and withdrawal in non-treatment seeking smokers with ADHD. Fifteen adult smokers with ADHD participated in the study, which consisted of an experimental phase and field monitoring phase to examine the acute and extended effects, respectively, of ADHD medication. During the experimental phase, smokers were asked to complete a Continuous Performance Task (CPT) and the Shiffman-Jarvik smoking withdrawal questionnaire during the following four conditions: (1) ADHD medication + cigarette smoking, (2) ADHD medication + overnight abstinence, (3) placebo + cigarette smoking, and (4) placebo + overnight abstinence. During the field monitoring phase, participants were asked to provide salivary cotinine samples and complete electronic diaries about smoking, smoking urge, ADHD

symptoms, and stress in everyday life for two days on ADHD medication and for two days on placebo. Results of the experimental phase showed that ADHD medication improved task performance on the CPT and reduced withdrawal during overnight abstinence. During the field monitoring phase, ADHD medication reduced salivary cotinine levels compared to placebo. In addition, the electronic diary revealed that ADHD medication improved difficulty concentrating during no smoking events and stress. The findings of the present study suggest that, along with other strategies, ADHD medication may be used to aid smoking withdrawal and cessation in smokers with ADHD. Gehricke JG, Hong N, Wigal TL, Chan V, Doan A. ADHD medication reduces cotinine levels and withdrawal in smokers with ADHD. Pharmacol Biochem Behav. 2011 May; 98(3): 485-491.

Internet-Based Group Contingency Management to Promote Abstinence from Cigarette Smoking: A Feasibility Study In contingency management (CM) interventions, monetary consequences are contingent on evidence of drug abstinence. Typically, these consequences are contingent on individual performance. Consequences contingent on group performance may promote social support (e.g., praise). Thus, to combine social support with the monetary incentives of CM, the authors integrated independent and interdependent group contingencies of reinforcement into an Internet-based intervention to promote smoking abstinence. Breath carbon monoxide (CO) measures were compared between treatment conditions and a baseline control condition. Thirteen participants were divided into 5 groups or "teams" (n=2-3 per team). Each participant submitted video recordings of CO measurement twice daily via the Internet. Teammates could monitor each other's progress and communicate with one another through an online peer support forum. During a 4-day tapering condition, vouchers exchangeable for goods were contingent on gradual reductions in breath CO. During a 10-day abstinence induction condition, vouchers were contingent on abstinence (CO≤4ppm). In both treatment conditions, concurrent independent and interdependent group contingencies were arranged (i.e., a mixed contingency arrangement). Less than 1% of CO samples submitted during baseline were ≤4ppm, compared to 57% submitted during abstinence induction. Sixty-five percent of participants' comments on the online peer support forum were rated as positive by independent observers. Participants rated the intervention favorably on a treatment acceptability questionnaire. The results suggest that the intervention is feasible and acceptable for promoting abstinence from cigarette smoking. Meredith SE, Grabinski MJ, Dallery J. Internet-based group contingency management to promote abstinence from cigarette smoking: A feasibility study. Drug Alcohol Depend. 2011 Mar 15. [Epub ahead of print].

Examining the Effect of the Life Enhancement Treatment for Substance Use (LETS ACT) on Residential Substance Abuse Treatment Retention Effective, parsimonious behavioral interventions that target reinforcement are needed for substance users with depression to improve mood as well as treatment retention. The Life Enhancement Treatment for Substance Use (LETS ACT; Daughters et al., 2008) is a behavioral activation-based approach tailored to increase levels of positive reinforcement among depressed substance users while in substance abuse treatment. The current study tested the efficacy of LETS ACT compared to a contact-time matched control condition, supportive counseling (SC), examining effects on depressed mood, substance abuse treatment retention, and behavioral activation outcomes. Fifty-eight adult substance users in residential substance abuse treatment presenting with depressive symptoms (BDI≥12) were randomly assigned to LETS ACT or SC. Assessments were administered at pre- and post-

treatment and included assessment of DSM-IV psychiatric diagnoses, depression severity, treatment motivation, overall activation, environmental reward, and substance abuse treatment retention. Patients in LETS ACT had significantly higher rates of substance abuse treatment retention and significantly greater increases in activation on the Behavioral Activation for Depression Scale (BADS) compared to those in SC. Both groups had decreased depression severity at post-treatment, although the group by time interaction was not significant. This study was the first to compare LETS ACT to a contact-time matched control treatment to evaluate effects on substance abuse treatment retention and two distinct measures of behavioral activation: overall activation and environmental reward. Findings suggest preliminary support for the feasibility, tolerability, and efficacy of a brief behavioral activation-based protocol that may be particularly useful to improve substance abuse treatment retention. Magidson JF, Gorka SM, MacPherson L, Hopko DR, Blanco C, Lejuez CW, Daughters SB. Examining the effect of the Life Enhancement Treatment for Substance Use (LETS ACT) on residential substance abuse treatment retention. Addict Behav. 2011 Jun; 36(6): 615-623.

Ten Year Revision of the Brief Behavioral Activation Treatment for Depression: Revised Treatment Manual Following from the seminal work of Ferster, Lewinsohn, and Jacobson, as well as theory and research on the Matching Law, Lejuez, Hopko, LePage, Hopko, and McNeil developed a reinforcement-based depression treatment that was brief, uncomplicated, and tied closely to behavioral theory. They called this treatment the brief behavioral activation treatment for depression (BATD), and the original manual was published in this journal. The current manuscript is a revised manual (BATD-R), reflecting key modifications that simplify and clarify key treatment elements, procedures, and treatment forms. Specific modifications include (a) greater emphasis on treatment rationale, including therapeutic alliance; (b) greater clarity regarding life areas, values, and activities; (c) simplified (and fewer) treatment forms; (d) enhanced procedural details, including troubleshooting and concept reviews; and (e) availability of a modified Daily Monitoring Form to accommodate low literacy patients. Following the presentation of the manual, the authors conclude with a discussion of the key barriers in greater depth, including strategies for addressing these barriers. Lejuez CW, Hopko DR, Acierno R, Daughters SB, Pagoto SL. Ten year revision of the brief behavioral activation treatment for depression: Revised treatment manual. Behav Modif. 2011 Mar; 35(2): 111-161.

A Pilot Study of the Accuracy of Onsite Immunoassay Urinalysis of Illicit Drug Use in Seriously Mentally Ill Outpatients This pilot study investigated the accuracy of onsite immunoassay urinalysis of illicit drug use in 42 outpatients with co-occurring substance use disorders and serious mental illness. Up to 40 urine samples were submitted by each participant as part of a larger study investigating the efficacy of contingency management in persons with co-occurring disorders. Each sample was analyzed for the presence of amphetamine, methamphetamine, cocaine, marijuana, and opiates or their metabolites using onsite qualitative immunoassays. One onsite urinalysis was randomly selected from each participant for confirmatory gas chromatography-mass spectrometry (GC-MS) analyses. Agreement between immunoassay and GC-MS was calculated. Agreement was high, with 98% agreement for amphetamine, methamphetamine, opiate, and marijuana. Agreement for cocaine was 93%. Results of this pilot study support the use of onsite immunoassay screening cups as an assessment and outcome measure in adults with serious mental illness. These data suggest that onsite urinalysis screenings may be a helpful assessment tool for measuring clinical and research

outcomes. McDonell MG, Angelo F, Sugar A, Rainey C, Srebnik D, Roll J, Short R, Ries RK. A pilot study of the accuracy of onsite immunoassay urinalysis of illicit drug use in seriously mentally ill outpatients. Am J Drug Alcohol Abuse. 2011 Mar; 37(2): 137-140.

Gender Differences in Substance Use, Consequences, Motivation to Change, and Treatment Seeking in People with Serious Mental Illness Gender differences in patterns and consequences of substance use, treatment-seeking, and motivation to change were examined in two samples of people with serious mental illness (SMI) and comorbid substance use disorders (SUDs): a community sample not currently seeking substance abuse treatment (N = 175) and a treatment-seeking sample (N = 137). In both groups, women and men demonstrated more similarities in the pattern and severity of their substance use than differences. However, treatment-seeking women showed greater readiness to change their substance use. Mental health problems and traumatic experiences may prompt people with SMI and SUD to enter substance abuse treatment, regardless of gender. Drapalski A, Bennett M, Bellack A. Gender differences in substance use, consequences, motivation to change, and treatment seeking in people with serious mental illness. Drapalski A, Bennett M, Bellack A. Subst Use Misuse. 2011; 46(6): 808-818.

Predictors of Initiation and Engagement in Substance Abuse Treatment Among Individuals with Co-occurring Serious Mental Illness and Substance Use Disorders
Research has documented the significant challenges of engaging individuals with comorbid serious mental illness (SMI) and substance use disorders (SUDs) in substance abuse treatment. To date it is unclear which factors predict treatment initiation and engagement in this group of individuals with SUDs. In this study the authors conducted two analyses using data from a randomized trial of substance abuse treatment in outpatients with SMI: the first examining predictors (collected during screening) of completing an initial intake assessment and the second examining predictors (collected during the intake assessment) of becoming engaged in treatment. Results indicated that males and those with schizophrenia spectrum diagnoses were less likely to complete the intake assessment. Participants who reported more positive feelings about their family were more likely to engage in substance abuse treatment. Participants who were recently arrested were less likely to engage in treatment. Those who met criteria for current drug dependence were less likely to engage in treatment. Overall, these findings are a useful step in determining factors that predict substance abuse treatment initiation and engagement in individuals with SMI and SUDs. Brown CH, Bennett ME, Li L, Bellack AS. Predictors of initiation and engagement in substance abuse treatment among individuals with co-occurring serious mental illness and substance use disorders. Addict Behav. 2011 May; 36(5): 439-447.

Measuring Pain Medication Expectancies in Adults Treated for Substance Use Disorders
The U.S. prevalence of misuse of prescription opioid analgesics has increased substantially over the past decade but research on the factors influencing misuse of these medications remains preliminary. In the literature on alcohol, marijuana and stimulants, substance-related expectancies have been found to predict level of substance use. A similar line of research is needed to better understand reasons for misusing pain medications. This study utilized a sample of adults presenting to a large residential addictions treatment program (N=351). Participants were administered a new instrument, the Pain Medication Expectancy Questionnaire (PMEQ) as well as questions about current alcohol, illegal drug and pain medication misuse. Exploratory factor analysis was used to determine underlying factors of the PMEQ. Results of the factor

analysis supported a three-factor solution focusing on pleasure/social enhancement, pain reduction and negative experience reduction. In general, greater perceived expectancy of the positive effects of Prescription Opiate Analgesics (POAs) in all three domains were correlated with greater frequency of substance use and poorer mental health functioning. Expectancies directly related to the pain-reducing properties of POAs were also related to greater pain and poorer physical functioning. This new measure of pain medication expectancies had sound psychometric properties and the resulting factors were associated with other clinically important aspects of patient functioning. The results highlight the need to assess for and address perceptions related to pain medication use in patients presenting to addictions treatment. Ilgen MA, Roeder KM, Webster L, Mowbray OP, Perron BE, Chermack ST, Bohnert AS. Measuring pain medication expectancies in adults treated for substance use disorders. Drug Alcohol Depend. 2011 May 1; 115(1-2): 51-56.

Longitudinal Predictors of Addictions Treatment Utilization in Treatment-Naïve Adults with Alcohol Use Disorders Despite the substantial prevalence of alcohol use disorders (AUDs), prior research indicates that most people with AUDs never utilize either formal or informal treatment services. Several prior studies have examined the characteristics of individuals with AUDs who receive treatment; however, limited longitudinal data are available on the predictors of receiving AUD services in treatment-naive individuals with AUDs. This study utilized data from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) to identify adults in Wave 1 who met criteria for an AUD within the last 12 months and reported no prior lifetime alcohol treatment (N = 2760). These individuals were surveyed again at Wave 2, approximately 3-4 years later (N = 2170). This study examined the Wave 1 demographic and psychiatric conditions that were associated with receipt of AUD treatment services between Waves 1 and 2. In multivariable analyses, use of AUD treatment services between Waves 1 and 2 was significantly more likely among those who were male, non-Caucasian, younger, had lower income, and who had health insurance. Additionally, those who met criteria for a baseline drug use disorder, anxiety disorder or a personality disorder were more likely to receive AUD treatment. Treatment was more often utilized in those who had more severe baseline psychopathology and in those with fewer economic resources. These findings highlight the need to broaden the types of care available to individuals with AUDs to increase the appeal of AUD services. Ilgen MA, Price AM, Burnett-Zeigler I, Perron B, Islam K, Bohnert AS, Zivin K. Longitudinal predictors of addictions treatment utilization in treatment-naïve adults with alcohol use disorders. Drug Alcohol Depend. 2011 Jan 15; 113(2-3): 215-221.

Cocaine-Related Attentional Bias following Trauma Cue Exposure among Cocaine: Dependent Inpatients with and without Posttraumatic Stress Disorder Although the co-occurrence of posttraumatic 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 inpatients 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 vs. non-PTSD) × 2 (neutral vs. trauma script) × 2 (male vs. 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 inpatients, 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 (vs. 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 toward 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 posttraumatic stress disorder patients and may be a potential target for brief posttraumatic 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. Addiction. Cocaine-related attentional bias following trauma cue exposure among cocaine: Dependent inpatients with and without Posttraumatic Stress Disorder. 2011 May 25. [Epub ahead of print].

Evidence of Greater Treatment Response Among GLB than non-GLB Street-Living Youth Researchers have found that adolescents who identify as gay, lesbian, or bisexual (GLB) are at a higher risk for increased substance use and mental health symptoms. The current study is a secondary analysis of two clinical trials for street-living youth. This analysis examines self-identification as GLB as a moderator of treatment effects and addresses whether street-living GLB youth respond differently to a therapeutic intervention than non-GLB street-living youth. Comparisons were made of treatment outcomes on two categories of variables (drug use and mental health symptoms) among 244 homeless GLB and non-GLB identified adolescents. Overall, GLB and non-GLB adolescents showed similar reductions in drug use and mental health symptoms. However, compared to non-GLB adolescents, GLB adolescents showed greater improvement in reduction of drug use and internalizing and depressive symptom scores. While both groups reported less drug use and fewer mental health symptoms from baseline to post-intervention, GLB youth's scores improved more drastically. Implications of using the identified treatment intervention are discussed. Grafsky EL, Letcher A, Slesnick N, Serovich JM. Comparison of treatment response among GLB and non-GLB street living youth. Child Youth Serv Rev. 2011 May 1; 33(5): v569-574.

Follow-up Completion Among Runaway Substance-Abusing Adolescents: Predictors and Implications Follow-up rates reported among longitudinal studies that focus on runaway adolescents and their families are relatively low. Identifying factors associated with follow-up completion might be useful for improving follow-up rates and therefore study validity. The present study explored how individual- and family-level constructs, as well as research project activities, influence the follow-up completion rate among runaway adolescents (N = 140) and their primary caregiver. Results showed that follow-up completion rates decreased as the number of research assistants (RA) assigned to each case increased and as participants' address changes increased. Additionally, among adolescents, more frequent alcohol use was associated with lower follow-up rates. The current findings suggest that researchers should (1) design their research so that one RA is assigned to each specific case, and (2) adjust their retention strategies to account for the differences in follow-up rates based upon the participants' drug of choice and residential stability. Patton R, Slesnick N, Bantchevska D, Guo X, Kim Y. Predictors of follow-up completion among runaway substance-abusing adolescents and their primary caretakers. Community Ment Health J. 2011 Apr; 47(2): 220-226.

Review of Adolescent Substance Abuse Treatment Alcohol and other drug use among adolescents has been a public health problem for decades. Although some substance use may be developmentally routine, a concerning number of adolescents meet criteria for a substance use disorder and could greatly benefit from a quality treatment experience. However, parents and health care providers want evidence of the efficacy of adolescent-specific treatment programs. This review summarizes four factors surrounding the efficacy of current adolescent treatment programs: 1) adolescent-specific treatment services; 2) the variety of therapeutic modalities; 3) relapse and recovery rates; and 4) the need for evidence-based, quality assessments and research. Current adolescent treatment efforts are summarized, and the recent literature regarding the efficacy of adolescent treatment and recovery rates is discussed. Winters KC, Botzet AM, Fahnhorst T. Advances in adolescent substance abuse treatment. Curr Psychiatry Rep. 2011 Jun 24. [Epub ahead of print].

Promising Adaptive Family Treatment for Drug Abusing Hispanic Youth A small randomized trial investigated a new family-based intervention for Hispanic adolescents who met DSM-IV criteria for substance abuse disorder. The Culturally Informed and Flexible Family-Based Treatment for Adolescents (CIFFTA) is a tailored/adaptive intervention that includes a flexible treatment manual and multiple treatment components. The study used an "add on" design to isolate the effects on substance abuse, behavior problems, and parenting practices attributable to the newly developed components. Twenty-eight Hispanic adolescents and their families were randomized either to the experimental treatment or to traditional family therapy (TFT) and were assessed at baseline and 8-month follow-up. Despite the small sample, results revealed statistically significant time × treatment effects on both self-reported drug use (marijuana + cocaine), $F(1, 22) = 10.59$, $p < .01$, $\eta 2 = .33$ and adolescent reports of parenting practices, $F(1, 22) = 9.01$, $p < .01$, $\eta 2 = .29$. Both sets of analyses favored CIFFTA participants. There was a significant time × treatment effect, $F(1, 22) = 6.72$, $p = .02$, $\eta 2 = .23$, favoring CIFFTA on parent report of parenting practices using a composite that matched the variables used for adolescents, but only a nonsignificant trend, $F(1, 22) = 2.43$, $p = .13$, $\eta 2 = .10$, with a composite that used all parenting subscales. Parent reports of adolescent behavior problems did not show a significant time or time × treatment effect. These results show the promise of this adaptive treatment for substance abuse in Hispanic adolescents and suggest the need for a larger randomized trial to fully investigate this treatment. Santisteban DA, Mena MP, McCabe BE. Preliminary results for an adaptive family treatment for drug abuse in Hispanic youth. J Fam Psychol. 2011 May 30. [Epub ahead of print].

Voucher Incentives Increase Treatment Participation in Telephone-Based Continuing Care for Cocaine Dependence Telephone-based monitoring is a promising approach to continuing care of substance use disorders, but patients often do not engage or participate enough to benefit. Voucher incentives can increase retention in outpatient treatment and continuing care, but may be less effective when reinforcement is delayed, as in telephone-based care. The authors compared treatment utilization rates among cocaine-dependent patients enrolled in telephone continuing care with and without voucher incentives to determine whether incentives increase participation in telephone-based care. Participants were 195 cocaine-dependent patients who completed two weeks of community-based intensive outpatient treatment for substance use disorders and were randomly assigned to receive telephone continuing care with or without voucher incentives for participation as part of a larger clinical trial. The 12-month intervention

included 2 in-person orientation sessions followed by up to 30 telephone sessions. Incentivized patients could receive up to $400 worth of gift cards. Patients who received incentives were not more likely to complete their initial orientation to continuing care. Incentivized patients who completed orientation completed 67% of possible continuing care sessions, as compared to 39% among non-incentivized patients who completed orientation. Among all patients randomized to receive incentives, the average number of completed sessions was 15.5, versus 7.2 for patients who did not receive incentives, and average voucher earnings were $200. Voucher incentives can have a large effect on telephone continuing care participation, even when reinforcement is delayed. Further research will determine whether increased participation leads to better outcome among patients who received incentives. Van Horn DH, Drapkin M, Ivey M,Thomas T, Domis SW, Abdalla O, Herd D, McKay JR. Voucher incentives increase treatment participation in telephone-based continuing care for cocaine dependence. Drug Alcohol Depend. 2011 Apr 1; 114(2-3): 225-228.

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 outcomesof 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). Cocaine addicts discounted significantly more in the C-C condition than in 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. Psychopharmacology (Berl). 2011 Apr 14. [Epub ahead of print].

An Initial Trial of a Computerized Behavioral Intervention for Cannabis Use Disorder The most potent outcomes for cannabis use disorders have been observed with a combination of three evidence-based interventions, motivational enhancement therapy (MET), cognitive-behavioral therapy (CBT), and abstinence-based contingency-management (CM). Access to this intervention remains limited because of cost and service availability issues. This report describes the initial stages of a project designed to develop and test a computer-assisted version of MET/CBT/CM that could address many of the current barriers to its dissemination. A nonrandomized, 12-week comparison study assigned 38 adults seeking treatment for a cannabis

use disorder to either therapist-delivered (n=22) or computer-delivered (n=16) MET/CBT/CM. Attendance, retention, and cannabis use outcomes did not differ significantly between groups, and there were no indications of superior outcomes favoring therapist delivery. Participants provided positive ratings of the computer-delivered sessions. These preliminary findings suggest that computer-assisted delivery of MET/CBT/CM is acceptable to outpatients and does not adversely impact compliance or outcomes achieved during treatment with MET/CBT/CM for cannabis use disorders. Assessment of post-treatment outcomes and replication in randomized trials are needed to determine reliability and longer term effects. As observed in a growing number of studies, computerized therapies have the potential to increase access to, reduce costs, and enhance fidelity of providing evidence-based treatments without sacrificing and possibly enhancing effectiveness. Budney AJ, Fearer S, Walker DD, Stanger C, Thostenson J, Grabinski M, Bickel WK. An initial trial of a computerized behavioral intervention for cannabis use disorder. Drug Alcohol Depend. 2011 May 1; 115(1-2): 74-79.

Childhood Trauma and Psychiatric Disorders as Correlates of School Dropout in a National Sample of Young Adults The effect of childhood trauma, psychiatric diagnoses, and mental health services on school dropout among U.S.-born and immigrant youth is examined using data from the Collaborative Psychiatric Epidemiology Surveys, a nationally representative probability sample of African Americans, Afro-Caribbeans, Asians, Latinos, and non-Latino Whites, including 2,532 young adults, aged 21-29. The dropout prevalence rate was 16% overall, with variation by childhood trauma, childhood psychiatric diagnosis, race/ethnicity, and nativity. Childhood substance and conduct disorders mediated the relation between trauma and school dropout. Likelihood of dropout was decreased for Asians, and increased for African Americans and Latinos, compared to non-Latino Whites as a function of psychiatric disorders and trauma. Timing of U.S. immigration during adolescence increased risk of dropout. Porche MV, Fortuna LR, Lin J, Alegria M. Childhood Trauma and Psychiatric Disorders as Correlates of School Dropout in a National Sample of Young Adults. Child Dev. 2011 May-Jun; 82(3): 982-988.

Acceptability of Drug Testing in an Outpatient Substance Abuse Program for Adolescents 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. The objective of this study was to describe 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.

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.

RESEARCH ON PHARMACOTHERAPIES FOR DRUG ABUSE

Poor Response to Sertraline in Methamphetamine Dependence is Associated With Sustained Craving for Methamphetamine Depression is common among individuals with methamphetamine (MA) use disorders. As agents that enhance serotonergic function are frequently used to treat depression, one might predict that they would be useful medications for MA dependence. However, clinical trials of serotonergic agents for MA addiction have been unsuccessful. The objective of this study was to identify factors that distinguish MA-dependent research participants who increased MA self-administration while receiving treatment with the selective serotonin reuptake inhibitor (SSRI) sertraline from other groups of participants. Using a dataset from a 12-week randomized, placebo-controlled trial of sertraline (100mg daily) for MA addiction, the authors identified participants who had completed at least 8 weeks of the trial (n=61 sertraline, n=68 placebo). They compared the proportions of MA-positive urine tests for weeks 8-12 of the trial for these subjects to their pre-randomization baseline, and identified those subjects who increased MA use during treatment. Using classification trees, they then assessed all data collected during the study to identify factors associated with increasing MA use during treatment with sertraline, compared to placebo. More subjects in the sertraline condition increased MA use during treatment (n=13) than in the placebo condition (n=5; p=0.03). Classification trees identified multiple factors from both pre-treatment and in-treatment data that were associated with increased MA use during treatment. Only elevated in-treatment craving for MA specifically characterized subjects in the sertraline group who increased their MA use. .Some MA-abusing individuals treated with SSRIs have sustained craving with an increased propensity to relapse during treatment despite psychosocial treatment interventions. Zorick T, Sugar, CA, Hellemanne G, Shoptaw S, London ED. Poor response to sertraline in methamphetamine dependence is associated with sustained craving for methamphetamine. Drug Alcohol Depend 2011 May 16 (Epub ahead of print).

A Method To Quantify Illicit Intake Of Drugs From Urine: Methamphetamine Qualitative urinalysis can verify abstinence of drug misuse but cannot detect changes in drug intake. For drugs with slow elimination, such as methamphetamine (MA), a single episode of abuse can result in up to 5 days of positive urine drug screens. Thus, interventions that produce substantial decreases in drug use but do not achieve almost complete abstinence are classified as ineffective. Using nonpharmacologic doses of deuterium-labeled l-methamphetamine (l-MA-d(3)) the authors have developed a simple, robust method that reliably estimates changes in MA intake. Twelve subjects were dosed with 5 mg of l-MA-d(3) daily and challenged with 15, 30, and 45 mg of nonlabeled d-MA (d-MA-d(0)) after reaching plasma steady status of l-MA-d(3). Urinary concentration ratios of d-MA-d(0) to l-MA-d(3) provided clear separation of the administered doses with as little as 15-mg dose increments. Administered doses could not be resolved using d-MA-d(0) concentrations alone. In conclusion, the urinary [d-MA-d(0)]: [l-MA-d(3)] provides a quantitative, continuous measure of illicit MA exposure. The method reliably detects small, clinically relevant changes in illicit MA intake from random urine specimens, is amenable to deployment in clinical trials, and can be used to quantify patterns of MA abuse. Li L, Galloway GP, Verotta D, Everhart ET, Baggott MJ, Coyle JR, Lopez JC, Mendelson J. A method to quantify illicit intake of drugs from urine: methamphetamine. J Pharmacol Exp Ther. 2011 Jul; 338(1): 31-36. Epub 2011 Mar 30.

A Direct Comparison Of The Behavioral And Physiological Effects Of Methamphetamine And 3,4-Methylenedioxymethamphetamine (MDMA) In Humans Despite their chemical similarities, methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) produce differing neurochemical and behavioral responses in animals. In humans, individual studies of methamphetamine and MDMA indicate that the drugs engender overlapping and divergent effects; there are only limited data comparing the two drugs in the same individuals .This study examined the effects of methamphetamine and MDMA using a within-subject design. Eleven adult volunteers completed this 13-day residential laboratory study, which consisted of four 3-day blocks of sessions. On the first day of each block, participants received oral methamphetamine (20, 40 mg), MDMA (100 mg), or placebo. Drug plasma concentrations, cardiovascular, subjective, and cognitive/psychomotor performance effects were assessed before drug administration and after. Food intake and sleep were also assessed. On subsequent days of each block, placebo was administered and residual effects were assessed. Acutely, both drugs increased cardiovascular measures and "positive" subjective effects and decreased food intake. In addition, when asked to identify each drug, participants had difficulty distinguishing between the amphetamines. The drugs also produced divergent effects: methamphetamine improved performance and disrupted sleep, while MDMA increased "negative" subjective-effect ratings. Few residual drug effects were noted for either drug. It is possible that the differences observed could explain the differential public perception and abuse potential associated with these amphetamines. Alternatively, the route of administration by which the drugs are used recreationally might account for the many of the effects attributed to these drugs (i. e. , MDMA is primarily used orally, whereas methamphetamine is used by routes associated with higher abuse potential). Kirkpatrick MG, Gunderson EW, Perez AY, Haney M, Foltin RW, Hart CL. A direct comparison of the behavioral and physiological effects of methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) in humans. Psychopharmacology (Berl). 2011 Jun 30. [Epub ahead of print]

Physiological And Subjective Effects Of Acute Intranasal Methamphetamine During Extended-Release Alprazolam Maintenance Medications development for methamphetamine dependence is ongoing, but no widely accepted, effective pharmacotherapy has been identified. Previous studies have demonstrated neurobiological perturbations to central GABA(A) activity following chronic stimulant use, and that positive modulation of GABA(A) receptors attenuates the neurochemical and behavioral response to stimulant drugs such as methamphetamine. Therefore, GABA(A) modulators could be useful as pharmacotherapies for stimulant-use disorders. This study tested the hypothesis that intranasal methamphetamine would be safe and well tolerated during maintenance on extended-release alprazolam (XR), and that the effects of methamphetamine would be attenuated. Eight non-treatment-seeking, stimulant-dependent individuals completed an inpatient experiment in which ascending doses of intranasal methamphetamine (0, 5, 10, 20 and 30mg) were administered after four days of alprazolam XR maintenance (0 and 1mg/day). Intranasal methamphetamine produced prototypical effects (e.g., increased positive subjective ratings and elevated cardiovascular signs). The combination of intranasal methamphetamine and alprazolam XR was safe and well tolerated. Alprazolam XR produced small, but orderly, reductions in some of the subjective effects of methamphetamine, and performance impairment. The present results demonstrate that methamphetamine use during alprazolam XR treatment would not pose a significant safety risk. Given the potential of GABA(A) positive modulators to manage certain aspects of stimulant abuse and dependence

(i.e., drug-induced seizures, anxiety and stress), but the relatively small impact on the acute abuse-related effects of methamphetamine observed here, additional research with GABA(A) positive modulators is warranted, but should consider their use as an adjunct component of combination behavioral and/or drug treatment. Lile JA, Stoops WW, Glaser PE, Hays LR, Rush CR. Physiological and subjective effects of acute intranasal methamphetamine during extended-release alprazolam maintenance. Drug Alcohol Depend. 2011 Jul 5. [Epub ahead of print]

Discriminative-Stimulus, Subject-Rated, And Physiological Effects Of Methamphetamine In Humans Pretreated With Aripiprazole Methamphetamine is thought to produce its behavioral effects by facilitating release of dopamine, serotonin (5-HT) and norepinephrine. Results from animal studies support this notion, whereas results from human laboratory studies have not consistently demonstrated the importance of monoamine systems in the behavioral effects of methamphetamine. Human drug-discrimination procedures are well suited to assess neuropharmacological mechanisms of the training drug by studying pharmacological manipulation. In this human laboratory study, 6 participants with a history of recreational stimulant use learned to discriminate 10 mg oral methamphetamine. After acquiring the discrimination (ie, ≥80% correct responding on 4 consecutive sessions), the effects of a range of doses of methamphetamine (0, 2.5, 5, 10, and 15 mg), alone and in combination with 0 and 20 mg aripiprazole (a partial agonist at D2 and 5-HT1A receptors), were assessed. Methamphetamine alone functioned as a discriminative stimulus, produced prototypical stimulant-like subject-rated drug effects (eg, increased ratings of Good Effects, Talkative-Friendly, and Willing to Pay For) and elevated cardiovascular indices. These effects were generally a function of dose. Aripiprazole alone did not occasion methamphetamine-appropriate responding or produce subject-rated effects but modestly impaired performance. Administration of aripiprazole significantly attenuated the discriminative-stimulus and cardiovascular effects of methamphetamine, as well as some of the subject-rated drug effects. These results indicate that monoamine systems likely play a role in the behavioral effects of methamphetamine in humans. Moreover, given the concordance between past results with d-amphetamine and the present findings, d-amphetamine can likely serve as a model for the pharmacological effects of methamphetamine. Sevak RJ, Vansickel AR, Stoops WW, Glaser PE, Hays LR, Rush CR. Discriminative-stimulus, subject-rated, and physiological effects of methamphetamine in humans pretreated with aripiprazole. J Clin Psychopharmacol. 2011 Aug; 31(4): 470-480.

Interventions For Non-Injection Substance Use Among Us Men Who Have Sex With Men: What Is Needed SUMSM are at high risk for HIV infection, yet there are critical gaps in knowledge regarding the contribution of non-injection substance use to the HIV epidemic among US MSM. The field will benefit from additional insights on the natural history of non-injection substance use and the predictors of different drug use trajectories. Substance treatment and HIV prevention services should be employed to address the needs of SUMSM. Efforts to develop evidence-based interventions need to be accelerated. Emphasis should be placed on finding sustainable, effective strategies that deal with non-injection substance use and risk for HIV infection. While the authors have focused on US MSM, emerging evidence indicates that non-injection substance use is also driving the MSM HIV epidemic in other regions; yet, the majority of intervention trials have been conducted within the US and other Western countries [5, 90–94]. Ultimately, researchers should strive to develop efficacious intervention strategies that are scalable, cost-effective and sustainable for the diversity of SUMSM. Santos GM, Das M, Colfax

GN. Interventions for non-injection substance use among US men who have sex with men: what is needed. AIDS Behav. 2011 Apr; 15 Suppl 1: S51-56.

Sertraline Delays Relapse in Recently Abstinent Cocaine-Dependent Patients with Depressive Symptoms The aim of this study was to determine whether the selective serotonin reuptake inhibitor sertraline at 200 mg/day delays relapse in recently abstinent cocaine dependent individuals The design was a 12-week, double blind, placebo-controlled clinical trial with 2-week residential stay followed by 10-wk outpatient participation The study setting was a Veterans Affairs residential unit and outpatient treatment research program Participants comprised 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 (wks 1-2) and randomized to receive sertraline or placebo. Participants then participated on an outpatient 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 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 toward 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 vs 13.2 + 10.5; $z = 2.89$, $p = 0.004$) and relapse (21.3 + 10.8 vs 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 two 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 2011 Jun 24. [Epub ahead of print]

Aripiprazole Maintenance Increases Smoked Cocaine Self-administration in Humans Partial dopamine receptor agonists have been proposed as candidate pharmacotherapies for cocaine dependence. This 42-day, within-subject, human laboratory study assessed how maintenance on aripiprazole, a partial D(2) receptor agonist, influenced smoked cocaine self-administration, cardiovascular measures, subjective effects, and cocaine craving in nontreatment-seeking, cocaine-dependent volunteers. In order to achieve steady-state concentrations, participants (n = 8 men) were administered placebo and aripiprazole (15 mg/day) capsules in counter-balanced order for 21 days. A smoked cocaine dose-response curve (0, 12, 25, 50 mg) was determined twice under placebo and aripiprazole maintenance. Sessions comprised a "sample" trial, when participants smoked the cocaine dose available that session, and five choice trials, when they responded on a progressive-ratio schedule of reinforcement to receive the cocaine dose or receive $5.00. Cocaine's reinforcing, subjective, and cardiovascular effects were dose-dependent. Aripiprazole significantly increased cocaine (12, 25 mg) self-administration. Following a single administration of cocaine (25 mg), aripiprazole decreased ratings of how much participants would pay for that dose. Following repeated cocaine (50 mg) self-administration, aripiprazole decreased ratings of cocaine quality, craving, and good drug effect

as compared to placebo. These data suggest that aripiprazole may have increased self-administration to compensate for a blunted subjective cocaine effect. Overall, the findings do not suggest aripiprazole would be useful for treating cocaine dependence. Haney M, Rubin E, Foltin RW. Aripiprazole maintenance increases smoked cocaine self-administration in humans. Psychopharmacology (Berl). 2011 Aug; 216(3): 379-387. Epub 2011 Mar 5.

Pharmacokinetics Of Intranasal Crushed Oxycontin And Intravenous Oxycodone In Nondependent Prescription Opioid Abusers This study evaluated the pharmacokinetic profile of IN OxyContin in comparison to IV oxycodone. The IN drug administration method used in this study is clinically relevant because OxyContin was administered in the manner by which it is commonly abused—by snorting crushed tablets. There are several important study results. First, crushed OxyContin was rapidly absorbed by the IN route and was reliably detected in plasma within 5 minutes of dosing. Second, OxyContin had high intranasal bioavailability: 78% and 75% after 15 mg/70 kg and 30 mg/70 kg, respectively. Third, the t1/2 of IN OxyContin was approximately 3. 5 hours and was not statistically different than the t1/2 of 3. 3 hours for IV oxycodone. These data demonstrate that crushing and snorting OxyContin tablets is a highly efficient drug delivery method that clearly bypasses the extended release Acrocontin (Purdue Pharma) drug delivery matrix. The major Lofwall MR, Moody DE, Fang WB, Nuzzo PA, Walsh SL. Pharmacokinetics of Intranasal Crushed OxyContin and Intravenous Oxycodone in Nondependent Prescription Opioid Abusers. J Clin Pharmacol. 2011 May 24. [Epub ahead of print]

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 pharmaco-therapies, 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. The study design was a randomized, double-blind, placebo-controlled, cross-over study conducted in an in-patient research unit at the University of Kentucky. Participant were healthy adults (n=10) abusing, but not physically dependent on, intranasal opioids. Six sessions (72 hours apart) tested five intranasal doses [0/0, crushed buprenorphine (2, 8mg), crushed buprenorphine/naloxone (2/0.5, 8/2mg)] and one intravenous dose (0.8 mg buprenorphine/0.2mg naloxone for bioavailability assessment). Plasma samples, physiological, subject- and observer-rated measures were collected before and for up to 72 hours after drug administration. Findings: 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 8mg compared to 8/2mg, 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 8/2mg, 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; 106(8): 1460-1473. Epub 2011 May 3.

A Placebo Controlled Trial Of Memantine As An Adjunct To Oral Naltrexone For Opioid Dependence Preclinical findings suggest that the inhibition of NMDA glutamatergic neurotransmission may have beneficial effects in the treatment of opioid dependence. The authors hypothesized that memantine, a low-potency, uncompetitive NMDA receptor antagonist, would be safe and effective when used as an adjunct to oral naltrexone in the treatment of opioid dependence, particularly in preventing relapse to opiate use in detoxified individuals. Opioid-dependent participants (N=112) were enrolled. Following detoxification all participants were inducted onto oral naltrexone and were randomized to receive memantine 15mg bid (N=27), memantine 30mg bid (N=27) or placebo (N=27) for 12-weeks in combination with naltrexone 50mg/day and individual relapse-prevention therapy. The primary outcome was the retention in treatment since treatment dropout is most commonly associated with relapse to opiate use. Twenty-six percent of participants withdrew from treatment prior to starting naltrexone. Of those that were randomized 35% completed 4 weeks only, and 24% completed all 12 weeks of treatment. There was no significant difference in treatment retention or heroin use, opiate withdrawal symptoms and craving between the groups treated with memantine vs. placebo. Thus, the efficacy of memantine 30 or 60mg/day as an adjunct to oral naltrexone for the treatment of opiate dependence was not supported. Bisaga A, Sullivan MA, Cheng WY, Carpenter KM, Mariani JJ, Levin FR, Raby WN, Nunes EV. A placebo controlled trial of memantine as an adjunct to oral naltrexone for opioid dependence. Drug Alcohol Depend. 2011 Jun 27. [Epub ahead of print]

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 KC, Stein JA, Heinzerling KG, Pan D, Magladry C, Hays RD. Clinical correlates of health-related quality of life among opioid-dependent patients. Qual Life Res 2011 Feb. 17 (Epub ahead of print).

Sleep Disturbance and the Effects Of Extended-Release Zolpidem During Cannabis Withdrawal Sleep difficulty is a common symptom of cannabis withdrawal, but little research has objectively measured sleep or explored the effects of hypnotic medication on sleep during cannabis withdrawal. Twenty daily cannabis users completed a within-subject crossover study. Participants alternated between periods of ad libitum cannabis use and short-term cannabis abstinence (3 days). Placebo was administered at bedtime during one abstinence period (withdrawal test) and extended-release zolpidem, a non-benzodiazepine GABA(A) receptor agonist, was administered during the other. Polysomnographic (PSG) sleep architecture measures, subjective ratings, and cognitive performance effects were assessed each day. During the placebo-abstinence period, participants had decreased sleep efficiency, total sleep time, percent time spent in Stage 1 and Stage 2 sleep, REM latency and subjective sleep quality, as well as increased sleep latency and time spent in REM sleep compared with when they were using cannabis. Zolpidem attenuated the effects of abstinence on sleep architecture and normalized sleep efficiency scores, but had no effect on sleep latency. Zolpidem was not associated with any significant side effects or next-day cognitive performance impairments. These data extend prior research that indicates abrupt abstinence from cannabis can lead to clinically significant sleep disruption in daily users. The findings also indicate that sleep disruption associated with cannabis withdrawal can be attenuated by zolpidem, suggesting that hypnotic medications might be useful adjunct pharmacotherapies in the treatment of cannabis use disorders. Vandrey R, Smith MT, McCann UD, Budney AJ, Curran EM. Sleep disturbance and the effects of extended-release zolpidem during cannabis withdrawal. Drug Alcohol Depend. 2011 Aug 1; 117 (1): 38-44. Epub 2011 Feb 5.

Comparison Of Clinical Trial Recruitment Populations: Treatment-Seeking Characteristics Of Opioid-, Cocaine-, and Cannabis-Using Participants This study examined the treatment history and intention to seek treatment among 489 individuals interested in substance use disorder clinical trial participation. Opioid and cocaine users were more likely than cannabis users to report having received treatment for substance use in the past and more likely than cannabis users to report planning to seek treatment for substance use before exposure to recruitment advertising. Free cost was the aspect of clinical trial participation that most influenced the decision to make an intake evaluation appointment for opioid-dependent patients as compared with cocaine- and cannabis-dependent participants, and the availability of individual psychotherapy most influenced those who were cannabis dependent. Cannabis-dependent individuals evaluated for clinical trial participation reported that recruitment advertising was an important factor in leading them to seek treatment. These results have implications for clinical trial recruitment and public health efforts directed at encouraging cannabis-dependent individuals to seek treatment. Mariani JJ, Cheng WY, Bisaga A, Sullivan M, Carpenter K, Nunes EV, Levin FR. Comparison of clinical trial recruitment populations: treatment-seeking characteristics of opioid-, cocaine-, and cannabis-using participants. J Subst Abuse Treat. 2011 Jun; 40(4): 426-430. Epub 2011 Mar 24.

The Association Between Outpatient Buprenorphine Detoxification Duration and Clinical Treatment Outcomes: A Review The association between buprenorphine taper duration and treatment outcomes is not well understood. This review evaluated whether duration of outpatient buprenorphine taper is significantly associated with treatment outcomes. Studies that were published in peer-reviewed journals, administered buprenorphine as an outpatient taper to

opioid-dependent participants, and provided data on at least one of three primary treatment outcome measures (opioid abstinence, retention, peak withdrawal severity) were reviewed. Primary treatment outcomes were evaluated as a function of taper duration using hierarchical linear regressions with pre-taper maintenance duration as a cofactor Twenty-eight studies were reviewed. Taper duration significantly predicted percent of opioid-negative samples provided during treatment, however pre-taper maintenance period predicted percent participants abstinent on the final day of treatment. High rates of relapse were reported. No significant association between taper duration and retention in treatment or peak withdrawal severity was observed. The data reviewed here suggest taper duration is associated with opioid abstinence achieved during detoxification but not with other markers of treatment outcome. The reviewed studies varied widely on several parameters (e.g., frequency of urinalysis testing, provision of ancillary medications) that may influence treatment outcome and thus could have interfered with the ability to identify relationships between taper duration and outcomes. Future studies evaluating opioid detoxification should utilize rigorous experimental methods and report a wider range of outcome measures in order to help advance our understanding of the association between taper duration and treatment outcomes. Dunn KE, Sigmon SC, Strain EC, Heil SH, Higgins ST The association between outpatient buprenorphine detoxification duration and clinical treatment outcomes: A review Drug Alcohol Depend. 2011 Jul 7. [Epub ahead of print]

Buprenorphine For Prescription Opioid Addiction In A Patient With Depression And Alcohol Dependence: Case Study Buprenorphine is an effective treatment for opioid dependence when used as directed, and if diverted or abused, it carries less risk of overdose than methadone or other full agonists. The combination product is recommended (except during pregnancy) because it appears to have lower abuse liability than the monotherapy product. It can be prescribed in specialized addiction treatment programs or through office-based treatment by certified physicians in any medical practice, including addiction medicine, psychiatry, and primary care. It may not work as well as methadone for some patients, but it has made agonist treatment more accessible to patients who needed it but were unwilling or unable to participate. It may assist with engaging patients in an array of ongoing complementary treatments. The case presented here reviews its use to treat a patient who was addicted to prescription opioids and alcohol, had comorbid depression, was ambivalent about stopping alcohol use, and felt demoralized by interpersonal problems. The treatment course was not always smooth, but through coordinated pharmacological and psychosocial interventions over several months, the case of Ms. B depicts characteristic positive outcomes. Buprenorphine as part of a comprehensive medicationassisted recovery approach—combined, for example, with counseling, treatment of additional nonopioid substance use disorders, and treatment of comorbid psychiatric illness— provides an important tool for relapse prevention and should be a mainstay of the standard repertoire for treating opioid dependence. Fishman MJ, Wu LT, Woody GE. Buprenorphine for prescription opioid addiction in a patient with depression and alcohol dependence. Am J Psychiatry. 2011 Jul; 168(7): 675-679.

Differences In Onset And Abuse/Dependence Episodes Between Prescription Opioids And Heroin: Results From The National Epidemiologic Survey On Alcohol And Related Conditions The purposes of this study were to examine patterns of onset and abuse/dependence episodes of prescription opioid (PO) and heroin use disorders in a national sample of adults, and to explore differences by gender and substance abuse treatment status. Analyses of data from the

2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (N = 43,093). Of all respondents, 5% (n = 1815) reported a history of nonmedical PO use (NMPOU) and 0.3% (n = 150) a history of heroin use. Abuse was more prevalent than dependence among NMPOUs (PO abuse, 29%; dependence, 7%) and heroin users (heroin abuse, 63%; dependence, 28%). Heroin users reported a short mean interval from first use to onset of abuse (1.5 years) or dependence (2.0 years), and a lengthy mean duration for the longest episode of abuse (66 months) or dependence (59 months); the corresponding mean estimates for PO abuse and dependence among NMPOUs were 2.6 and 2.9 years, respectively, and 31 and 49 months, respectively. The mean number of years from first use to remission from the most recent episode was 6.9 years for PO abuse and 8.1 years for dependence; the mean number of years from first heroin use to remission from the most recent episode was 8.5 years for heroin abuse and 9.7 years for dependence. Most individuals with PO or heroin use disorders were remitted from the most recent episode. Treated individuals, whether their problem was heroin or POs, tended to have a longer mean duration of an episode than untreated individuals. Periodic remissions from opioid or heroin abuse or dependence episodes occur commonly but take a long time. Timely and effective use of treatment services are needed to mitigate the many adverse consequences from opioid/heroin abuse and dependence. Wu LT, Woody GE, Yang C, Mannelli P, Blazer DG. Differences in onset and abuse/dependence episodes between prescription opioids and heroin: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Subst Abuse Rehabil. 2011 May; 2011(2): 77-88.

Discriminative Stimulus Effects of Tramadol in Humans Tramadol is an unscheduled atypical analgesic that acts as an agonist at μ-opioid receptors and inhibits monoamine reuptake. Tramadol can suppress opioid withdrawal, and chronic administration can produce opioid physical dependence; however, diversion and abuse of tramadol is low. The present study further characterized tramadol in a three-choice discrimination procedure. Nondependent volunteers with active stimulant and opioid use (n = 8) participated in this residential laboratory study. Subjects were trained to discriminate between placebo, hydromorphone (8 mg), and methylphenidate (60 mg), and tests of acquisition confirmed that all volunteers could discriminate between the training drugs. The following drug conditions were then tested during discrimination test sessions: placebo, hydromorphone (4 and 8 mg), methylphenidate (30 and 60 mg), and tramadol (50, 100, 200, and 400 mg). In addition to discrimination measures, which included discrete choice, point distribution, and operant responding, subjective and physiological effects were measured for each test condition. Both doses of hydromorphone and methylphenidate were identified as hydromorphone- and methylphenidate-like, respectively. Lower doses of tramadol were generally identified as placebo, with higher doses (200 and 400 mg) identified as hydromorphone, or opioid-like. The highest dose of tramadol increased ratings on the stimulant scale, but was not significantly identified as methylphenidate-like. Tramadol did not significantly increase subjective ratings associated with reinforcement. Taken together, these results extend previous work with tramadol as a potential medication for the treatment of opioid dependence and withdrawal, showing acute doses of tramadol exhibit a profile of effects similar to opioid agonists and may have abuse liability in certain populations. Duke AN, Bigelow GE**,** Lanier RK, Strain EC. Discriminative stimulus effects of tramadol in humans. J Pharmacol Exp Ther. 2011 Jul; 338(1): 255-262.

Cigarette and Cannabis Use Trajectories Among Adolescents in Treatment for Attention-Deficit/Hyperactivity Disorder and Substance Use Disorders Cigarette smoking is common in adolescents with attention-deficit/hyperactivity disorder (ADHD) and substance use disorders (SUD). However, little is known about the relationship between cigarette and cannabis use trajectories in the context of treatment for both ADHD and SUD. To address this research gap, the authors report collateral analyses from a 16-week randomized, controlled trial (n=303) of osmotic-release methylphenidate (OROS-MPH) in adolescents with ADHD concurrently receiving cognitive behavioral therapy (CBT) targeting non-nicotine SUD. Participants completed cigarette and cannabis use self-report at baseline and throughout treatment. Analyses were performed to explore the relationships between cigarette smoking, cannabis use, and other factors, such as medication treatment assignment (OROS-MPH versus placebo). Baseline (pre-treatment) cigarette smoking was positively correlated with cannabis use. Negligible decline in cigarette smoking during treatment for non-nicotine SUD was observed in both medication groups. Regular cigarette and cannabis users at baseline who reduced their cannabis use by >50% also reduced cigarette smoking (from 10.8±1.1 to 6.2±1.1 cigarettes per day). Findings highlight the challenging nature of concurrent cannabis and cigarette use in adolescents with ADHD, but demonstrate that changes in use of these substances during treatment may occur in parallel. Gray KM, Riggs PD, Min SJ, Mikulich-Gilbertson SK, Bandyopadhyay D, Winhusen T. Cigarette and cannabis use trajectories among adolescents in treatment for attention-deficit/hyperactivity disorder and substance use disorders. Drug Alcohol Depend. 2011 Mar 14. [Epub ahead of print]

Stress- and Cue-Elicited Craving and Reactivity In Marijuana-Dependent Individuals Cue-elicited craving and stress responses have been identified as predictors of relapse in drug dependence, but little research exists on the contribution of these factors to marijuana use specifically. The aims of the present study were to evaluate (1) responses to a psychological stressor, (2) responses to marijuana-related cues, and (3) if an exposure to a psychological stressor augmented craving subsequently elicited by marijuana-related cue exposure in marijuana-dependent individuals. Subjective (craving, stress), neuroendocrine (adrenocortico-tropic hormone (ACTH), cortisol), and physiologic responses to the presentation of neutral and marijuana cues were assessed after randomization to a stress (Trier Social Stress Task (TSST)) or non-stress control condition in marijuana-dependent individuals. Outcome measures were assessed at baseline, post-stressor/pre-neutral cue, post-neutral cue, and post-marijuana cue. Eighty-seven participants completed procedures (stress group, $n = 45$; non-stress group, $n = 42$). The stress group had a significant increase over the non-stress group in stress rating ($p < 0.001$), craving ($p = 0.028$), cortisol ($p < 0.001$), and ACTH ($p < 0.001$) after the completion of the TSST. An increased craving response for all participants was seen following the presentation of the marijuana cues ($p = 0.005$). Following the TSST or non-stress condition, the non-stress group had an increase in craving to marijuana cues as compared to neutral cues ($p = 0.002$); an increase in craving was not observed in the stress group ($p = 0.404$). Marijuana cue exposure and a social stressor increased craving in marijuana-dependent individuals. Completion of the TSST did not increase craving response to subsequent marijuana cue exposure. McRae-Clark AL, Carter RE, Price KL, Baker NL, Thomas S, Saladin ME, Giarla K, Nicholas K, Brady KT. Stress- and cue-elicited craving and reactivity in marijuana-dependent individuals. Psychopharmacology (Berl). 2011 Jun 28. [Epub ahead of print]

Dose Response Effects Of Lisdexamfetamine Dimesylate Treatment In Adults With ADHD: An Exploratory Study The objective of this study was to explore dose-response effects of lisdexamfetamine dimesylate (LDX) treatment for ADHD. This was a 4-week, randomized, double-blinded, placebo-controlled, parallel-group, forced-dose titration study in adult participants, aged 18 to 55 years, meeting Diagnostic and Statistical Manual of Mental Disorders (4th ed. , text rev.) criteria for ADHD. Nearly all participants assigned to an LDX dose achieved their assigned dose with the exception of about 4% of participants assigned to the 50 mg or 14% assigned to the 70 mg doses. Higher doses of LDX led to greater improvements in ADHD-rating scale scores, independent of prior pharmacotherapy. This was evident for both inattentive and hyperactive-impulsive symptoms. The authors found some evidence for an interaction between LDX dose and baseline severity of ADHD symptoms. For LDX doses between 30 and 70 mg/d, the dose-response efficacy effect for LDX is not affected by prior pharmacotherapy, but patients with a greater severity of illness may benefit more from higher doses, especially for hyperactive-impulsive symptoms. The results do not provide information about doses above 70 mg/d, which is the maximum approved dose of LDX and the highest dose studied in ADHD clinical trials. (J. of Att. Dis. 2011. Faraone SV, Spencer TJ, Kollins SH, Glatt SJ, Goodman D. Dose Response Effects of Lisdexamfetamine Dimesylate Treatment in Adults With ADHD: An Exploratory Study. J Atten Disord. 2011 Apr 28. [Epub ahead of print]

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 Jul 8. [Epub ahead of print]

Chronic Tiagabine Administration And Aggressive Responding In Individuals With A History Of Substance Abuse And Antisocial Behavior Anticonvulsants, notably those which modulate GABA activity, have shown efficacy in reducing aggressive behavior. Previously, the authors found dose-related decreases in human aggressive responding following acute tiagabine administration. Here, they examined the effects of chronic tiagabine over a 5-week period. Twelve individuals at increased risk for aggressive and violent behavior (currently on parole/probation with personality and/or substance use disorders) were randomly assigned to placebo (n = 6) or an escalating dose sequence of placebo, 4 mg, 8 mg, 12 mg, placebo (n = 6). Data were analyzed using both frequentist and Bayesian mixed models, evaluating aggressive behavior as a function of time, dose condition, and their interaction. For aggressive responding, there was a significant interaction of drug condition and time. Aggression in the tiagabine condition decreased for each additional week in the study, while participants in the placebo condition failed to demonstrate similar change over time. For monetary-reinforced responding, no drug or drug by time interactions were observed, suggesting specificity of drug effects on aggression. The small number of subjects limits the generality of the findings, and previous studies with tiagabine are limited to acute dosing and case report investigations. However, the present data provide an indication that tiagabine merits further examination as an agent for management of impulsive aggression. Gowin JL, Green CE, Alcorn JL, Swann AC, Moeller FG, Lane SD. Chronic tiagabine administration and aggressive responding in individuals with a history of substance abuse and antisocial behavior. J Psychopharmacol. 2011 Jul 5. [Epub ahead of print]

Association Between CHRNA5 Genetic Variation At Rs16969968 And Brain Reactivity To Smoking Images In Nicotine Dependent Women Tobacco smoking is the leading preventable cause of death in the developed world. Identifying risk factors for smoking may lead to more effective treatments. Genome wide association studies revealed a relationship between development of nicotine dependence and a single-nucleotide polymorphism (SNP, rs16969968) of the nicotine acetylcholine receptor (nAChR) alpha-5 subunit gene (CHRNA5). The relationship between this SNP and other factors contributing to smoking behavior such as smoking cue reactivity is unclear. The authors assessed the role of rs16969968 on brain functional MRI (fMRI) reactivity to smoking cues by studying nicotine dependent women with the nicotine dependence 'risk' allele (A allele, N=14) and without the 'risk' allele (G/G smokers, N=10). Nicotine dependence severity, as assessed with the Fagerstrom test for nicotine dependence, smoking pack-years, and expired carbon monoxide levels, were equivalent in these groups. They observed a group difference in fMRI reactivity; women without the A allele (G/G smokers) showed greater fMRI reactivity to smoking images in brain areas related to memory and habitual behavior such as the hippocampus and dorsal striatum. Their finding suggests that nicotine-dependent smokers lacking the rs16969968 A allele are more likely to recall smoking-related memories and engage in habitual responding to smoking cues than A allele smokers. Although more studies are necessary to determine the mechanism underlying and significance of this cue reactivity difference, these data suggest that smokers may develop and remain nicotine dependent due to different factors including genetics and cue reactivity. This finding may have implications for personalizing smoking treatment. Janes AC, Smoller JW, David SP, Frederick BD, Haddad S, Basu A, Fava M, Evins AE, Kaufman MJ. Association between CHRNA5 genetic variation at rs16969968 and brain reactivity to smoking images in nicotine dependent women. Drug Alcohol Depend. 2011 Jul 14. [Epub ahead of print]

Varenicline As A Smoking Cessation Aid In Schizophrenia: Effects On Smoking Behavior And Reward Sensitivity Smoking rates are up to five times higher in people with schizophrenia than in the general population, placing these individuals at high risk for smoking-related health problems. Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, is a promising aid for smoking cessation in this population. To maximize treatment efficacy while minimizing risks, it is critical to identify reliable predictors of positive response to varenicline in smokers with schizophrenia. Negative symptoms of schizophrenia are related to dysfunctions in the brain reward system, are associated with nicotine dependence, and may be improved by nicotine or nicotinic receptor agonists, suggesting that smoking cessation may be especially difficult for patients with substantial negative symptoms. The purpose of the study was to evaluate negative symptoms as predictors of response to varenicline. Patients with schizophrenia (N = 53) completed a 12-week smoking cessation trial combining varenicline with cognitive behavioral therapy. Negative symptoms were assessed via the Scale for the Assessment of Negative Symptoms (Andreasen 1983). Outcomes included smoking abstinence as assessed by self-report and expired carbon monoxide. Change in performance on a probabilistic reward task was used as an index of change in reward sensitivity during treatment. At week 12, 32 participants met criteria for 14-day point-prevalence abstinence. Patients with lower baseline symptoms of affective flattening (more typical affect) were more likely to achieve smoking abstinence and demonstrated larger increases in reward sensitivity during treatment. These data suggest that affective flattening symptoms in smokers with schizophrenia may predict response to varenicline. Dutra SJ, Stoeckel LE, Carlini SV, Pizzagalli DA, Evins AE. Varenicline as a smoking cessation aid in schizophrenia: effects on smoking behavior and reward sensitivity. Psychopharmacology (Berl). 2011 Jun 22. [Epub ahead of print]

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. 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 15. [Epub ahead of print]

Cigarette Smoking Status In Pathological Gamblers: Association With Impulsivity And Cognitive Flexibility While the majority of pathological gamblers are current cigarette smokers (CS), some have quit smoking (former smokers, FS) while others never smoked (never smokers, NS). The reasons for elevated smoking rates in pathological gambling are not known, but gamblers may use nicotine as a putative cognitive enhancer. This study evaluated impulsivity and cognitive flexibility in a sample of pathological gamblers with differing smoking status. Fifty-five subjects with pathological gambling (CS, n=34; FS, n=10; NS, n=11) underwent cognitive assessments using the Stop-Signal (SST) and Intradimensional/Extra-dimensional (ID/ED) set-shift tasks. CS reported less severe gambling problems than either FS or NS on the Yale Brown Obsessive Compulsive Scale modified for Pathological Gambling, and CS was associated with significantly fewer directional errors on the SST task, compared to NS. In addition, in CS, higher daily cigarette consumption was associated with fewer total errors on the ID/ED task. The potential role of nicotine as a cognitive enhancer was supported by objective tests of impulsivity and cognitive flexibility. Human laboratory studies using nicotine challenges in pathological gambling will shed further light on this relationship. Mooney ME, Odlaug BL, Kim SW, Grant JE. Cigarette smoking status in pathological gamblers: Association with impulsivity and cognitive flexibility. Drug Alcohol Depend. 2011 Aug 1; 117(1): 74-77. Epub 2011 Feb 5.

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 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), nontreatment 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. 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. The results of this study suggest 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, our 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 May 12. [Epub ahead of print]

Mindfulness Impairments In Individuals Seeking Treatment For Substance Use Disorders
Mindfulness training may be an effective treatment for substance use disorders (SUDs). Little research has been done, however, on baseline levels of mindfulness in the substance using population. The authors investigated mindfulness levels using the Mindful Attention Awareness Scale (MAAS) in individuals presenting for substance use treatment, and compared polydrug vs. monodrug users, as well as investigated for differences between groups based on substance used, predicting that group means would fall below the mean obtained from a lare ge national adult sample, that the different drug groups would have comparable scores, and that the polydrug users would have a significantly lower score than do monodrug users. They found that the means of most drug groups were below the national mean, and that the polydrug users had a lower score on the MAAS than did monodrug users (4 vs. 3.6, $p = 0.04$). They were also surprised to find that opiate users had a significantly higher score (4.31) than did users of other substances ($p = 0.02$). These results suggest that mindfulness deficits may be common in the substance using population, that there may be sub-groups in which these deficits are more pronounced, and that they may be a suitable focus of SUD treatment. These findings lend support to the ongoing development of mindfulness-based treatments for SUDs, and suggest that particular sub-groups may benefit more than others. Future research can aim at clarifying these deficits, and at elucidating their clinical relevance. Dakwar E, Mariani JP, Levin FR. Mindfulness impairments in individuals seeking treatment for substance use disorders. Am J Drug Alcohol Abuse. 2011 May; 37(3): 165-169. Epub 2011 Mar 17.

Examining Naltrexone and Alcohol Effects In A Minority Population: Results From An Initial Human Laboratory Study Prior clinical findings have indicated a potential lack of naltrexone efficacy among African Americans with alcohol dependence. However, no definitive conclusions have been drawn due to the relatively small numbers of African Americans in most alcohol treatment trials. The purpose of this study was to examine alcohol and naltrexone effects on healthy African-American individuals in a laboratory environment. Nonalcohol-dependent social drinking adults of African descent ($n = 43$) were recruited for participation. After consenting and completing the baseline assessment, they participated in four separate alcohol challenge sessions each separated by at least 10 days. During each of the sessions, subjects were administered alcohol or sham drinks, after pretreatment with either naltrexone (50 mg/day) or placebo in a double-blind fashion. The order of the four sessions was randomly assigned. During each session, breath alcohol levels and subjective responses were measured. Results indicate an alcohol effect among these subjects for subjective responses, but no naltrexone effect. Similar to the apparent lack of clinical efficacy findings, naltrexone does not appear to impact alcohol effects in African-American social drinkers. Future studies should investigate African-American populations with heavy drinking as well as alcohol-dependent subjects in order to strengthen the parallels to clinical findings. Plebani JG, Oslin DW, Lynch KG. Examining naltrexone and alcohol effects in a minority population: results from an initial human laboratory study. Am J Addict. 2011 Jul; 20(4): 330-336.Epub 2011 May 31.

Methylphenidate Increases Cigarette Smoking In Participants With ADHD
Methylphenidate (Ritalin) is commonly prescribed for behavioral problems associated with attention deficit/hyperactivity disorder (ADHD). The results of previous studies suggest that methylphenidate increases cigarette smoking in participants without psychiatric diagnoses. Whether methylphenidate increases cigarette smoking in participants diagnosed with ADHD is

unknown. In this within-subjects, repeated measures experiment, the acute effects of a range of doses of methylphenidate (10, 20, and 40 mg) and placebo were assessed in nine cigarette smokers who were not attempting to quit and met diagnostic criteria for ADHD but no other Axis I psychiatric disorders other than nicotine dependence. Each dose of methylphenidate was tested once while placebo was tested twice. One hour after ingesting drug, participants were allowed to smoke ad libitum for 4 h. Measures of smoking included total cigarettes smoked, total puffs, and carbon monoxide levels. Snacks and decaffeinated drinks were available ad libitum; caloric intake during the 4-h smoking session was calculated. Methylphenidate increased the total number of cigarettes smoked, total number of puffs, and carbon monoxide levels. Methylphenidate decreased the number of food items consumed and caloric intake. The results of this experiment suggest that acutely administered methylphenidate increases cigarette smoking in participants with ADHD, which is concordant with findings from previous studies that tested healthy young adults. These data indicate that clinicians may need to consider non-stimulant options or counsel their patients before starting methylphenidate when managing ADHD-diagnosed individuals who smoke. Vansickel AR, Stoops WW, Glaser PE, Poole MM, Rush CR. Methylphenidate increases cigarette smoking in participants with ADHD. Psychopharmacology (Berl). 2011 May 18. [Epub ahead of print]

Human Mu Opioid Receptor (OPRM1 A118G) Polymorphism Is Associated With Brain Mu-Opioid Receptor Binding Potential In Smokers Evidence points to the endogenous opioid system, and the mu-opioid receptor (MOR) in particular, in mediating the rewarding effects of drugs of abuse, including nicotine. A single nucleotide polymorphism (SNP) in the human MOR gene (OPRM1 A118G) has been shown to alter receptor protein level in preclinical models and smoking behavior in humans. To clarify the underlying mechanisms for these associations, the authors conducted an in vivo investigation of the effects of OPRM1 A118G genotype on MOR binding potential (BP(ND) or receptor availability). Twenty-two smokers prescreened for genotype (12 A/A, 10 */G) completed two [(11)C]carfentanil positron emission tomography (PET) imaging sessions following overnight abstinence and exposure to a nicotine-containing cigarette and a denicotinized cigarette. Independent of session, smokers homozygous for the wild-type OPRM1 A allele exhibited significantly higher levels of MOR BP(ND) than smokers carrying the G allele in bilateral amygdala, left thalamus, and left anterior cingulate cortex. Among G allele carriers, the extent of subjective reward difference (denicotinized versus nicotine cigarette) was associated significantly with MOR BP(ND) difference in right amygdala, caudate, anterior cingulate cortex, and thalamus. Future translational investigations can elucidate the role of MORs in nicotine addiction, which may lead to development of novel therapeutics. Ray R, Ruparel K, Newberg A, Wileyto EP, Loughead JW, Divgi C, Blendy JA, Logan J, Zubieta JK, Lerman C. Human Mu Opioid Receptor (OPRM1 A118G) polymorphism is associated with brain mu-opioid receptor binding potential in smokers. Proc Natl Acad Sci U S A. 2011 May 31; 108(22): 9268-9273. Epub 2011 May 16.

Association of the Nicotine Metabolite Ratio and CHRNA5/CHRNA3 Polymorphisms With Smoking Rate Among Treatment-Seeking Smokers Genome-wide association studies have linked single-nucleotide polymorphisms (SNPs) in the CHRNA5/A3/B4 gene cluster with heaviness of smoking. The nicotine metabolite ratio (NMR), a measure of the rate of nicotine metabolism, is associated with the number of cigarettes per day (CPD) and likelihood of cessation. The authors tested the potential interacting effects of these two risk factors on CPD.

Pretreatment data from three prior clinical trials were pooled for analysis. One thousand and thirty treatment seekers of European ancestry with genotype data for the CHRNA5/A3/B4 SNPs rs578776 and rs1051730 and complete data for NMR and CPD at pretreatment were included. Data for the third SNP, rs16969968, were available for 677 individuals. Linear regression models estimated the main and interacting effects of genotype and NMR on CPD. The authors confirmed independent associations between the NMR and CPD as well as between the SNPs rs16969968 and rs1051730 and CPD. They did not detect a significant interaction between NMR and any of the SNPs examined. This study demonstrates the additive and independent association of the NMR and SNPs in the CHRNA5/A3/B4 gene cluster with smoking rate in treatment-seeking smokers. Falcone M, Jepson C, Benowitz N, Bergen AW, Pinto A, Wileyto EP, Baldwin D, Tyndale RF, Lerman C, Ray R. Association of the nicotine metabolite ratio and CHRNA5/CHRNA3 polymorphisms with smoking rate among treatment-seeking smokers. Nicotine Tob Res. 2011 Jun; 13(6): 498-503. Epub 2011 Mar 8.

Lorcaserin, a 5HT2c Agonist, Decreases Nicotine Self-Administration in Female Rats
Lorcaserin, a selective 5HT2c agonist, has been shown to facilitate weight loss in obese populations. It was assessed for its efficacy in reducing nicotine self-administration in young adult female Sprague Dawley rats. The effect of acute doses (sc) on nicotine self-administration (0.03 mg/kg/infusion) with FR1 was assessed in 3-hour sessions. Acute lorcaserin doses (0.3125-20 mg/kg) were administered in a counterbalanced order. Significant reduction of nicotine self-administration was achieved with all of the acute doses in this range. Tests of lorcaserin on locomotor activity detected prominent sedative effects at doses above 1.25 mg/kg with more modest transient effects seen at 0.625-1.25 mg/kg. Chronic effects of lorcaserin on locomotor activity were tested with repeated injections with 0.625 mg/kg of lorcaserin ten times over two weeks. This low lorcaserin dose did not cause an overall change in locomotor activity relative to saline injected controls. Chronic lorcaserin (0.625 mg/kg) significantly reduced nicotine self-administration over a two-week period of repeated injections. Chronic lorcaserin at this same dose had no significant effects on food self-administration over the same two-week period of repeated injections. These studies support development of the 5HT2c agonist lorcaserin to aid tobacco smoking cessation. Levin ED, Johnson J, Slade S, Wells C, Cauley M, Petro A, Rose JE. Lorcaserin, a 5HT2c Agonist, Decreases Nicotine Self-Administration in Female Rats. J Pharmacol Exp Ther. 2011 Jun 2. [Epub ahead of print]

Cigarette Smoking Reduction And Changes In Nicotine Dependence The relationship of nicotine dependence (ND) to smoking behavior and cessation has been well characterized. However, little is known about the association between smoking reduction (SR) and ND. The authors retrospectively evaluated the lifetime prevalence and extent of SR and whether ND as assessed by a modified Fagerström Test for Nicotine Dependence (FTND) score without cigarettes per day (CPD) and time-to-first cigarette changed with reductions in CPD. As part of the Collaborative Study of the Genetics of Nicotine Dependence (COGEND), 47,777 individuals from 2 mid-Western metropolitan areas were identified for a community-based telephone screening, yielding 6,955 current daily smokers ages 25-44 years (European-American, n = 5,135 and Black, n = 1,820). The FTND was administered to measure current ND and peak ND in respondents whose current daily CPD is lower than their reported lifetime peak. About 44% (n = 3,077) of the sample reported reducing their smoking from their lifetime peak, with a mean reduction of 14.4 CPD (SD = 8.9) or a 54.0% reduction compared with peak smoking.

Controlling for peak smoking and years smoked, the magnitude of SR was associated with declines in ND excluding the direct contribution of CPD. Self-reported SR was associated with reduced levels of ND. The impact of this reduction on smoking cessation and health risks and smoking cessation requires further study, particularly given the retrospective nature of the present dataset. Mooney ME, Johnson EO, Breslau N, Bierut LJ, Hatsukami DK. Cigarette smoking reduction and changes in nicotine dependence. Nicotine Tob Res. 2011 Jun; 13(6): 426-430. Epub 2011 Mar 2.

Working Memory Load Modulation Of Parieto-Frontal Connections: Evidence From Dynamic Causal Modeling Previous neuroimaging studies have shown that working memory load has marked effects on regional neural activation. However, the mechanism through which working memory load modulates brain connectivity is still unclear. In this study, this issue was addressed using dynamic causal modeling (DCM) based on functional magnetic resonance imaging (fMRI) data. Eighteen normal healthy subjects were scanned while they performed a working memory task with variable memory load, as parameterized by two levels of memory delay and three levels of digit load (number of digits presented in each visual stimulus). Eight regions of interest, i.e., bilateral middle frontal gyrus (MFG), anterior cingulate cortex (ACC), inferior frontal cortex (IFC), and posterior parietal cortex (PPC), were chosen for DCM analyses. Analysis of the behavioral data during the fMRI scan revealed that accuracy decreased as digit load increased. Bayesian inference on model structure indicated that a bilinear DCM in which memory delay was the driving input to bilateral PPC and in which digit load modulated several parieto-frontal connections was the optimal model. Analysis of model parameters showed that higher digit load enhanced connection from L PPC to L IFC, and lower digit load inhibited connection from R PPC to L ACC. These findings suggest that working memory load modulates brain connectivity in a parieto-frontal network, and may reflect altered neuronal processes, e.g., information processing or error monitoring, with the change in working memory load. Ma L, Steinberg JL, Hasan KM, Narayana PA, Kramer LA, Moeller FG. Working memory load modulation of parieto-frontal connections: Evidence from dynamic causal modeling. Hum Brain Mapp. 2011 Jun 20. [Epub ahead of print]

Prevalence of Levamisole in Urine Toxicology Screens Positive for Cocaine in an Inner-City Hospital This study demonstrates that levamisole used to adulterate cocaine was systemically absorbed by cocaine users and, in 1 institution, was common in urine samples positive for cocaine. The 17% of samples positive for cocaine by immunoassay but negative by GC/MS may be due to degradation of cocaine metabolites during storage. The low incidence of levamisole present in samples alone without cocaine may indicate a more rapid degradation or excretion of cocaine metabolites compared with levamisole metabolites. Buchanan J A; Heard K, Burbach C, Wilson ML, Dart R. JAMA 2011; 305(16): 1657-1658.

Validation of a 6-hourObservation Period for Cocaine Body Stuffers Often, patients are brought in to the emergency department after ingesting large amounts of cocaine in an attempt to conceal it. This act is known as body stuffing. The observation period required to recognize potential toxic adverse effects in these patients is not well described in the literature. The authors sought to validate a treatment algorithm for asymptomatic cocaine body stuffers using a 6-hour observation period by observing the clinical course of cocaine body stuffers over a 24-hour period. A retrospective chart review was performed on all patients evaluated for witnessed or

suspected stuffing over 2 years using a standardized protocol. One hundred six patients met final inclusion criteria as adult cocaine stuffers. No patients developed life-threatening symptoms, and no patients died during observation. In this medical setting, stuffers could be discharged after a 6-hour observation period if there was either complete resolution or absence of clinical symptoms. Moreira M, Buchanan J, Heard K. Am J Emerg Med. 2011; 29(3): 299-303.

False Positive in the Intravenous Drug Self-AdministrationTest in C57BL/6J Mice The objective of this study was to examine C57BL/6J (B6) mice during extinction conditions, after food training, and for rates and patterns of operant behavior that seems similar to behavior maintained by intravenous cocaine injections. The rationale was to evaluate the potential for false positives in the intravenous self-administration test using protocols common in studies of knockout mice backcrossed to B6. An additional aim was to assess the influence of food-associated and drug-associated cues and mouse strain. Mice were allowed to acquire lever pressing reinforced by sweetened condensed milk under a fixed ratio 1 then fixed ratio 2 schedule of reinforcement accompanied by a flashing light. A catheter base was then implanted for simulation of intravenous self-administration conditions. Mice were allowed to lever press with cues remaining the same as during food training but without further scheduled consequences (i.e. no drug or food reinforcers delivered). All mice sustained lever pressing for several weeks, and over half met commonly used criteria for 'self-administration behavior.' Thus, B6 mice showed perseveration of a previously reinforced behavior that closely resembled rates and patterns of drug self-administration. This effect in B6 mice was greater than with A/J mice, and the lack of extinction was even more robust in the presence of cocaine-associated cues than with food-associated cues. The authors suggest that a necessary criterion for positive results in the intravenous drug self-administration test include an increase in responding when cocaine is made available after extinction with saline self-administration. Thomsen M, Caine SB. Behav Pharmacol. 2011; 22(3): 239-247.

Computer-Controlled Drug Doses for IV Drug Self-Administration This report describes a novel procedure for computer-controlled drug-dose determination for IV drug self-administration studies. By modifying the duration of each infusion of a single concentration of a drug solution, five or more unit doses (mg/kg/inj) can be dispensed from the same syringe. The advantages of this procedure include the following: (a) it is not necessary to prepare a new syringe for each dose change, (b) the sterility of the IV catheter line is broken less often and, (c) the confounding effect of flushing through the catheter line with the previous drug dose is avoided. This procedure is accurate and reliable and can be applied to multiple sessions of any duration across days or weeks. Fivel PA. Exp Clin Psychopharmacol. 2011; 19(2): 131-133.

Influence of Cocaine History on the Behavioral Effects of Dopamine D(3) Receptor-Selective Compounds in Monkeys Although dopamine D(3) receptors have been associated with cocaine abuse, little is known about the consequences of chronic cocaine on functional activity of D(3) receptor-preferring compounds. This study examined the behavioral effects of D(3) receptor-selective 4-phenylpiperazines with differing in vitro functional profiles in adult male rhesus monkeys with a history of cocaine self-administration and controls. In vitro assays found that PG 619 (N-(3-hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-4-(pyridin-2-yl)benzamide HCl) was a potent D(3) antagonist in the mitogenesis assay, but a fully efficacious agonist in the adenylyl cyclase assay, NGB 2904 (N-(4-(4-(2,3-dichlorophenyl)piperazin-1-

yl)butyl)-9H-fluorene-2-carboxamide HCl) was a selective D(3) antagonist, whereas CJB 090 (N-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butyl)-4-(pyridin-2-yl)benzamide HCl) exhibited a partial agonist profile in both in vitro assays. In behavioral studies, the D(3) preferential agonist quinpirole (0.03-1.0 mg/kg, i.v.) dose-dependently elicited yawns in both groups of monkeys. PG 619 and CJB 090 elicited yawns only in monkeys with an extensive history of cocaine, whereas NGB 2904 did not elicit yawns, but did antagonize quinpirole and PG 619-elicited yawning in cocaine-history monkeys. In another experiment, doses of PG 619 that elicited yawns did not alter response rates in monkeys self-administering cocaine (0.03-0.3 mg/kg per injection). Following saline extinction, cocaine (0.1 mg/kg) and quinpirole (0.1 mg/kg), but not PG 619 (0.1 mg/kg), reinstated cocaine-seeking behavior. When given before a cocaine prime, PG 619 decreased cocaine-elicited reinstatement. These findings suggest that (1) an incongruence between in vitro and in vivo assays, and (2) a history of cocaine self-administration can affect in vivo efficacy of D(3) receptor-preferring compounds PG 619 and CJB 090, which appear to be dependent on the behavioral assay. Blaylock BL, Gould RW, Banala A, Grundt P, Luedtke RR, Newman AH, Nader MA. Neuropsychopharmacology. 2011 Apr; 36(5): 1104-1113.

Chronic Δ^9-tetrahydrocannabinol Treatment in Rhesus Monkeys: Differential Tolerance and Cross-Tolerance Among Cannabinoids The extent to which behavioural effects vary as a function of CB_1 receptor agonist efficacy is not clear. These studies tested the hypothesis that cannabinoid tolerance and cross-tolerance depend upon the CB_1 agonist efficacy of drugs to which tolerance/cross-tolerance develops. Sensitivity to cannabinoids, including the cannabinoid antagonist rimonabant, low efficacy agonist Δ^9-tetrahydrocannabinol (Δ^9-THC), and high efficacy agonists CP 55940 and WIN 55212-2, was determined before and after chronic Δ^9-THC treatment in rhesus monkeys. Two measures of behavioural effect were assessed: effects of drugs to decrease fixed ratio responding for food presentation and stimulus-shock termination and discriminative stimulus effects in monkeys discriminating Δ^9-THC (0.1 mg·kg^{-1}, i.v.). Δ^9-THC decreased responding for both food presentation and stimulus-shock termination; these effects were antagonized by the CB_1 antagonist rimonabant. Chronic Δ^9-THC (1 mg·kg^{-1} per 12 h, s.c.) resulted in tolerance to the rate-decreasing effects of Δ^9-THC and cross-tolerance to CP 55940 and WIN 55212-2; however, cross-tolerance was less than tolerance. Chronic Δ^9-THC increased sensitivity to rimonabant without changing sensitivity to the non-cannabinoids midazolam and ketamine. In monkeys discriminating Δ^9-THC (0.1 mg·kg^{-1}, i.v.), both CP 55940 and WIN 55212-2 produced high levels of drug-lever responding. Chronic Δ^9-THC (1 mg·kg^{-1} per day, s.c.) decreased sensitivity to Δ^9-THC without producing cross-tolerance to CP 55940 or WIN 55212-2. In Δ^9-THC-treated monkeys, the magnitude of tolerance and cross-tolerance to other CB_1 receptor agonists varied inversely with agonist efficacy, suggesting that CB_1 agonist efficacy is an important determinant of behavioural effects. McMahon LR. Br J Pharmacol. 2011 Mar; 162(5): 1060-1073.

Inactivation of the Bed Nucleus of the Stria Terminalis in an Animal Model of Relapse: Effects on Conditioned Cue-Induced Reinstatement and Its Enhancement by Yohimbine Drug-associated cues and stress increase craving and lead to greater risk of relapse in abstinent drug users. Animal models of reinstatement of drug seeking have been utilized to study the neural circuitry by which either drug-associated cues or stress exposure elicit drug seeking. Recent evidence has shown a strong enhancing effect of yohimbine stress on subsequent cue-elicited reinstatement; however, there has been no examination of the neural substrates of this

interactive effect. The current study examined whether inactivation of the bed nucleus of the stria terminalis (BNST), an area previously implicated in stress activation of drug seeking, would affect reinstatement of cocaine seeking caused by conditioned cues, yohimbine stress, or the combination of these factors. Male rats experienced daily IV cocaine self-administration, followed by extinction of lever responding in the absence of cocaine-paired cues. Reinstatement of responding was measured during presentation of cocaine-paired cues, following pretreatment with the pharmacological stressor, yohimbine (2.5 mg/kg, IP), or the combination of cues and yohimbine. All three conditions led to reinstatement of cocaine seeking, with the highest responding seen after the combination of cues and yohimbine. Reversible inactivation of the BNST using the gamma-aminobutyric acid receptor agonists, baclofen+muscimol, significantly reduced all three forms of reinstatement. These results demonstrate a role for the BNST in cocaine seeking elicited by cocaine-paired cues, and suggest the BNST as a key mediator for the interaction of stress and cues for the reinstatement of cocaine seeking. Buffalari DM, See RE. Psychopharmacology (Berl). 2011 Jan; 213(1): 19-27.

Discriminative and Reinforcing Stimulus Effects of Nicotine, Cocaine, and Cocaine + Nicotine Combinations in Rhesus Monkeys Concurrent cigarette smoking and cocaine use is well documented. However, the behavioral pharmacology of cocaine and nicotine combinations is poorly understood, and there is a need for animal models to examine this form of polydrug abuse. The purpose of this study was twofold: first to assess the effects of nicotine on the discriminative stimulus effects of cocaine, and second, to study self-administration of nicotine/cocaine combinations in a novel polydrug abuse model. In drug discrimination experiments, nicotine increased the discriminative stimulus effects of low cocaine doses in two of three monkeys, but nicotine did not substitute for cocaine in any monkey. Self-administration of cocaine and nicotine alone, and cocaine + nicotine combinations was studied under a second-order fixed ratio 2, variable ratio 16 (FR2[VR16:S]) schedule of reinforcement. Cocaine and nicotine alone were self-administered in a dose-dependent manner. The combination of marginally reinforcing doses of cocaine and nicotine increased drug self-administration behavior above levels observed with the same dose of either cocaine or nicotine alone. These findings indicate that nicotine may increase cocaine's discriminative stimulus and reinforcing effects in rhesus monkeys, and illustrate the feasibility of combining cocaine and nicotine in a preclinical model of polydrug abuse. Further studies of the behavioral effects of nicotine + cocaine combinations will contribute to our understanding the pharmacology of dual nicotine and cocaine dependence, and will be useful for evaluation of new treatment medications. Mello NK, Newman JL. Exp Clin Psychopharmacol. 2011; 19(3): 203-214.

Phenyl Ring-Substituted Lobelane Analogs: Inhibition of [^{3}H]Dopamine Uptake at the Vesicular Monoamine Transporter-2 Lobeline attenuates the behavioral effects of methamphetamine via inhibition of the vesicular monoamine transporter (VMAT2). To increase selectivity for VMAT2, chemically defunctionalized lobeline analogs, including lobelane, were designed to eliminate nicotinic acetylcholine receptor affinity. The current study evaluated the ability of lobelane analogs to inhibit [^{3}H]dihydrotetrabenazine (DTBZ) binding to VMAT2 and [^{3}H]dopamine (DA) uptake into isolated synaptic vesicles and determined the mechanism of inhibition. Introduction of aromatic substituents in lobelane maintained analog affinity for the [^{3}H]DTBZ binding site on VMAT2 and inhibitory potency in the [^{3}H]DA uptake assay assessing VMAT2 function. The most potent (K(i) = 13-16 nM) analogs in the series included para-

methoxyphenyl nor-lobelane (GZ-252B), para-methoxyphenyl lobelane (GZ-252C), and 2,4-dichlorphenyl lobelane (GZ-260C). Affinity of the analogs for the [³H]DTBZ binding site did not correlate with inhibitory potency in the [³H]DA uptake assay. It is noteworthy that the N-benzylindole-, biphenyl-, and indole-bearing meso-analogs 2,6-bis[2-(1-benzyl-1H-indole-3-yl)ethyl]-1-methylpiperidine hemifumarate (AV-1-292C), 2,6-bis(2-(biphenyl-4-yl)ethyl)piperidine hydrochloride (GZ-272B), and 2,6-bis[2-(1H-indole-3-yl)ethyl]-1-methylpiperidine monofumarate (AV-1-294), respectively] inhibited VMAT2 function (K(i) = 73, 127, and 2130 nM, respectively), yet had little to no affinity for the [³H]DTBZ binding site. These results suggest that the analogs interact at an alternate site to DTBZ on VMAT2. Kinetic analyses of [³H]DA uptake revealed a competitive mechanism for 2,6-bis(2-(4-methoxyphenyl) ethyl)piperidine hydrochloride (GZ-252B), 2,6-bis(2-(4-methoxyphenyl)ethyl)-1-methylpiperi-dine hydrochloride (GZ-252C), 2,6-bis(2-(2,4-dichlorophenyl)ethyl)piperidine hydrochloride (GZ-260C), and GZ-272B. Similar to methamphetamine, these analogs released [³H]DA from the vesicles, but with higher potency. In contrast to methamphetamine, these analogs had higher potency (>100-fold) at VMAT2 than DAT, predicting low abuse liability. Thus, modification of the lobelane molecule affords potent, selective inhibitors of VMAT2 function and reveals two distinct pharmacological targets on VMAT2. Nickell JR, Zheng G, Deaciuc AG, Crooks PA, Dwoskin LP. J Pharmacol Exp Ther. 2011 Mar; 336(3): 724-733.

Meso-Transdiene Analogs Inhibit Vesicular Monoamine Transporter-2 Function and Methamphetamine-Evoked Dopamine Release Lobeline, a nicotinic receptor antagonist and neurotransmitter transporter inhibitor, is a candidate pharmacotherapy for methamphetamine abuse. meso-Transdiene (MTD), a lobeline analog, lacks nicotinic receptor affinity, retains affinity for vesicular monoamine transporter 2 (VMAT2), and, surprisingly, has enhanced affinity for dopamine (DA) and serotonin transporters [DA transporter (DAT) and serotonin transporter (SERT), respectively]. In the current study, MTD was evaluated for its ability to decrease methamphetamine self-administration in rats relative to food-maintained responding. MTD specifically decreased methamphetamine self-administration, extending the authors' previous work. Classical structure-activity relationships revealed that more conformationally restricted MTD analogs enhanced VMAT2 selectivity and drug likeness, whereas affinity at the dihydrotetra-benazine binding and DA uptake sites on VMAT2 was not altered. Generally, MTD analogs exhibited 50- to 1000-fold lower affinity for DAT and were equipotent or had 10-fold higher affinity for SERT, compared with MTD. Representative analogs from the series potently and competitively inhibited [(3)H]DA uptake at VMAT2. (3Z,5Z)-3,5-bis(2,4-dichlorobenzylidene)-1-methylpiperidine (UKMH-106), the 3Z,5Z-2,4-dichlorophenyl MTD analog, had improved selectivity for VMAT2 over DAT and importantly inhibited methamphetamine-evoked DA release from striatal slices. In contrast, (3Z,5E)-3,5-bis(2,4-dichlorobenzylidene)-1-methylpiperidine (UKMH-105), the 3Z,5E-geometrical isomer, inhibited DA uptake at VMAT2, but did not inhibit methamphetamine-evoked DA release. Taken together, these results suggest that these geometrical isomers interact at alternate sites on VMAT2, which are associated with distinct pharmacophores. Thus, structural modification of the MTD molecule resulted in analogs exhibiting improved drug likeness and improved selectivity for VMAT2, as well as the ability to decrease methamphetamine-evoked DA release, supporting the further evaluation of these analogs as treatments for methamphetamine abuse. Horton DB, Siripurapu KB, Norrholm SD, Culver JP, Hojahmat M, Beckmann JS, Harrod SB, Deaciuc AG, Bardo MT, Crooks PA, Dwoskin LP. J Pharmacol Exp Ther. 2011 Mar; 336(3): 940-951.

Design, Synthesis and Interaction at the Vesicular Monoamine Transporter-2 of Lobeline Analogs: Potential Pharmacotherapies for the Treatment of Psychostimulant Abuse The vesicular monoamine transporter-2 (VMAT2) is considered as a new target for the development of novel therapeutics to treat psychostimulant abuse. Current information on the structure, function and role of VMAT2 in psychostimulant abuse are presented. Lobeline, the major alkaloidal constituent of Lobelia inflata, interacts with nicotinic receptors and with VMAT2. Numerous studies have shown that lobeline inhibits both the neurochemical and behavioral effects of amphetamine in rodents, and behavioral studies demonstrate that lobeline has potential as a pharmacotherapy for psychostimulant abuse. Systematic structural modification of the lobeline molecule is described with the aim of improving selectivity and affinity for VMAT2 over neuronal nicotinic acetylcholine receptors and other neurotransmitter transporters. This has led to the discovery of more potent and selective ligands for VMAT2. In addition, a computational neural network analysis of the affinity of these lobeline analogs for VMAT2 has been carried out, which provides computational models that have predictive value in the rational design of VMAT2 ligands and is also useful in identifying drug candidates from virtual libraries for subsequent synthesis and evaluation. Crooks PA, Zheng G, Vartak AP, Culver JP, Zheng F, Horton DB, Dwoskin LP. Curr Top Med Chem. 2011; 11(9): 1103-1127.

Repeated Exposure to Morphine Alters Surface Expression of AMPA Receptors in the Rat Medial Prefrontal Cortex Behavioral sensitization describes the intensification of motor activity that results from repeated exposure to drugs of misuse, and the underlying neuronal adaptations are hypothesized to model aspects of the brain changes that occur in humans misusing such drugs. The α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor is an ionotropic glutamate receptor involved in the neuroplasticity that accompanies acute and repeated drug administration. Changing surface expression is one means to regulate AMPA receptor function, and the present study tested the hypothesis that behavioral sensitization to the μ-opioid receptor agonist morphine is accompanied by changes in the subcellular distribution of AMPA receptors in limbic brain regions. To test this hypothesis, the authors used a protein cross-linking assay to assess cell surface and intracellular levels of GluA1 and GluA2 subunits in the nucleus accumbens, medial prefrontal cortex and ventral pallidum. Repeated morphine treatment decreased surface expression of GluA1 in the medial prefrontal cortex without affecting levels of GluA2. In contrast, surface levels of GluA1 or GluA2 were unchanged in the nucleus accumbens and ventral pallidum, demonstrating that although AMPA receptors in accumbal and pallidal regions are critical mediators of behaviors induced by repeated opiate exposure, these effects are not accompanied by changes in surface expression. The findings reveal that the involvement of AMPA receptor trafficking in opiate-induced behavioral sensitization is relegated to selective regions and that AMPA receptors in the medial prefrontal cortex may be particularly sensitive to these actions. Mickiewicz AL, Napier TC. Eur J Neurosci. 2011 Jan; 33(2): 259-265.

Administration of GABA(B) Receptor Positive Allosteric Modulators Inhibit the Expression of Previously Established Methamphetamine-Induced Conditioned Place Preference Little is known about the role of GABA(B) receptors (GABA(B)Rs) in the maintenance of memories associated with using abused substances. The authors have embarked on a series of studies designed to determine if enhancing the efficacy of GABA-occupied GABA(B)Rs with positive allosteric modulators (PAMs) can negate previously established

conditioned place preference (CPP) induced by methamphetamine. In the current study, they evaluated the effects of acute administration of GABA(B)R PAMs, GS39783 and CGP7930. They determined that post-conditioning treatments with these PAMs, administered in the home cage, blocked the subsequent expression of methamphetamine-induced CPP. These data indicate that selectively augmenting GABA-occupied GABA(B)R signaling is sufficient to reduce memory maintenance and/or the salience of contextual cues previously associated with methamphet-amine. Voigt RM, Herrold AA, Riddle JL, Napier TC. Behav Brain Res. 2011 Jan 1; 216(1): 419-423.

Baclofen Facilitates the Extinction of Methamphetamine-Induced Conditioned Place Preference in Rat The powerful, long-lasting association between the rewarding effects of a drug and contextual cues associated with drug administration can be studied using conditioned place preference (CPP). The GABA(B) receptor agonist baclofen facilitates the extinction of morphine-induced CPP in mice. The current study extended this work by determining if baclofen could enhance the extinction of methamphetamine (Meth) CPP. CPP was established using a six-day conditioning protocol wherein Meth-pairings were alternated with saline-pairings. Rats were subsequently administered baclofen (2 mg/kg i.p. or vehicle) immediately after each daily forced extinction session, which consisted of a saline injection immediately prior to being placed into the previously Meth- or saline-paired chamber. One extinction training cycle, consisted of six once-daily forced extinction sessions, mimicking the alternating procedure established during conditioning, followed by a test for preference (Ext test). CPP persisted for at least four extinction cycles in vehicle-treated rats. In contrast, CPP was inhibited following a single extinction training cycle. These data indicate that Meth-induced CPP was resistant to extinction, but extinction training was rendered effective when the training was combined with baclofen. These findings converge with the prior demonstration of baclofen facilitating the extinction of morphine-induced CPP indicating that GABA(B) receptor actions are independent of the primary (unconditioned) stimulus (i.e., the opiate or the stimulant) and likely reflect mechanisms engaged by extinction learning processes per se. Thus, baclofen administered in conjunction with extinction training may be of value for addiction therapy regardless of the class of drug being abused. Voigt RM, Herrold AA, Napier TC. Behav Neurosci. 2011 Apr; 125(2): 261-267.

Mirtazapine Alters Cue-Associated Methamphetamine Seeking in Rats Methamphetamine (METH) is a potent psychostimulant, repeated use of which can result in a substance abuse disorder. Withdrawn individuals are highly prone to relapse, which may be driven, at least in part, by a hyperresponsivity to METH-associated cues that can prompt METH-seeking. Clinically efficacious pharmacotherapies for METH abuse are critically needed. Mirtazapine (Remeron) is an atypical antidepressant that antagonizes activated norepinephrine$(\alpha)_2$, histamine$_1$ serotonin (5-HT)$_2$(A/C), and 5-HT$_3$ receptors. This pharmacologic profile prompted our interest in its potential for preventing relapse to METH-taking. This study tested the hypothesis that mirtazapine would attenuate METH-seeking in rats trained to self-administer METH. Rats were trained to self-administer METH in a lever-pressing operant task. The effect of mirtazapine on METH-seeking was determined by evaluating lever pressing in the presence of cues previously associated with METH, but in the absence of METH reinforcement. Two paradigms were used: cue reactivity, wherein rats do not undergo extinction training, and a cue-induced reinstatement paradigm after extinction. Mirtazapine (5.0 mg/kg) pretreatment reduced METH-seeking by ~ 50% in the first 15 min of cue reactivity and cue-induced reinstatement

testing. This mirtazapine dose did not significantly affect motor performance. This study revealed the overlapping nature of cue reactivity and cue-induced reinstatement procedures and provided preclinical evidence that mirtazapine can attenuate METH-seeking behavior. Graves SM, Napier TC. Biol Psychiatry. 2011 Feb 1; 69(3): 275-281.

Active Site Gating and Substrate Specificity of Butyrylcholinesterase and Acetylcholinesterase: Insights from Molecular Dynamics Simulations Butyrylcholinesterase (BChE) and acetylcholinesterase (AChE) are highly homologous proteins with distinct substrate preferences. In this study the authors compared the active sites of monomers and tetramers of human BChE and human AChE after performing molecular dynamics (MD) simulations in water-solvated systems. By comparing the conformational dynamics of gating residues of AChE and BChE, they found that the gating mechanisms of the main door of AChE and BChE are responsible for their different substrate specificities. The authors simulation of the tetramers of AChE and BChE indicates that both enzymes could have two dysfunctional active sites due to their restricted accessibility to substrates. Further study on catalytic mechanisms of multiple forms of AChE and BChE would benefit from our comparison of the active sites of the monomers and tetramers of both enzymes. Fang L, Pan Y, Muzyka JL, Zhan CG. J Phys Chem B. 2011 Jul 14; 115(27): 8797-8805.

Synthesis and Characterization of Selective Dopamine D_2 Receptor Ligands Using Aripiprazole as the Lead Compound A series of compounds structurally related to aripiprazole (1), an atypical antipsychotic and antidepressant used clinically for the treatment of schizophrenia, bipolar disorder, and depression, have been prepared and evaluated for affinity at D($_2$-like) dopamine receptors. These compounds also share structural elements with the classical D($_2$-like) dopamine receptor antagonists, haloperidol, N-methylspiperone, domperidone and benperidol. Two new compounds, 7-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butoxy)-3,4-dihydroquinolin-2(1H)-one oxalate (6) and 7-(4-(4-(2-(2-fluoroethoxy) phenyl)piperazin-1-yl)butoxy)-3,4-dihydroquinolin-2(1H)-one oxalate (7) were found to (a) bind to the D_2 receptor subtype with high affinity (K(i) values < 0.3 nM), (b) exhibit >50-fold D_2 versus D_3 receptor binding selectivity and (c) be partial agonists at both the D_2 and D_3 receptor subtype. Vangveravong S, Zhang Z, Taylor M, Bearden M, Xu J, Cui J, Wang W, Luedtke RR, Mach RH. Bioorg Med Chem. 2011 Jun 1; 19(11): 3502-3511.

Catalytic Mechanism of Cytochrome P450 for 5'-hydroxylation of Nicotine: Fundamental Reaction Pathways and Stereoselectivity A series of computational methods were used to study how cytochrome P450 2A6 (CYP2A6) interacts with (S)-(-)-nicotine, demonstrating that the dominant molecular species of (S)-(-)-nicotine in CYP2A6 active site exists in the free base state (with two conformations, SR(t) and SR(c)), despite the fact that the protonated state is dominant for the free ligand in solution. The computational results reveal that the dominant pathway of nicotine metabolism in CYP2A6 is through nicotine free base oxidation. Further, first-principles quantum mechanical/molecular mechanical free energy (QM/MM-FE) calculations were carried out to uncover the detailed reaction pathways for the CYP2A6-catalyzed nicotine 5'-hydroxylation reaction. In the determined CYP2A6-(S)-(-)-nicotine binding structures, the oxygen of Compound I (Cpd I) can abstract a hydrogen from either the trans-5'- or the cis-5'-position of (S)-(-)-nicotine. CYP2A6-catalyzed (S)-(-)-nicotine 5'-hydroxylation consists of two reaction steps, that is, the hydrogen transfer from the 5'-position of (S)-(-)-nicotine to the oxygen of Cpd I (the H-transfer step), followed by the recombination of the (S)-

(-)-nicotine moiety with the iron-bound hydroxyl group to generate the 5'-hydroxynicotine product (the O-rebound step). The H-transfer step is rate-determining. The 5'-hydroxylation proceeds mainly with the stereoselective loss of the trans-5'-hydrogen, that is, the 5'-hydrogen trans to the pyridine ring. The calculated overall stereoselectivity of ~97% favoring the trans-5'-hydroxylation is close to the observed stereoselectivity of 89-94%. This is the first time it has been demonstrated that a CYP substrate exists dominantly in one protonation state (cationic species) in solution, but uses its less-favorable protonation state (neutral free base) to perform the enzymatic reaction. Li D, Huang X, Han K, Zhan CG. J Am Chem Soc. 2011 May 18; 133(19): 7416-7427.

Reaction Mechanism for Cocaine Esterase-Catalyzed Hydrolyses of (+)- and (-)- Cocaine: Unexpected Common Rate-Determining Step First-principles quantum mechanical/molecular mechanical free energy calculations have been performed to examine the catalytic mechanism for cocaine esterase (CocE)-catalyzed hydrolysis of (+)-cocaine in comparison with CocE-catalyzed hydrolysis of (-)-cocaine. It has been shown that the acylation of (+)-cocaine consists of nucleophilic attack of the hydroxyl group of Ser117 on the carbonyl carbon of (+)-cocaine benzoyl ester and the dissociation of (+)-cocaine benzoyl ester. The first reaction step of deacylation of (+)-cocaine, which is identical to that of (-)-cocaine, is rate-determining, indicating that CocE-catalyzed hydrolyses of (+)- and (-)-cocaine have a common rate-determining step. The computational results predict that the catalytic rate constant of CocE against (+)-cocaine should be the same as that of CocE against (-)-cocaine, in contrast with the remarkable difference between human butyrylcholinesterase-catalyzed hydrolyses of (+)- and (-)-cocaine. The prediction has been confirmed by experimental kinetic analysis on CocE-catalyzed hydrolysis of (+)-cocaine in comparison with CocE-catalyzed hydrolysis of (-)-cocaine. The determined common rate-determining step indicates that rational design of a high-activity mutant of CocE should be focused on the first reaction step of the deacylation. Furthermore, the obtained mechanistic insights into the detailed differences in the acylation between the (+)- and (-)-cocaine hydrolyses provide indirect clues for rational design of amino acid mutations that could more favorably stabilize the rate-determining transition state in the deacylation and, thus, improve the catalytic activity of CocE. This study provides a valuable mechanistic base for rational design of an improved esterase for therapeutic treatment of cocaine abuse. Liu J, Zhao X, Yang W, Zhan CG. J Phys Chem B. 2011 May 5; 115(17): 5017-5025.

Role of Corticotropin-Releasing Factor in Drug Addiction: Potential for Pharmacological Intervention Drug dependence is a chronically relapsing disorder that places an enormous strain on healthcare systems. For treatments to have long-term clinical value, they must address the causes of relapse. Corticotropin-releasing factor (CRF), a neuropeptide central to the stress response, may be one key to solving the relapse cycle. CRF is hypothesized to mediate the elevated anxiety and negative emotional states experienced during the development of dependence. This review summarizes existing data on changes in the CRF system produced by drugs of abuse and the function of CRF receptors in regulating behavioral responses to drugs of abuse, with an emphasis on drug dependence. Drug-induced changes in neuronal excitability throughout the limbic system, as well as the reversal of these neuroadaptations by CRF receptor antagonists, are also addressed. CRF receptor antagonists, by reducing the motivational effects of drug withdrawal and protracted abstinence, are proposed to be novel therapeutic targets for drug abuse and addiction. Logrip ML, Koob GF, Zorrilla EP. CNS Drugs. 2011 Apr 1; 25(4): 271-287.

Adrenal Activity During Repeated Long-Access Cocaine Self-Administration Is Required for Later CRF-Induced and CRF-Dependent Stressor-Induced Reinstatement in Rats Understanding the neurobiological processes that contribute to the establishment and expression of stress-induced regulation of cocaine use in addicted individuals is important for the development of new and better treatment approaches. It has been previously shown that rats self-administering cocaine under long-access conditions (6h daily) display heightened susceptibility to the reinstatement of extinguished cocaine seeking by a stressor, electric footshock, or i.c.v. administration of the stressor-responsive neuropeptide, corticotropin-releasing factor (CRF). This study tested the hypothesis that adrenal responsiveness during earlier long-access cocaine self-administration (SA) is necessary for the establishment of later CRF-dependent stress-induced reinstatement. Reinstatement by footshock, but not a cocaine challenge (10mg/kg, i.p.) following long-access SA, was blocked by i.c.v. administration of the CRF receptor antagonist, α-helical CRF(9-41) (10μg). Elimination of SA-induced adrenal responses through surgical adrenalectomy and diurnal corticosterone replacement (ADX/C) before 14 days of SA under long-access conditions had minimal impact on cocaine SA, but blocked later footshock-induced reinstatement. By contrast, ADX/C after SA, but before extinction and reinstatement testing, failed to reduce footshock-induced reinstatement. Likewise, ADX/C before 14 days long-access SA prevented later reinstatement by i.c.v. CRF (0.5 or 1.0μg). However, significant CRF-induced reinstatement was observed when rats underwent ADX/C following SA, but before extinction and reinstatement testing, although a modest but statistically nonsignificant reduction in sensitivity to CRF's reinstating effects was observed. Taken together, these findings suggest that adrenal-dependent neuroadaptations in CRF responsiveness underlie the increased susceptibility to stress-induced relapse that emerges with repeated cocaine use. Graf EN, Hoks MA, Baumgardner J, Sierra J, Vranjkovic O, Bohr C, Baker DA, Mantsch JR. Neuropsychopharmacology. 2011 Jun; 36(7): 1444-1454.

Effect of Structural Modification in the Amine Portion of Substituted Aminobutyl-Benzamides as Ligands for Binding Σ1 and Σ2 Receptors 5-Bromo-N-[4-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-butyl)]-2,3-dimethoxy-benzamide (1) is one of the most potent and selective σ(2) receptor ligands reported to date. A series of new analogs, where the amine ring fused to the aromatic ring was varied in size (5-7) and the location of the nitrogen in this ring was modified, has been synthesized and assessed for their σ(1)/σ(2) binding affinity and selectivity. The binding affinity of an open-chained variant of 1 was also evaluated. Only the five-membered ring congener of 1 displayed a higher σ(1)/σ(2) selectivity, derived from a higher σ(2) affinity and a lower σ(1) affinity. Positioning the nitrogen adjacent to the aromatic ring in the five-membered and six-membered ring congeners dramatically decreased affinity for both subtypes. Thus, location of the nitrogen within a constrained ring is confirmed to be key to the exceptional σ(2) receptor binding affinity and selectivity for this active series. Fan KH, Lever JR, Lever SZ. Bioorg Med Chem. 2011 Mar 15; 19(6): 1852-1859.

Computational Design of a Thermostable Mutant of Cocaine Esterase via Molecular Dynamics Simulation Cocaine esterase (CocE) has been known as the most efficient native enzyme for metabolizing naturally occurring cocaine. A major obstacle to the clinical application of CocE is the thermoinstability of native CocE with a half-life of only 11 min at physiological temperature (37 °C). It is highly desirable to develop a thermostable mutant of CocE for therapeutic treatment of cocaine overdose and addiction. To establish a structure-thermostability relationship, the authors carried out molecular dynamics (MD) simulations at 400 K on wild-type

CocE and previously known thermostable mutants, demonstrating that the thermostability of the active form of the enzyme correlates with the fluctuation (characterized as the root-mean square deviation and root-mean square fluctuation of atomic positions) of the catalytic residues (Y44, S117, Y118, H287, and D259) in the simulated enzyme. In light of the structure-thermostability correlation, further computational modelling including MD simulations at 400 K predicted that the active site structure of the L169K mutant should be more thermostable. The prediction has been confirmed by wet experimental tests showing that the active form of the L169K mutant had a half-life of 570 min at 37 °C, which is significantly longer than those of the wild-type and previously known thermostable mutants. The encouraging outcome suggests that the high-temperature MD simulations and the structure-thermostability relationship may be considered as a valuable tool for the computational design of thermostable mutants of an enzyme. Huang X, Gao D, Zhan CG. Org Biomol Chem. 2011 Jun 7; 9(11): 4138-4143.

A Methodology for Radiolabeling of the Endocannabinoid 2-Arachidonoylglycerol (2-AG)

The metabolic intermediate and endocannabinoid signaling lipid 2-arachidonoylglycerol (2-AG) has not been readily labeled, primarily because of its instability toward rearrangement. The authors now detail a synthetic method that easily gives tritiated 2-AG from [5,6,8,9,11,12,14,15-(3)H(N)]arachidonic acid in two steps. They utilized a short chain 1,3-diacylglycerol and proceeded through the "structured lipid" [5",6",8",9",11",12",14",15"-(3)H(N)]2-arachidonoyl-1,3-dibutyrylglycerol, a triacylglycerol that was conveniently deprotected in ethanol with acrylic beads containing Candida antarctica lipase B to give [5",6",8",9",11",12",14",15"-(3)H(N)]2-arachidonoylglycerol ([(3)H]2-AG). The flash chromatographic separation necessary to isolate the labeled 2-acylglycerol [(3)H]2-AG resulted in only 4% of the rearrangement byproducts that have been a particular problem with previous methodologies. This reliable "kit" method to prepare the radiolabeled endocannabinoid as needed gave tritiated 2-arachidonoylglycerol [(3)H]2-AG with a specific activity of 200 Ci/mmol for enzyme assays, metabolic studies, and tissue imaging. It has been run on unlabeled materials on over 10 mg scales and should be generally applicable to other 2-acylglycerols. Duclos RI Jr, Johnston M, Vadivel SK, Makriyannis A, Glaser ST, Gatley SJ. J Org Chem. 2011 Apr 1; 76(7): 2049-2055.

Immunopharmacotherapeutic Manifolds and Modulation of Cocaine Overdose

Cocaine achieves its psychostimulant, reinforcing properties through selectively blocking dopamine transporters, and this neurobiological mechanism impedes the use of classical receptor-antagonist pharmacotherapies to outcompete cocaine at CNS sites. Passive immunization with monoclonal antibodies (mAb) specific for cocaine circumvents this problem as drug is sequestered in the periphery prior to entry into the brain. To optimize an immunopharmacotherapeutic strategy for reversing severe cocaine toxicity, the therapeutic properties of mAb GNC92H2 IgG were compared to those of its engineered formats in a mouse overdose model. Whereas the extended half-life of an IgG justifies its application to the prophylactic treatment of addiction, the rapid, thorough biodistribution of mAb-based fragments, including $F(ab')_2$, Fab and scFv, may correlate to accelerated scavenging of cocaine and reversal of toxicity. To test this hypothesis, mice were administered the anti-cocaine IgG (180 mg/kg, i.v.) or GNC92H2-based agent after receiving an LD_{50} cocaine dose (93 mg/kg, i.p.), and the timeline of overdose symptoms was recorded. All formats lowered the rate of lethality despite the >100-fold molar excess of drug to antibody binding capacity. However, only $F(ab')_2$-92H2 and Fab-92 H2 significantly attenuated the progression of premorbid behaviors, and Fab-92H2 prevented seizure generation in a percentage of mice. The calculation of serum half-life of each

format demonstrated that the pharmacokinetic profile of Fab-92H2 (elimination half-life, t½~100 min) best approximated that of cocaine. These results not only confirm the importance of highly specific and tight drug binding by the mAb, but also highlight the benefit of aligning the pharmacokinetic and pharmacodynamic properties of the immunopharmacotherapeutic with the targeted drug. Treweek JB, Roberts AJ, Janda KD. Pharmacol Biochem Behav. 2011 May; 98(3): 474-484.

Synthesis and Pharmacological Evaluation of Fluorine-Containing D_3 Dopamine Receptor Ligands A series of fluorine-containing N-(2-methoxyphenyl)piperazine and N-(2-fluoroethoxy)piperazine analogues were synthesized, and their affinities for human dopamine D(2), D(3), and D(4) receptors were determined. Radioligand binding studies identified five compounds, 18a, 20a, 20c, 20e, and 21e, which bind with high affinity at D(3) (K(i) = 0.17-5 nM) and moderate to high selectivity for D(3) vs D(2) receptors (ranging from ~25- to 163-fold). These compounds were also evaluated for intrinsic activity at D(2) and D(3) receptors using a forskolin-dependent adenylyl cyclase assay. This panel of compounds exhibits varying receptor subtype binding selectivity and intrinsic activity at D(2) vs D(3) receptors. These compounds may be useful for behavioral pharmacology studies on the role of D(2)-like dopamine receptors in neuropsychiatric and neurological disorders. Furthermore, compound 20e, which has the highest binding affinity and selectivity for the D(3) receptor (K(i) = 0.17 nM for D(3), 163-fold selectivity for D(3) vs D(2) receptors), represents a candidate fluorine-18 radiotracer for in vivo PET imaging studies on the regulation of D(3) receptor expression. Tu Z, Li S, Cui J, Xu J, Taylor M, Ho D, Luedtke RR, Mach RH. J Med Chem. 2011 Mar 24; 54(6): 1555-1564.

Perinatal Lead Exposure Alters Locomotion Induced by Amphetamine Analogs in Rats The precise neurochemical perturbations through which perinatal (gestation/lactation) lead exposure modifies the reinforcement efficacy of various psychoactive drugs (e.g., cocaine, opiates) are unknown. The present study considers the role of altered serotonin and dopamine functionality in perinatal lead-psychostimulant interactions. Female rats were administered a 16-mg lead or a control solution (p.o.) for 30 days prior to breeding with non-exposed males. Lead exposure was discontinued at weaning (postnatal day [PND] 21). Starting at PND 120, male rats born to control or lead-exposed dams were injected with either PAL-287 or PAL-353, at doses of 0, 2, 4, 8, or 16umol/kg (i.p.) with each dose given prior to an acute (45min) locomotion test. Whereas PAL-287 is a potent releaser of serotonin, PAL-353 is not. Each drug induces comparable release of norepinephrine (NE) and of dopamine (DA). Control and lead rats exhibited minimal locomotion to PAL-287. PAL-353 produced a dose-dependent activation of locomotion in control rats relative to the effects of PAL-287 in control rats. Lead-exposed rats exhibited a subsensitivity to PAL-353 at doses of 4 and 8umol/kg. The subsensitivity of lead rats to PAL-353 is consistent with a lead-induced diminution of dopamine function, an effect noted earlier for the reuptake inhibitor cocaine (Nation et al. 2000). The similar response of lead and control rats to PAL-287 is inconsistent with diminished serotonin function. Clifford PS, Hart N, Rothman RB, Blough BE, Bratton GR, Wellman PJ. Life Sci. 2011 Mar 28; 88(13-14): 586-589.

In Vivo Effects of Amphetamine Analogs Reveal Evidence for Serotonergic Inhibition of Mesolimbic Dopamine Transmission in the Rat Evidence suggests that elevations in extracellular serotonin (5-HT) in the brain can diminish stimulant effects of dopamine (DA). To assess this proposal, the authors evaluated the pharmacology of amphetamine analogs (m-fluoroamphetamine, p-fluoroamphetamine, m-methylamphetamine, p-methylamphetamine),

which display similar in vitro potency as DA releasers (EC(50) = 24-52 nM) but differ in potency as 5-HT releasers (EC(50) = 53-1937 nM). In vivo microdialysis was used to assess the effects of drugs on extracellular DA and 5-HT in rat nucleus accumbens, while simultaneously measuring ambulation (i.e., forward locomotion) and stereotypy (i.e., repetitive movements). Rats received two intravenous injections of drug, 1 mg/kg at time 0 followed by 3 mg/kg 60 min later. All analogs produced dose-related increases in dialysate DA and 5-HT, but the effects on DA did not agree with in vitro predictions. Maximal elevation of dialysate DA ranged from 5- to 14-fold above baseline and varied inversely with 5-HT response, which ranged from 6- to 24-fold above baseline. All analogs increased ambulation and stereotypy, but drugs causing greater 5-HT release (e.g., p-methylamphetamine) were associated with significantly less forward locomotion. The magnitude of ambulation was positively correlated with extracellular DA ($p < 0.001$) and less so with the ratio of DA release to 5-HT release (i.e., percentage DA increase divided by percentage 5-HT increase) ($p < 0.029$). Collectively, the author's findings are consistent with the hypothesis that 5-HT release dampens stimulant effects of amphetamine-type drugs, but further studies are required to address the precise mechanisms underlying this phenomenon. Baumann MH, Clark RD, Woolverton WL, Wee S, Blough BE, Rothman RB. J Pharmacol Exp Ther. 2011 Apr; 337(1): 218-225.

Behavioral Sensitization to Cocaine in Rats: Evidence for Temporal Differences in Dopamine D3 and D2 Receptor Sensitivity Cocaine-induced changes in D(2) receptors have been implicated in the expression of sensitized behavioral responses and addiction-like behaviors; however, the influence of D(3) receptors is less clear. To characterize the effects of repeated cocaine administration on the sensitivity of rats to D(2)- and D(3)-mediated behaviors, as well as the binding properties of ventral striatal D(2)-like and D(3) receptors, Pramipexole was used to assess the sensitivity of rats to D(3)/D(2) agonist-induced yawning, hypothermia, and locomotor activity, 24 h, 72 h, 10, 21, and 42 days after repeated cocaine or saline administration. The locomotor effects of cocaine (42 day) and the binding properties of ventral striatal D(2)-like and D(3) receptors (24 h and 42 days) were also evaluated. Cocaine-treated rats displayed an enhanced locomotor response to cocaine, as well as a progressive and persistent leftward/upward shift of the ascending limb (72 h-42 day) and leftward shift of the descending limb (42 days) of the pramipexole-induced yawning dose-response curve. Cocaine treatment also decreased B (max) and K (d) for D(2)-like receptors and increased D(3) receptor binding at 42 days. Cocaine treatment did not change pramipexole-induced hypothermia or locomotor activity or yawning induced by cholinergic or serotonergic agonists. These studies suggest that temporal differences exist in the development of cocaine-induced sensitization of D(3) and D(2) receptors, with enhancements of D(3)-mediated behavioral effects observed within 72 h and enhancements of D(2)-mediated behavioral effects apparent 42 days after cocaine. These findings highlight the need to consider changes in D(3) receptor function when thinking about the behavioral plasticity that occurs during abstinence from cocaine use. Collins GT, Truong YN, Levant B, Chen J, Wang S, Woods JH. Psychopharmacology (Berl). 2011 Jun; 215(4): 609-620.

Discovery of Molecular Switches within the ADX-47273 mGlu5 PAM Scaffold That Modulate Modes of Pharmacology to Afford Potent mGlu5 Nams, Pams and Partial Antagonists This Letter describes a chemical lead optimization campaign directed at a weak mGlu(5) NAM discovered while developing SAR for the mGlu(5) PAM, ADX-47273. An iterative parallel synthesis effort discovered multiple, subtle molecular switches that afford potent mGlu(5) NAMs, mGlu(5) PAMs as well as mGlu(5) partial antagonists. Lamb JP, Engers

DW, Niswender CM, Rodriguez AL, Venable DF, Conn JP, Lindsley CW. Bioorg Med Chem Lett. 2011 May 1; 21(9): 2711-2714.

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, Peterson EC, Owens SM. J Med Chem. 2011 Jul 28; 54(14): 5221-5228. 82289

The Affinity of d2-like Dopamine Receptor Antagonists Determines the Time to Maximal Effect on Cocaine Self-Administration Differences in the time to maximal effect (T(max)) of a series of dopamine receptor antagonists on the self-administration of cocaine are not consistent with their lipophilicity (octanol-water partition coefficients at pH 7.4) and expected rapid entry into the brain after intravenous injection. It was hypothesized that the T(max) reflects the time required for maximal occupancy of receptors, which would occur as equilibrium was approached. If so, the T(max) should be related to the affinity for the relevant receptor population. This hypothesis was tested using a series of nine antagonists having a 2500-fold range of K(i) or K(d) values for D(2)-like dopamine receptors. Rats self-administered cocaine at regular intervals and then were injected intravenously with a dose of antagonist, and the self-administration of cocaine was continued for 6 to 10 h. The level of cocaine at the time of every self-administration (satiety threshold) was calculated throughout the session. The satiety threshold was stable before the injection of antagonist and then increased approximately 3-fold over the baseline value at doses of antagonists selected to produce this approximately equivalent maximal magnitude of effect (maximum increase in the equiactive cocaine concentration, satiety threshold; C(max)). Despite the similar C(max), the mean T(max) varied between 5 and 157 min across this series of antagonists. Furthermore, there was a strong and significant correlation between the in vivo T(max) values for each antagonist and the affinity for D(2)-like dopamine receptors measured in vitro. It is concluded that the cocaine self-administration paradigm offers a reliable and predictive bioassay for measuring the affinity of a competitive antagonist for D(2)-like dopamine receptors. Norman AB, Tabet MR, Norman MK, Fey BK, Tsibulsky VL, Millard RW. J Pharmacol Exp Ther. 2011 Aug; 338(2): 724-728.

Impact of Distinct Chemical Structures for the Development of a Methamphetamine Vaccine (+)-Methamphetamine (METH) use and addiction has grown at alarming rates over the past two decades, while no approved pharmacotherapy exists for its treatment. Immunopharmacotherapy has the potential to offer relief through producing highly specific antibodies that prevent drug penetration across the blood-brain barrier thus decreasing reinforcement of the behavior. Current immunotherapy efforts against methamphetamine have focused on a single hapten structure, namely linker attachment at the aromatic ring of the METH molecule. Hapten design is largely responsible for immune recognition, as it affects presentation of the target antigen and thus the quality of the response. In the current paper the authors report the systematic generation of a series of haptens designed to target the most stable conformations of methamphetamine as determined by molecular modeling. On the basis of the authors' previous studies with nicotine, they show that introduction of strategic molecular constraint is able to maximize immune recognition of the target structure as evidenced by higher antibody affinity. Vaccination of GIX(+) mice with six unique METH immunoconjugates resulted in high antibody titers for three particularly promising formulations (45-108 μg/mL, after the second immunization) and high affinity (82, 130, and 169 nM for MH2, MH6, and MH7 hapten-based vaccines, respectively). These findings represent a unique approach to the design of new vaccines against methamphetamine abuse. Moreno AY, Mayorov AV, Janda KD. J Am Chem Soc. 2011 May 4; 133(17): 6587-6595.

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

HIV Infection and Cocaine Use Induce Endothelial Damage and Dysfunction in African Americans Clinical and epidemiological evidence suggests that HIV infection and cocaine use are associated with an increased risk of premature atherosclerosis. The underlying mechanisms linking HIV infection and cocaine use with early atherosclerosis remain elusive. Endothelin-1 (ET-1) levels in 360 African American participants in Baltimore, Maryland were measured. Quantile regression analysis was performed to examine the associations between ET-1, HIV infection, cocaine use, and other relevant clinical factors. The median of ET-1 in plasma, (1.05 pg/mL with interquartile range: 0.73, 1.40) for those with HIV infection was significantly higher than values for those without HIV infection (0.74 pg/mL with interquartile range: 0.61, 0.93). The median of ET-1 was markedly higher in chronic cocaine users (0.96 pg/mL with interquartile range: 0.71, 1.36) than that in non-cocaine users (0.72 pg/mL with interquartile range: 0.58, 1.06). Multivariate quantile regression suggested that HIV infection and duration of cocaine use were independently associated with plasma ET-1 levels after controlling for potential confounding factors. This study may provide insight into the mechanism of premature atherosclerosis in HIV-infected cocaine users and suggest that measurement of ET-1 in plasma can be used as a marker of early atherosclerosis in HIV infected patients and cocaine users. Tai H, Lai H, Jani J, Lai S, Kickler TS. Int J Cardiol. 2011 May 18.

Tipranavir/Ritonavir Induction of Buprenorphine Glucuronide Metabolism in HIV-Negative Subjects Chronically Receiving Buprenorphine/Naloxone Previous reports on the pharmacokinetic of tipranavir (TPV) and buprenorphine (BUP)/ naloxone found that coadministration resulted in an 80% reduction in the area under the curve AUC of the primary BUP metabolite, norBUP, without any pharmacodynamic consequences. This study was conducted to characterize how tipranivir/ritonavir effects the glucuronide metabolites of BUP and may explain the reduction in the norBUP. HIV-seronegative subjects stabilized on at least 3 weeks of BUP/naloxone sequentially underwent baseline and steady-state pharmacokinetic evaluation of twice daily TPV 500 mg coadministered with ritonavir 200 mg (TPV/r). Twelve subjects were enrolled and ten completed the study. The steady-state pharmacokinetics for BUP-3-glucuronide (BUP-3G) and norBUP-3-glucuronide (norBUP-3G) in the presence and absence of steady-state TPV/r were analyzed. The C(max) of BUP-3G was 8.78+/-5.23 ng/mL without TPV/r and increased to 12.7+/-11.7 after steady state of TPV/r was achieved. The AUC of BUP-3G was 31.1+/- 19.4 (ng/mL) (h) without TPV/r and increased to 58. 6 +/- 49.5 after steady state of TPV/r was achieved (p=.0966). In contrast, steady-state norBUP-3G AUC(0-24h) (p=.0216) and C(max) (p=.0088) were significantly decreased in the presence of steady-state TPV/r. This study further elucidates the effects of TPV/r on glucuronidation. The current evaluation of glucuronide metabolites of BUP and norBUP are suggestive of combined inhibition of Uridine diphosphate (UDP)-glucuronosyltransferase of the 1A family and cytochrome P450 3A4 that spares UGT2B7 leading to a shunting of BUP away from production of norBUP and toward BUP-3G as seen by a statistically significant increase in the AUC of BUP-3G. Bruce RD, Moody DE, Fang WB, Chodkowski D, Andrews L, Friedland GH. Am J Drug Alcohol Abuse. 2011 Jul; 37(4): 224-228. Epub 2011 Mar 28.

HIV-1 Tat-Induced Platelet Activation and Release of CD154 Contribute to HIV-1-Associated Autoimmune Thrombocytopenia Enhanced platelet activation in human immunodeficiency virus (HIV)-1-infected patients has been reported and shown to strongly correlate with plasma viral load. Activated platelets are known to express and to release a variety of proteins that can modulate the immune system. Specifically, platelet-derived CD154 has been shown to be directly involved in the development of autoimmune thrombocytopenia (ITP). The mechanism by which HIV-1 infection leads to platelet activation and the effect of this activation on the development of HIV-1 ITP, however, is not fully understood. The authors have investigated the effect of HIV-1 Trans activating factor (Tat) on platelet activation. They report that HIV-1 Tat directly interacts with platelets and induces platelet activation resulting in platelet micro-particle release. This activation by Tat requires the chemokine receptor CCR3 and β3-integrin expression on platelets, as well as calcium flux. Tat-induced activation of platelets releases platelet CD154, an immune modulator. Enhanced B-cell activity is found in mouse spleen B cells co-cultured with platelets treated with Tat in vitro. An early antibody response against adenovirus is found in Tat-injected mouse immunized with adenovirus, suggesting an enhanced immune response in vivo. They have described a role of Tat-induced platelet activation in the modulation of the immune system, with implications for the development of HIV-1-associated thrombocytopenia. Wang J, Zhang W, Nardi MA, Li Z. J Thromb Haemost. 2011 Mar; 9(3): 562-573.

Complex Drug Interactions of HIV Protease Inhibitors 1: Inactivation, Induction, and Inhibition of Cytochrome P450 3A by Ritonavir or Nelfinavir Conflicting drug-drug interaction (DDI) studies with the HIV protease inhibitors (PIs) suggest net induction or inhibition of intestinal or hepatic CYP3A. As part of a larger DDI study in healthy volunteers, the authors determined the effect of extended administration of two PIs, ritonavir (RTV) or nelfinavir (NFV), or the induction-positive control rifampin on intestinal and hepatic CYP3A activity as measured by midazolam (MDZ) disposition after a 14-day treatment with the PI in either staggered (MDZ 12 h after PI) or simultaneous (MDZ and PI coadministered) manner. Oral and intravenous MDZ areas under the plasma concentration-time curves were significantly increased by RTV or NFV and were decreased by rifampin. Irrespective of method of administration, RTV decreased net intestinal and hepatic CYP3A activity, whereas NFV decreased hepatic but not intestinal CYP3A activity. The magnitude of these DDIs was more accurately predicted using PI CYP3A inactivation parameters generated in sandwich-cultured human hepatocytes rather than human liver microsomes. Kirby BJ, Collier AC, Kharasch ED, Whittington D, Thummel KE, Unadkat JD. Drug Metab Dispos. 2011 Jun; 39(6): 1070-1078.

Substance Abuse, Adherence with Antiretroviral Therapy, and Clinical Outcomes Among HIV-Infected Individuals Substance abuse and addiction are highly prevalent in HIV-infected individuals. Substance abuse is an important comorbidity that affects the delivery and outcomes of HIV medical management. In this paper the author reviews data examining the associations between substance abuse and HIV treatment and potential strategies to improve outcomes in this population that warrant further investigation. Current - but not past - substance abuse adversely affects engagement in care, acceptance of antiretroviral therapy, adherence with therapy, and long-term persistence in care. Substance abuse treatment appears to facilitate engagement in HIV care, and access to evidence-based treatment for substance abuse is central to addressing the HIV epidemic. Strategies that show promise for HIV-infected substance abusers include integrated

treatment models, directly observed therapy, and incentive-based interventions. Lucas GM. Life Sci. 2011 May 23; 88(21-22): 948-952.

Drug Interactions Associated with Methadone, Buprenorphine, Cocaine, and HIV Medications: Implications for Pregnant Women Pregnancy in substance-abusing women with HIV/AIDS presents a complex clinical challenge. Opioid-dependent women need treatment with opioid therapy during pregnancy to protect the health of mother and developing fetus. However, opioid therapies, methadone and buprenorphine, may have drug interactions with some HIV medications that can have adverse effects leading to suboptimal clinical outcomes. Further, many opioid-dependent individuals have problems with other forms of substance abuse, for example, cocaine abuse, that could also contribute to poor clinical outcomes in a pregnant woman. Physiological changes, including increased plasma volume and increased hepatic and renal blood flow, occur in the pregnant woman as the pregnancy progresses and may alter medication needs with the potential to exacerbate drug interactions, although there is sparse literature on this issue. Knowledge of possible drug interactions between opioids, other abused substances such as cocaine, HIV therapeutics, and other frequently required medications such as antibiotics and anticonvulsants is important to assuring the best possible outcomes in the pregnant woman with opioid dependence and HIV/AIDS. McCance-Katz EF. Life Sci. 2011 May 23; 88(21-22): 953-958.

Effect of Methamphetamine on Expression of HIV Coreceptors and CC-Chemokines by Dendritic Cells The United States is currently experiencing an entangled epidemic of HIV infection and use of different drugs of abuse, especially of methamphetamine (Meth). Blood monocyte-derived dendritic cells (DC) are the first line of defense against HIV-1 infection, and are the initial target of HIV-1 infection in injection drug users. DC-SIGN present on dendritic cells is the first molecule that facilitates HIV-1 infection independent of CD4 or HIV coreceptors. The aim of this study was to evaluate whether Meth acts as a cofactor in the pathogenesis of HIV-1 infection. Monocyte derived DCs, obtained from normal subjects were cultured with and without Meth±HIV-1B, followed by analyzing the gene and protein expression by real-time quantitative polymerase chain reaction (RT-PCR) and fluorescence-activated cell-sorting analyses, respectively. The authors results show that Meth significantly enhances HIV infection, and downregulates the gene expression of chemokines and costimulatory molecules with reciprocal upregulation of HIV coreceptors and DC-SIGN by dendritic cells. Better understanding of the role of Meth in HIV-1 disease susceptibility and the mechanism through which Meth mediates its effects on HIV-1 infection may help to devise novel therapeutic strategies against HIV-1 infection in Meth using HIV-1 infected population. Nair MP, Saiyed ZM. Life Sc. 2011 May 23; 88(21-22): 987-994.

Human Immunodeficiency Virus Type 1 Clade B and C Gp120 Differentially Induce Neurotoxin Arachidonic Acid in Human Astrocytes: Implications for NeuroAIDS HIV-1 clades (subtypes) differentially contribute to the neuropathogenesis of HIV-associated dementia (HAD) in neuroAIDS. HIV-1 envelop protein, gp120, plays a major role in neuronal function. It is not well understood how these HIV-1 clades exert these neuropathogenic differences. The N-methyl-D: -aspartate (NMDA) receptor-reduced glutamine synthesis could lead to secretion of neurotoxins such as arachidonic acid (AA) which plays a significant role in the neuropathogenic mechanisms in neuroAIDS. The authors hypothesize that clade B and C gp120 proteins exert

differential effects on human primary astrocytes by production of the neurotoxin arachidonic acid. Their results indicate that clade B gp120 significantly downregulated NMDA receptor gene and protein expression, and level of glutamine while increasing expression of prostaglandin E2 (PGE(2)) and thromboxane A2 receptor (TBXA(2) R) compared to HIV-1 clade C gp120 protein. Thus, the author's studies for the first time demonstrate that HIV-1 clade B-gp120 protein appears to induce higher levels of expression of the neuropathogenic molecule cyclooxygenase-2 (COX-2)-mediated arachidonic acid by-products, PGE(2), and TBXA(2) R compared to HIV-1 clade C gp120 protein. These studies suggest that HIV-1 clade B and C gp120 proteins may play a differential role in the neuropathogenesis of HAD in neuroAIDS. Samikkannu T, Agudelo M, Gandhi N, Reddy PV, Saiyed ZM, Nwankwo D, Nair MP. J Neurovirol. 2011 Jun; 17(3): 230-238.

HIV Mono-Infection is Associated with FIB-4 - A Noninvasive Index of Liver Fibrosis - in Women FIB-4 represents a noninvasive, composite index that is a validated measure of hepatic fibrosis, which is an important indicator of liver disease. To date, there are limited data regarding hepatic fibrosis in women. FIB-4 was evaluated in a cohort of 1227 women, and associations were evaluated in univariate and multivariate regression models among 4 groups of subjects classified by their human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection status. The median FIB-4 scores were 0.60 in HIV-/HCV- women, 0.83 in HIV-/HCV+ women, 0.86 in HIV+/HCV- women, and 1.30 in HIV+/HCV+ women. In the HIV/HCV co-infected group, multivariate analysis showed that CD4(+) cell count and albumin level were negatively associated with FIB-4 ($P < .0001$), whereas antiretroviral therapy (ART) was positively associated with FIB-4 score ($P = .0008$). For the HIV mono-infected group, multivariate analysis showed that CD4(+) cell count ($P < .0001$) and albumin level ($P = .0019$) were negatively correlated with FIB-4 score, ART was positively associated with FIB-4 score ($P = .0008$), and plasma HIV RNA level was marginally associated with FIB-4 score ($P = .080$). In 72 HIV mono-infected women who were also hepatitis B surface antigen negative, ART naive, and reported no recent alcohol intake, plasma HIV RNA level was associated with increased FIB-4 score ($P = .030$). HIV RNA level was associated with increased FIB-4 score in the absence of hepatitis B, hepatitis C, ART, or alcohol use, suggesting a potential relationship between HIV infection and hepatic fibrosis in vivo. A better understanding of the various demographic and virologic variables that contribute to hepatic fibrosis may lead to more effective treatment of HIV infection and its co-morbid conditions. Blackard JT, Welge JA, Taylor LE, Mayer KH, Klein RS, Celentano DD, Jamieson DJ, Gardner L, Sherman KE. Clin Infect Dis. 2011 Mar 1; 52(5): 674-680.

Chronic Pain and Hepatitis C Virus Infection in Opioid Dependent Injection Drug Users It is unknown whether infection with hepatitis C is a risk factor for pain among people who have used injection drugs. Multivariate regression was used to determine whether hepatitis C was associated with greater likelihood of reporting significant chronic pain and discomfort intolerance in a cohort of 97 injection drug users dependent on opioids. Study results suggest that participants with hepatitis C may be more likely to experience chronic pain (aOR=1.98; 95% confidence interval=0.76 to 5.12, p=0.16). Furthermore, hepatitis C was found to be associated with a higher discomfort intolerance scale score, reflecting intolerance to physical discomfort (β=2.34; 95% confidence interval=0.06 to 4.62; p=0.04). Hepatitis C may be a cause for chronic pain and discomfort intolerance that is overlooked among injection drug users dependent on

opioids. Tsui JI, Herman DS, Kettavong M, Anderson BJ, Stein MD. J Addict Dis. 2011 Apr; 30(2): 91-97.

Progression of Biopsy-Measured Liver Fibrosis in Untreated Patients with Hepatitis C Infection: Non-Markov Multistate Model Analysis Fibrosis stages from liver biopsies reflect liver damage from hepatitis C infection, but analysis is challenging due to their ordered but non-numeric nature, infrequent measurement, misclassification, and unknown infection times. The authors used a non-Markov multistate model, accounting for misclassification, with multiple imputation of unknown infection times, applied to 1062 participants of whom 159 had multiple biopsies. Odds ratios (OR) quantified the estimated effects of covariates on progression risk at any given time. Models estimated that progression risk decreased the more time participants had already spent in the current stage, African American race was protective (OR 0.75, 95% confidence interval 0.60 to 0.95, p=0.018), and older current age increased risk (OR 1.33 per decade, 95% confidence interval 1.15 to 1.54, p=0.0002). When controlled for current age, older age at infection did not appear to increase risk (OR 0.92 per decade, 95% confidence interval 0.47 to 1.79, p=0.80). There was a suggestion that co-infection with human immunodeficiency virus increased risk of progression in the era of highly active antiretroviral treatment beginning in 1996 (OR 2.1, 95% confidence interval 0.97 to 4.4, p=0.059). Other examined risk factors may influence progression risk, but evidence for or against this was weak due to wide confidence intervals. The main results were essentially unchanged using different assumed misclassification rates or imputation of age of infection. The analysis avoided problems inherent in simpler methods, supported the previously suspected protective effect of African American race, and suggested that current age rather than age of infection increases risk. Decreasing risk of progression with longer time already spent in a stage was also previously found for post-transplant progression. This could reflect varying disease activity, with recent progression indicating active disease and high risk, while longer time already spent in a stage indicates quiescent disease and low risk. Bacchetti P, Boylan R, Astemborski J, Shen H, Mehta SH, Thomas DL, Terrault NA, Monto A. PLoS One. 2011; 6(5): e20104. Epub 2011 May 27.

Buprenorphine and Buprenorphine/Naloxone Diversion, Misuse, and Illicit Use: an International Review The diversion, misuse, and non-medically supervised use of buprenorphine and buprenorphine/naloxone by opioid users are reviewed. Buprenorphine and buprenorphine/naloxone are used globally as opioid analgesics and in the treatment of opioid dependency. Diversion of buprenorphine and buprenorphine/naloxone represents a complex medical and social issue, and has been widely documented in various geographical regions throughout the world. The authors first discuss the clinical properties of buprenorphine and its abuse potential. Second, they discuss its diversion and illicit use on an international level, as well as motivations for those activities. Third, they examine the medical risks and benefits of buprenorphine's non-medically supervised use and misuse. These risks and benefits include the effect of buprenorphine's use on HIV risk and the risk of its concomitant use with other medications and drugs of abuse. Finally, they discuss the implications of diversion, misuse, and non-medically supervised use (including potential measures to address issues of diversion); and potential areas for further research. Yokell MA, Zaller ND, Green TC, Rich JD. Curr Drug Abuse Rev 2011 Mar 1; 4(1): 28-34.

Simultaneous Determination of Alfentanil And Midazolam in Human Plasma Using Liquid Chromatography and Tandem Mass Spectrometry A fast, sensitive and selective liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for the determination of alfentanil and midazolam in human plasma has been developed and validated. Alfentanil and midazolam were extracted from plasma using a mixed-mode cation exchange solid phase extraction method, with recoveries of both compounds greater than 80% at 3 different concentrations (1, 10 and 100ng/ml). Compounds were analyzed on a C(18) column with a water and methanol mobile phase gradient with acetic acid as an additive, at a flow rate of 0.3ml/min. The working assay range was linear from 0.25 to 100ng/ml for each compound. The signal to noise ratio was 80 and 40 for alfentanil and midazolam, respectively, at the lowest concentration calibration standard, with less than 10% matrix suppression by human plasma at this concentration. Alfentanil and midazolam were stable in human plasma during storage at -80°C, processing, and analysis. The procedure was validated and applied to the analysis of plasma samples from healthy human subjects administered oral and intravenous alfentanil and midazolam. Kim T, London A, Kharasch ED. J Pharm Biomed Anal. 2011 Jun 1; 55(3): 487-493. Epub 2011 Mar 5.

LC-MS/MS Method for the Determination of Carbamathione In Human Plasma Liquid chromatography-tandem mass spectrometry methodology is described for the determination of S-(N,N-diethylcarbamoyl)glutathione (carbamathione) in human plasma samples. Sample preparation consisted of a straightforward perchloric acid medicated protein precipitation, with the resulting supernatant containing the carbamathione (recovery ~98%). For optimized chromatography/mass spec detection a carbamathione analog, S-(N,N-di-i-propylcarbamoyl) glutathione, was synthesized and used as the internal standard. Carbamathione was found to be stable over the pH 1-8 region over the timeframe necessary for the various operations of the analytical method. Separation was accomplished via reversed-phase gradient elution chromatography with analyte elution and re-equilibration accomplished within 8 min. Calibration was established and validated over the concentration range of 0.5-50 nM, which is adequate to support clinical investigations. Intra- and inter-day accuracy and precision determined and found to be <4% and <10%, respectively. The methodology was utilized to demonstrate the carbamathione plasma-time profile of a human volunteer dosed with disulfiram (250 mg/d). Interestingly, an unknown but apparently related metabolite was observed with each human plasma sample analyzed. Heemskerk AA, van Haandel L, Woods JM, McCance-Katz EF, Williams TD, Stobaugh JF, Faiman MD. J Pharm Biomed Anal. 2011 Mar 25; 54(4): 799-806.

Suicide by Asphyxiation Due to Helium Inhalation Suicide by asphyxiation using helium is the most widely-promoted method of "self-deliverance" by right-to-die advocates. However, little is known about persons committing such suicides or the circumstances and manner in which they are completed. Prior reports of suicides by asphyxiation involving helium were reviewed and deaths determined by the North Carolina Office of the Chief Medical Examiner to be helium-associated asphyxial suicides occurring between January 1, 2000 and December 31, 2008 were included in a new case series examined in this article. The 10 asphyxial suicides involving helium identified in North Carolina tended to occur almost exclusively in non-Hispanic, white men who were relatively young (M age = 41.1 T 11.6). In 6 of 10 cases, decedents suffered from significant psychiatric dysfunction; in 3 of these 6 cases, psychiatric

disorders were present comorbidly with substance abuse. In none of these cases were decedents suffering from terminal illness. Most persons committing suicide with helium were free of terminal illness but suffered from psychiatric and/or substance use disorders. Howard MO, Hall MT, Edwards JD, Vaughn MG, Perron BE, Winecker RE. 2011 Mar; 32(1): 61-70.

Indolizidine (-)-235B' and Related Structural Analogs: Discovery of Nicotinic Receptor Antagonists that Inhibit Nicotine-Evoked [3H]Dopamine Release Although several therapeutic agents are available to aid in tobacco smoking cessation, relapse rates continue to be high, warranting the development of alternative pharmacotherapies. Nicotine-evoked dopamine release from its presynaptic terminals in the central nervous system leads to reward which maintains continued tobacco use. The ability of indolizidine (-)-235B' and a sub-library of structurally related analogs to inhibit nicotine-evoked [(3)H]dopamine release from rat striatal slices was determined in the current study. Indolizidine (-)-235B' inhibited nicotine-evoked [(3)H]dopamine release in a concentration-dependent manner (IC(50)=42 nM, I(max)=55%). Compound (-)-237D, the double bond-reduced analog, afforded the greatest inhibitory potency (IC(50)=0.18 nM, I(max)=76%), and was 233-fold more potent than indolizidine (-)-235B'. The des-8-methyl aza-analog of indolizidine (-)-235B', ZZ-272, also inhibited nicotine-evoked [(3)H]dopamine release (IC(50)=413 nM, I(max)=59%). Concomitant exposure to maximally effective concentrations of indolizidine (-)-235B', ZZ-272 or (-)-237D with a maximally effective concentration of α-conotoxin MII, a selective antagonist for α6β2-containing nicotinic receptors, resulted in inhibition of nicotine-evoked [(3)H]dopamine release no greater than that produced by each compound alone. The latter results suggest that indolizidine (-)-235B', (-)-237D, ZZ-272 and α-conotoxin MII inhibit the same α-conotoxin MII-sensitive nicotinic receptor subtypes. Thus, indolizidine (-)-235B' and its analogs act as antagonists of α6β2-nicotinic receptors and constitute a novel structural scaffold for the discovery of pharmacotherapies for smoking cessation. Pivavarchyk M, Smith AM, Zhang Z, Zhou D, Wang X, Toyooka N, Tsuneki H, Sasaoka T, McIntosh JM, Crooks PA, Dwoskin LP. Eur J Pharmacol. 2011 May 11; 658(2-3): 132-139.

SERVICES RESEARCH

Moving beyond Parity — Mental Health and Addiction Care under the ACA Enactment of the Mental Health Parity and Addiction Equity Act in 2008 was the culmination of a decades-long effort to improve insurance coverage for mental health and addiction treatment. The law's passage constituted a critical first step toward bringing care for people with mental health and addiction disorders — including depression, anxiety, psychoses, and substance abuse and dependence — into the mainstream of the U.S. medical care system by requiring parity in coverage (benefits for mental health and substance abuse, often referred to collectively as "behavioral health," that are equivalent to all other medical and surgical benefits). Now, the passage of the Affordable Care Act (ACA) has the potential to affect the financing and delivery of mental health and addiction care even more profoundly. Barry CL, Huskamp HA, Moving beyond Parity — Mental Health and Addiction Care under the ACA. New England Journal of Medicine, Epub August 17, 2011 DOI: 10.1056/NEJMp1108649.

Improving Adherence to HIV Quality of Care Indicators in Persons with Opioid Dependence: The Role of Buprenorphine Opioid-dependent HIV-infected patients are less likely to receive HIV quality of care indicators (QIs) compared with nondependent patients. Buprenorphine/naloxone maintenance therapy (bup/nx) could affect the quality of HIV care for opioid-dependent patients. The authors abstracted 16 Qis from medical records at nine HIV clinics 12 months before and after initiation of bup/nx versus other treatment for opioid dependence. Summary quality scores (number of Qis received/number eligible × 100) were calculated. They compared change in Qis and summary quality scores in patients receiving bup/nx versus other participant. One hundred ninety-four of 268 participants (72%) received bup/nx and 74 (28%) received other treatment. Mean summary quality scores increased over 12 months for participants receiving bup/nx (45.6% to 51.6%, $P < 0.001$) but not other treatment (48.6% to 47.8%, $P = 0.788$). Bup/nx participants experienced improvements in six of 16 HIV Qis versus three of 16 Qis in other participants. Improvements were mostly in preventive and monitoring care domains. In multivariable analysis, bup/nx was associated with improved summary quality score (² 8.55; 95% confidence interval, 2.06-15.0). In this observational cohort study, HIV-infected patients with opioid dependence received approximately half of HIV Qis at baseline. Buprenorphine treatment was associated with improvement in HIV Qis at 12 months. Integration of bup/nx into HIV clinics may increase receipt of high-quality HIV care. Further research is required to assess the effect of improved quality of HIV care on clinical outcomes. Korthuis P, Fiellin D, Fu R, Lum P, Altice F, Sohler N, Tozzi M, Asch S, Botsko M, Fishl M, Flanigan T, Boverman J, McCarty D, McCarty D. Improving Adherence To HIV Quality Of Care Indicators In Persons With Opioid Dependence: The Role of Buprenorphine. J Acquir Immune Defic Syndr. 2011; 56 Suppl 1 (N/A): S83-s90.

The Impact of Cocaine Use on Outcomes in HIV-infected Patients Receiving Buprenorphine/Naloxone Cocaine use is common in opioid-dependent HIV-infected patients, but its impact on treatment outcomes in these patients receiving buprenorphine/naloxone is not known. The authors conducted a prospective study in 299 patients receiving buprenorphine/naloxone who provided baseline cocaine data and a subset of 266 patients who remained in treatment for greater than or equal to one quarter. Assessments were conducted at baseline and

quarterly for 1 year. They evaluated the association between baseline and in-treatment cocaine use on buprenorphine/naloxone retention, illicit opioid use, antiretroviral adherence, CD4 counts, HIV RNA, and risk behaviors. Sixty-six percent (197 of 299) of patients reported baseline cocaine use and 65% (173 of 266) of patients with follow-up data reported in-treatment cocaine use. Baseline and in-treatment cocaine use did not impact buprenorphine/naloxone retention, antiretroviral adherence, CD4 lymphocytes, or HIV risk behaviors. However, baseline cocaine use was associated with a 14.8 (95% confidence interval [CI], 9.0-24.2) times greater likelihood of subsequent cocaine use (95% CI, 9.0-24.2), a 1.4 (95% CI, 1.02-2.00) times greater likelihood of subsequent opioid use, and higher log10 HIV RNA ($P < 0.016$) over time. In-treatment cocaine use was associated with a 1.4 (95% CI, 1.01-2.00) times greater likelihood of concurrent opioid use. Given cocaine use negatively impacts opioid and HIV treatment outcomes, interventions to address cocaine use in HIV-infected patients receiving buprenorphine/naloxone treatment are warranted. Sullivan L, Botsko M, Cunningham C, O 'Connor P, Hersh D, Mitty J, Lum P, Schottenfeld R, Fiellin D, Fiellin D. The Impact Of Cocaine Use On Outcomes In HIV-Infected Patients Receiving Buprenorphine/Naloxone. J Acquir Immune Defic Syndr. 2011; 56 Suppl 1: S54-S61.

HIV/AIDS Services in Private Substance Abuse Treatment Programs HIV infection among substance abusers is a growing concern in the United States. Little research, however, has examined the provision of HIV/AIDS services in substance abuse treatment programs. This study examines the provision of onsite HIV/AIDS services in a nationally representative sample of 345 privately funded substance abuse treatment programs. Data were collected via face-to-face interviews with administrators and/or clinical directors of treatment programs in 2007-2008. Results show that larger programs and programs with a higher percentage of both African American and injection drug using (IDU) patients were more likely to offer onsite HIV/AIDS support groups and a dedicated HIV/AIDS treatment track. Multinomial logistic regression reveals that the odds of offering onsite HIV testing services were higher for hospital based programs, programs providing medical services onsite, and programs with higher percentages of African American patients, relative to the odds of offering no HIV testing or referring patients to an external provider for HIV testing services. The odds of providing onsite testing were lower for outpatient-only treatment programs, relative to the odds of offering no HIV testing or referring patients to an external provider for HIV testing services. Our findings highlight critical barriers to the adoption of onsite HIV/AIDS services and suggest treatment programs are missing the opportunity to significantly impact HIV-related health outcomes. Abraham A, O 'Brien L, Bride B, Roman P. HIV/AIDS Services In Private Substance Abuse Treatment Programs. Drug Alcohol Depend. 2011; 115 (1-2): 16-22.

Adoption and Implementation of Medications in Addiction Treatment Programs Little is known about the extent to which medications are being implemented as routine care in addiction treatment programs. This research describes medication adoption and implementation within the privately funded treatment sector. Face-to-face interviews were conducted with 345 administrators of a nationally representative sample of privately funded substance treatment organizations in the United States. Rates of adoption of addiction treatment medications in private sector programs were lower than the adoption of psychiatric medications. Even when analyses were restricted to programs with access to physicians, adoption of each addiction treatment medication had occurred in less than 50% of programs. Within adopting programs,

implementation was highly variable. While about 70% of patients with co-occurring psychiatric diagnoses received psychiatric medications, rates of implementation of medication-assisted treatment for opioid dependence and alcohol use disorders were just 34.4% and 24.0%, respectively. Although previous research has documented higher rates of medication adoption in privately funded treatment programs, this study revealed that both adoption and implementation of pharmacotherapies to treat addiction remains modest. Future research should examine the different types of barriers to implementation, such as physician decision-making, patient preferences, and system-level barriers stemming from financing and public policy. Knudsen H, Abraham A, Roman P. Adoption And Implementation Of Medications In Addiction Treatment Programs. J Addict Med. 2011; 5 (1): 21-27.

The Relationship Between Program Characteristics, Therapeutic Alliance, and Patient Outcomes The authors explored patient, therapist, and program variability in the alliance in relation to drug and alcohol use during treatment, and whether alliance mediates the relation of program characteristics to drug/alcohol use. Data (N = 1,613 patients) were drawn from a randomized clinical trial investigating the efficacy of an intervention that provided alliance and outcome feedback to 112 counselors across 20 community-based outpatient substance abuse treatment clinics in the northeast United States. Program characteristics were measured using the Organization Readiness for Change scale. Using multilevel modeling, the authors found that alliance was related to both drug and alcohol use during the past week at the patient and program levels of analysis, but not the counselor level. Several program characteristics were related to average drug and alcohol use. The alliance was not a mediator of these relationships. Program variability in the alliance is important to the alliance-outcome relationship in the treatment of substance abuse. Better outcomes can be achieved by improving both organizational functioning and the patient-counselor alliance. Crits-Christoph P, Hamilton J, Ring-Kurtz S, Gallop R, McClure B, Kulaga A, Rotrosen J. Program, Counselor, And Patient Variability In The Alliance: A Multilevel Study Of The Alliance In Relation To Substance Use Outcomes. J Subst Abuse Treat. 2011; 40 (4): 405-413.

Efficacy Studies to Large-Scale Transport: the Development and Validation of Multisystemic Therapy Programs The 35-year progression of multi-systemic therapy (MST) from modest university-based efficacy studies to large-scale transport to community practice settings is described in this review. The success of early efficacy research led to effectiveness trials, and their success in decreasing rates of youth re-arrest and incarceration led to multisite transportability trials and adaptations of the MST model for treating youth presenting other types of challenging clinical problems. To support the transport of MST programs to community settings, an intensive quality improvement system modeled after that used in clinical trials has been implemented in community-based MST programs for the past 15 years. With the association between therapist treatment fidelity and youth outcomes well established, transportability research has demonstrated the significant roles played by clinical supervisors, expert consultants, and provider organizations in supporting therapist adherence and youth outcomes. This body of work has been facilitated by federal and state initiatives to support evidence-based services. Henggeler S. Efficacy Studies To Large-Scale Transport: The Development And Validation Of Multi-Systemic Therapy Programs. Annu Rev Clin Psychol. 2011; 7: 351-381.

Depression's Moderation of the Effectiveness of Intensive Case Management With Substance-Dependent Women Intensive case management (ICM) is effective for facilitating entry into and retention in outpatient substance use disorder treatment (OSUDT) for low-income substance-dependent women; however, no studies have specifically examined the moderating impact of depressive symptoms on ICM. The purpose of this study was to investigate whether depressive symptoms moderated ICM's effect on OSUDT engagement, attendance, and outcomes for substance-dependent women on Temporary Assistance for Needy Families (TANF). It was hypothesized that highly depressed women would demonstrate worse outcomes on all indicators. Logistic regression and generalized estimating equations were used to determine depression's moderating impact on ICM in a secondary analysis of data from a randomized controlled trial comparing the effectiveness of ICM to usual care provided by local public assistance offices in Essex County, NJ. Substance-dependent women ($N = 294$) were recruited while being screened for TANF eligibility and were followed for 24 months. Findings revealed that high levels of depressive symptoms moderated the effectiveness of ICM in unexpected directions for two outcome variables. Subjects with high levels of depressive symptoms in ICM were (a) significantly more likely to engage in at least one treatment program than those in usual care and (b) associated with the fewest mean drinks per drinking day across the 24-month follow-up period. Independent effects for high levels of depressive symptoms and ICM were also found to positively influence engagement, attendance, and percentage days abstinent. ICM is effective for substance-dependent women with a broad spectrum of depressive symptoms in enhancing OSUDT utilization and outcomes. Kuerbis AN, Neighbors CJ, Morgenstern J. Depression's Moderation of the Effectiveness of Intensive. J Stud Alcohol Drugs. 2011; 72: 297-307.

The 'Check Effect' Reconsidered The 'check effect' refers to the use of disability payments to purchase illegal drugs or alcohol. This paper describes subsequent research concerning three interrelated issues: the check effect, whether receipt of disability payments is associated with more overall substance use, and potential policy responses to misuse of disability payments for substances. Review and synthesis of published papers. Increased substance use at the beginning of the month has been described in a variety of settings. The tendency to purchase substances at the beginning of the month is impacted by household wealth, the tendency to discount future rewards and cyclical economic activity. However, in naturalistic observational cohort studies, beneficiaries who receive disability payments had no greater substance use than those without disability payments. Potential policy responses to mis-spending of disability checks include financial counseling that discourages spending on drugs and the assignment of a representative payee to prevent misuse of benefits for substances. Assignment of a representative payee per se has not been associated with reduced substance use, but payeeship administered by agencies that integrate payee practice into treatment has been. Disability payments impact the timing of substance use, but receipt of disability payments is not associated with more overall substance use than unalleviated poverty. Money management-based clinical interventions, which may involve assignment of a representative payee, can minimize the purchase of substances with disability payments. Rosen M. The 'Check Effect ' Reconsidered. Addiction. 2011; 106 (6): 1071-1077.

Gender Differences in Provider's Use of a Standardized Screening Tool for Prenatal Substance Use Prenatal substance use contributes birth defects, prematurity, and infant mortality in the U.S. As such, it is critical that medical professionals receive appropriate education and actively engage in screening patients; however, a physician's gender may influence differences in screening practices. The purpose of this study is to examine male and female Ob/Gyn physician's beliefs and practices related to perinatal substance use screening and to identify the significant correlates of using a standardized screening tool. Data were collected from 131 Ob/Gyn physician's in Kentucky using a web-based survey. Chi-square and t-tests were used to distinguish differences between male (n=84) and female (n=47) providers. Binary logistic regression was also used to assess the independent correlates of the use of a standardized screening tool. Female Ob/Gyn physician 's were more likely to "believe in" the effectiveness of screening, to discuss sensitive topics with patients, and were motivated to screen as a part of comprehensive care or because screening could produce a behavioral change. Female providers were also more likely to use a screening tool in a multivariate model; however, being female was no longer significant after additional variables were included in the model. Specifically, younger Ob/Gyn physicians who frequently discussed mental health issues with female patients of childbearing age, and were motivated to screen because it is part of comprehensive care were significantly more likely to use a standardized substance use screening tool. In summary, less than half of Ob/Gyn physicians were using a standardized screening tool and the majority of physicians were using the CAGE. This suggests additional training is needed to increase their use of substance use screening tools, especially those geared towards pregnant women. Oser C, Biebel E, Harris M, Klein E, Leukefeld C. Gender Differences In Provider's Use Of A Standardized Screening Tool For Prenatal Substance Use. J Addict Med. 2011; 5 (1): 36-42.

Nurse Turnover in Substance Abuse Treatment Programs Affiliated with the National Drug Abuse Treatment Clinical Trials Network Voluntary nurse turnover, which is costly and disrupts patient care, has not been studied as an organizational phenomenon within substance abuse treatment organizations. In this exploratory study, thew authors examined the frequency and correlates of nurse turnover within treatment programs affiliated with the National Drug Abuse Treatment Clinical Trials Network. During face-to-face interviews conducted in 2005-2006, 215 program administrators reported the number of nurses currently employed. Leaders of programs with nursing staff then described the number of nurses who had voluntarily quit in the past year, the degree to which filling vacant nursing positions was difficult, and the average number of days to fill a vacant position. About two thirds of these programs had at least one nurse on staff. In programs with nurses, the average rate of voluntary turnover was 15.0%. Turnover was significantly lower in hospital-based programs and programs offering adolescent treatment but higher in facilities offering residential treatment. Most of the administrators indicated that filling vacant nurse positions was difficult and took more than 2 months to complete. These findings suggest that nurse turnover is a significant issue facing many substance abuse treatment facilities. Efforts to improve retention of the addiction treatment workforce should be expanded to include nursing professionals. Knudsen H, Abraham A, Roman P, Studts J. Nurse Turnover In Substance Abuse Treatment Programs Affiliated With The National Drug Abuse Treatment Clinical Trials Network. J Subst Abuse Treat. 2011; 40 (3): 307-312.

HIV/AIDS Services in Private Substance Abuse Treatment Programs HIV infection among substance abusers is a persistent concern in the United States. Little research, however, has examined the provision of HIV/AIDS services in substance abuse treatment programs. This study examines the provision of onsite HIV/AIDS services in a nationally representative sample of 345 privately funded substance abuse treatment programs. Data were collected via face-to-face interviews with administrators and/or clinical directors of treatment programs in 2007–2008. Results show that larger programs and programs with a higher percentage of both African American and injection drug using (IDU) patients were more likely to offer onsite HIV/AIDS support groups and a dedicated HIV/AIDS treatment track. Multinomial logistic regression reveals that the odds of offering onsite HIV testing services were higher for hospital based programs, programs providing medical services onsite, and programs with higher percentages of African American patients, relative to the odds of offering no HIV testing or referring patients to an external provider for HIV testing services. The odds of providing onsite testing were lower for outpatient-only treatment programs, relative to the odds of offering no HIV testing or referring patients to an external provider for HIV testing services. Findings from these private sector programs are inconsistent with prior studies of public sector services, and highlight critical barriers to the adoption of onsite HIV/AIDS services. Findings suggest these relatively well-resourced treatment programs are missing the opportunity to significantly impact HIV-related health outcomes. Abraham AJ, O'Brien LA, Bride BE, Roman PM. HIV/AIDS Services In Private Substance Abuse Treatment Programs. Drug Alcohol Depend. 2011; 115: 16-22.

Injection Risk Behaviors Among Rural Drug Users: Implications for HIV Prevention The purpose of this study was to examine injection drug use (IDU) among a cohort of felony probationers from rural Appalachian Kentucky. An interviewer-administered questionnaire given to 800 rural felony probationers ascertained data regarding demographics, drug use, criminal behavior, psychological distress, and HIV-risk behaviors. The sample was primarily white (95.1%) and male (66.5%) and the median age was 32.3 years (interquartile range: 25.2, 40.5).There were no cases of HIV in the sample. Of the 800 rural probationers, 179 (22.4%) reported lifetime IDU. Receptive syringe sharing (RSS) and distributive syringe sharing (DSS) were reported by 34.5% and 97.1% of the IDUs, respectively. Independent correlates of risky injection behaviors included cocaine injection (adjusted odds ratio (AOR): 14.9, 95% confidence interval (CI): 8.0, 27.7) and prescription opioid injection (AOR: 14.7, 95% CI: 7.7, 28.1). Although HIV was not prevalent, data suggest that the rural felony probationers in this sample were engaging in risky injection practices that could facilitate transmission of HIV. This is especially problematic since those involved in the criminal justice system may be more likely to be exposed to HIV. Therefore, prevention aimed at reducing HIV-risk behaviors among rural, criminally involved individuals is warranted. Havens J, Oser C, Leukefeld C. Injection Risk Behaviors Among Rural Drug Users: Implications For HIV Prevention. AIDS Care. 2011; 23 (5): 638-645.

Child Welfare Agency Ties to Providers and Schools and Substance Abuse Treatment Use by Adolescents Policy makers and advocates are increasingly encouraging child-serving organizations to work together. This study examined how child welfare agency ties with substance abuse treatment providers and schools correlated with substance abuse treatment for adolescents receiving child protective services. A sample of adolescents with substance use risk was extracted from a national survey of families engaged with child welfare. Logistic regressions

with djustments for complex survey design used child welfare agency ties to substance abuse treatment providers and schools to predict treatment. As expected, adolescents were more likely to report treatment when child protective services and substance abuse treatment were in the same agency and when child welfare agency directors reported joint planning with schools. However, child welfare agency agreements with substance abuse treatment providers were negatively associated with treatment. This unexpected finding implies that agencies may sometimes cooperate to address problems and to improve service utilization. Wells R, Chuang E, Haynes L, Lee I, Bai Y. Child Welfare Agency Ties To Providers And Schools And Substance Abuse Treatment Use By Adolescents. J Subst Abuse Treat. 2011; 40 (1): 26-34.

Occupational Turnover Intentions Among Substance Abuse Counselors This study examined predictor, moderator, and mediator variables of occupational turnover intention (OcTI) among substance abuse counselors. Data were obtained via questionnaires from 929 counselors working in 225 private substance abuse treatment (SAT) programs across the United States. Hierarchical multiple regression models were conducted to assess predictor, moderator, and mediator variables of OcTI. OcTI scores were relatively low on a 7-point scale, indicating that very few counselors definitely intended to leave the SAT field. Age, certification, positive perceptions of procedural and distributive justice, and hospital-based status negatively predicted OcTI. Counselors' substance use disorder–impacted history moderated the association between organizational commitment and OcTI. Organizational turnover intention partially mediated the link between organizational commitment and OcTI. Workforce stability might be achieved by promoting perceptions of advantages to working in a particular treatment program, having organizational commitment, showing appreciation for counselors' work, and valuing employees from diverse backgrounds. Rothrauff TC, Abraham AJ, Bride BE, Roman PM. Occupational Turnover Intentions Among Substance Abuse Counselors. J Subst Abuse Treat. 2011; 40: 67-76.

Adding Coaching to Provider Performance Feedback May Not Improve Quality Indicators A randomized trial of substance abuse treatment programs tested whether "enhanced profiles," consisting of feedback and coaching about performance indicators, improved the performance of residential, methadone, and detoxification programs. These enhanced profiles were reviewed during quarterly on-site visits between October 2005 and July 2007. The performance indicators were the percentage of clients completing referrals to a lower level of care, and the percentage of cliens admitted to a higher level of care within 30 days of discharge. Control programs received only "basic profiles," consisting of emailed quarterly printouts of these performance indicators. Effectiveness was evaluated using hierarchical linear models with client-level information nested within agencies and regions of the state. Treatment programs receiving enhanced profiles (n = 74) did not perform significantly differently from those receiving only basic profiles (n = 29) on either performance measure. To improve performance, interventions with greater scope and incentives may be needed. Daley M, Shepard DS, Tompkins C, Dunigan R, Reif S, Perloff J, Siembab L, Horgan C. Randomized Trial Of Enhanced Profiling In Substance Abuse Treatment. Adm Policy Ment Health. 2011; 38 (2): 96-104.

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's 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 dru 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. Korthuis P, Saha S, Chander G, McCarty D, Moore R, Cohn J, Sharp V, Beach M. Substance Use And The Quality Of Patient-Provider Communication In HIV Clinics. AIDS Behav. 2011; 15 (4): 832-841.

Accounting for Time-Invariant Unobserved Individual Heterogeneity Reduces Estimates of the Effect of Drug Use on Health Services Utilization The objective of this study was to analyze the relationships between illicit drug use and three types of health services utilization: emergency room utilization, hospitalization, and medical attention required due to injury(s). Data. Waves 1 and 2 (11,253 males and 13,059 females) from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Study Design. The authors derive benchmark estimates by employing standard cross-sectional data models to pooled waves of NESARC data. To control for potential bias due to time-invariant unobserved individual heterogeneity, they re-estimate the relationships with fixed-effects models. The cross-sectional data models suggest that illicit drug use is positively and significantly related to health services utilization in almost all specifications. Conversely, the only significant ($p<.05$) relationships in the fixed-effects models are the odds of receiving medical attention for an injury and the number of injuries requiring medical attention for men, and the number of times hospitalized for men and women. Failing to control for time-invariant individual heterogeneity could lead to biased coefficients when estimating the effects of illicit drug use on health services utilization. Moreover, it is important to distinguish between types of drug user (casual versus heavy) and estimate gender-specific models. French M, Fang H, Balsa A. Longitudinal Analysis Of Changes In Illicit Drug Use And Health Services Utilization. Health Serv Res. 2011; 46 (3): 877-899.

Improved Quality of Life For Opioid-Dependent Patients Receiving Buprenorphine Treatment In HIV Clinics Opioid dependence and HIV infection are associated with poor health-related quality of life (HRQOL). Buprenorphine/naloxone (bup/nx) provided in HIV care settings may improve HRQOL. The authors surveyed 289 HIV-infected opioid-dependent persons treated with clinic-based bup/nx about HRQOL using the Short Form Health Survey (-12) administered at baseline, 3, 6, 9, and 12 months. They used normalized SF-12 scores, which correspond to a mean HRQOL of 50 for the general US population (SD 10, possible range 0-100). They compared mean normalized mental and physical composite and component scores in quarters 1, 2, 3, and 4 with baseline scores using generalized estimating equation models. We assessed the effect of clinic-based bup/nx prescription on HRQOL composite scores using mixed effects regression with site as random effect and time as repeated effect. Baseline normalized SF-12 scores were lower than the general US population for all HRQOL domains. Average composite mental HRQOL improved from 38.3 (SE 12.5) to 43.4 (SE 13.2) [² 1.13 (95% CI: 0.72 to 1.54)] and composite physical HRQOL remained unchanged [² 0.21 (95% CI: -0.16 to

0.57)] over 12 months follow-up. Continued bup/nx treatment across all 4 quarters was associated with improvements in both physical [² 2.38 (95% CI: 0.63 to 4.12)] and mental [² 2.51 (95% CI: 0.42 to 4.60)] HRQOL after adjusting for other contributors to HRQOL. Clinic-based bup/nx maintenance therapy is potentially effective in ameliorating some of the adverse effects of opioid dependence on HRQOL for HIV-infected populations. Korthuis P, Tozzi M, Nandi V, Fiellin D, Weiss L, Egan J, Botsko M, Acosta A, Gourevitch M, Hersh D, Hsu J, Boverman J, Altice F. Improved Quality Of Life For Opioid-Dependent Patients Receiving Buprenorphine Treatment In HIV Clinics. J Acquir Immune Defic Syndr. 2011; 56 Suppl 1: S39-S45.

Rural Drug Users: Factors Associated With Substance Abuse Treatment Utilization The purpose of this study is to use a modified version of Andersen's Behavioral Model of Health Services Use to identify the correlates of the number of substance abuse treatment episodes received by rural drug users. Data were collected from face-to-face interviews with 711 drug users in rural areas of Ohio, Arkansas, and Kentucky. Descriptive analyses examine rural drug users' substance use histories and retrospective substance abuse treatment service utilization patterns. A negative binomial regression model indicated that selected predisposing, historical health, and enabling factors were significantly associated with the utilization of substance abuse treatment among rural drug users. Despite high levels of recent and lifetime self-reported substance use among these rural drug users, treatment services were underutilized. Future studies are needed to examine the impact of the health care system and characteristics of the external environment associated with rural substance abuse treatment in order to increase utilization among drug users. Oser C, Leukefeld C, Staton Tindall M, Garrity T, Carlson R, Falck R, Jichuan Wang , Booth B. Rural Drug Users: Factors Associated With Substance Abuse Treatment Utilization. Int J Offender Ther Comp Criminol. 2011; 55 (4): 567-586.

Training Physician-Scientists: A Model for Integrating Research into Psychiatric Residency The number of physicians engaged in research careers has declined significantly over the past two decades. Physicians with in-depth experience and formal training in research design, development, implementation, statistical analysis, and interpretation of scientific information are rare. In response to this shortage, the Medical University of South Carolina (MUSC) launched an NIH-funded research track in 2006 to address the institutional, financial, and regulatory barriers to research training during residency. The primary aim was to incorporate a research track within a 4-year psychiatric residency program for physicians. A secondary goal was to extend recruitment into earlier phases of medical training by offering summer research fellowships to medical and undergraduate students. This article describes the program including core mechanisms of training, recruitment, and outcomes to date. The program provides a model to effectively integrate research training during residency without increasing the number of years of residency training. The training components described herein should be exportable to other psychiatric residency training programs and potentially other specialties of medicine. Back S, Book S, Santos A, Brady K. Training Physician-Scientists: A Model For Integrating Research Into Psychiatric Residency. Acad Psychiatry. 2011; 35 (1): 40-45.

Maladaptive Coping as a Mediator of Family Stress Family members of women substance users may be at risk for stress-related problems. Family coping responses may affect outcomes for both families and women in treatment. Eighty-two women in treatment for substance use disorders (56 with comorbid psychiatric conditions) and 82 family members were interviewed.

Stressors related to women's disorders were significantly related to increased family member burden. Women's behavioral problems predicted greater family member Worry, Displeasure, and Impact. Extent of women's drug or alcohol use predicted greater family member Stigma and Impact. Family member maladaptive coping partially mediated relationships between family member stressors and family member Displeasure and Impact. Family member maladaptive coping also functioned as a moderator between the stressors and Impact. Moore B, Biegel D, McMahon T. Maladaptive Coping As A Mediator Of Family Stress. J Soc Work Pract Addict. 2011; 11 (1): 17-39.

Substance Use Diagnosis Statistically Associated with Excess Mortality Even among HIV-Infected Patients with Access to Medical Services In a retrospective cohort design, HIV-infected patients (GE 14 years old) from a large health plan (northern California) were studied to examine mortality associated with diagnosis of SU dependence or Abuse over an 11-year period. At study entry or during follow-up, 2,279(25%) or 9,178 HIV-infected patients had received a diagnosis of SU disorder. Diagnoses were categorized as alcohol dependence/abuse only, illicit drugs only, or both. Cause of death differed by the category of SU diagnosis. Mortality rates ranged from 35.5 deaths per 1,000 person years in patients with an SU disorder to 17.5 deaths among patients without an SU disorder. Regression results indicated mortality risk was significantly higher in all patients without an SU disorder. Regression results indicated mortality risk was significantly higher in all categories of SU disorder compared to no SU disorder (hazard ratios ranging from 1.65 to 1.67) after adjustment for SU treatment and confounders. A Diagnosis of SU dependence/abuse is associated with higher mortality among HIV-infected patients for whom access to medical services is not a significant factor. Delorenze GN, Weisner C, Tsai A, Satre DD, Quesenberry CP. Excess Mortality Among HIV-Infected Patients Diagnosed With Substance Use Dependence Or Abuse Receiving Care In A Fully Integrated Medical Care Program. Alcohol Clin Exp Res. 2011; 32 (2): 203-210.

CTN-RELATED RESEARCH

Use of Item Response Theory and Latent Class Analysis To Link Poly-Substance Use Disorders With Addiction Severity, HIV Risk, and Quality of Life Among Opioid-Dependent Patients In the Clinical Trials Network This study applied item response theory (IRT) and latent class analysis (LCA) procedures to examine the dimensionality and heterogeneity of comorbid substance use disorders (SUDs) and explored their utility for standard clinical assessments, including the Addiction Severity Index (ASI), HIV Risk Behavior Scale (HRBS), and SF-36 quality-of-life measures. The sample included 343 opioid-dependent patients enrolled in two national multisite studies of the U.S. National Drug Abuse Treatment Clinical Trials Network (CTN001-002). Patients were recruited from inpatient and outpatient addiction treatment settings at 12 programs. Data were analyzed by factor analysis, IRT, LCA, and latent regression procedures. A two-class LCA model fit dichotomous SUD data empirically better than one-parameter and two-parameter IRT models. LCA distinguished 10% of severe comorbid opioid-dependent individuals who had high rates of all SUDs examined-especially amphetamine and sedative abuse/dependence-from the remaining 90% who had SUDs other than amphetamine and sedative abuse/dependence (entropy=0.99). Item-level results from both one-parameter and two-parameter IRT models also found that amphetamine and sedative abuse/dependence tapped the more severe end of the latent poly-SUD trait. Regardless of whether SUDs were defined as a continuous trait or categorically, individuals characterized by a high level of poly-SUD demonstrated more psychiatric problems and HIV risk behaviors. A combined application of categorical and dimensional latent approaches may improve the understanding of comorbid SUDs and their associations with other clinical indicators. Abuse of sedatives and methamphetamine may serve as a useful marker for identifying subsets of opioid-dependent individuals with needs for more intensive interventions. Wu LT, Ling W, Burchett B, Blazer DG, Yang C, Pan JJ, Reeve BB, Woody GE. Use of item response theory and latent class analysis to link poly-substance use disorders with addiction severity, HIV risk, and quality of life among opioid-dependent patients in the Clinical Trials Network. Drug Alcohol Depend. 2011 Apr 16. [Epub ahead of print]

Barriers To Providing Health Services For HIV/AIDS, Hepatitis C Virus Infection and Sexually Transmitted Infections In Substance Abuse Treatment Programs In the United States The authors sought to identify barriers to offering services for HIV/AIDS, hepatitis C virus, and sexually transmitted infections in substance abuse treatment programs. The authors surveyed treatment program administrators and clinicians within the National Drug Abuse Treatment Clinical Trials Network to evaluate the availability of medical and non-medical services for patients with or at risk for acquiring these infections. A substantial proportion of programs do not offer services (particularly medical services) for these infections. The most commonly cited barriers were funding, health insurance benefits, patient acceptance, and staff training. The findings highlight a missed opportunity to positively impact these infectious disease epidemics. Bini EJ (deceased), Kritz S, Brown Jr LS, Robinson J, Alderson D, Rotrosen J. Barriers to providing health services for HIV/AIDS, hepatitis C virus infection and sexually transmitted infections in substance abuse treatment programs in the United States. J of Addict Dis. 2011 Apr; 30(2): 98-109.

Divergence by ADHD Subtype in Smoking Cessation Response to OROS-Methylphenidate Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric condition subclassified in DSM-IV according to its core symptoms domains as (a) predominantly inattentive (ADHD-IN), (b) predominantly hyperactive/impulsive (ADHD-H), and (c) combined inattentive and hyperactive/impulsive (ADHD-C). Whether these subtypes represent distinct clinical entities or points on a severity continuum is controversial. Divergence in treatment response is a potential indicator of qualitative heterogeneity. This study examined smoking cessation response by ADHD subtype to osmotic-release oral system methylphenidate (OROS-MPH). Male and female adult smokers (ADHD-C = 167 and ADHD-IN = 87) were randomized to receive OROS-MPH or placebo as augmentation treatment to nicotine patch and counseling. Logistic regression was conducted to test the effect of OROS-MPH versus placebo on prolonged smoking abstinence by ADHD subtype. The subtypes were similar in baseline demographic, smoking, and psychiatric history but differed in smoking cessation response to OROS-MPH or placebo as a function of nicotine dependence level. The 3-way interaction was significant; $\chi(2)(1) = 8.22$, $p < .01$. Among highly dependent smokers, the prolonged abstinence rates were greater with OROS-MPH than with placebo in the ADHD-C group (60% vs. 31.3%, respectively, $p < .05$) but higher with placebo than with OROS-MPH in the ADHD-IN group (60% vs. 11.8%, respectively, $p < .01$). Abstinence rates did not differ by subtype or treatment among smokers who were less nicotine dependent. Contrasting treatment response and divergence in the impact of nicotine dependence level support the hypothesis of ADHD subtypes as distinct clinical entities and may indicate the need and directions for personalized targeted treatments of smokers with ADHD. Covey LS, Hu MC, Weissman J, Croghan I, Adler L, Winhusen T. Divergence by ADHD subtype in smoking cessation response to OROS-Methylphenidate. Nicotine Tob Res. 2011 Jun 7. [Epub ahead of print].

The Potential Impact of Recruitment Method On Sample Characteristics and Treatment Outcomes In A Psychosocial Trial For Women With Co-Occurring Substance Use Disorder and PTSD Recruitment method can impact the sample composition of a clinical trial and, thus, the generalizability of the results, but the importance of recruitment method in substance use disorder trials has received little attention. The present paper sought to address this research gap by evaluating the association between recruitment method and sample characteristics and treatment outcomes in a substance use disorder trial. In a multi-site trial evaluating Seeking Safety (SS), relative to Women's Health Education (WHE), for women with co-occurring PTSD (either sub-threshold or full PTSD) and substance use disorders, one site assessed the method by which each participant was recruited. Data from this site (n=106), which recruited participants from newspaper advertising and clinic intakes, were analyzed. Participants recruited through advertising, relative to those from the clinic, had significantly higher levels of baseline drug use and higher rates of meeting DSM-IV-TR criteria for full PTSD. Results suggest that the effectiveness of SS in decreasing PTSD symptoms was greater for participants recruited through advertising relative to those recruited from the clinic. Conversely, the results revealed a significant treatment effect in the clinic-recruited participants, not seen in the advertising-recruited participants, with SS, relative to WHE, participants being more likely to report past week drug use during the follow-up phase. Recruitment method may impact sample composition and treatment effects. Replication of this finding would have important implications for substance use disorder efficacy trials which often utilize advertising to recruit participants. Winhusen T, Winstanley EL, Somoza E, Brigham G. The potential impact of recruitment method

on sample characteristics and treatment outcomes in a psychosocial trial for women with co-occurring substance use disorder and PTSD. Drug Alcohol Depend. 2011 Jul 11. [Epub ahead of print].

Co-Occurring Amphetamine Use and Associated Medical and Psychiatric Comorbidity Among Opioid-Dependent Adults: Results From the Clinical Trials Network In response to the rising rate of treatment admissions related to illicit use of amphetamines (eg, methamphetamine), the authors examined the prevalence of amphetamine use among treatment-seeking, opioid-dependent adults, explored whether amphetamine users were as likely as nonamphetamine users to enroll in opioid-dependence treatment trials, and determined whether amphetamine users manifested greater levels of medical and psychiatric comorbidity than nonusers. The sample included 1257 opioid-dependent adults screened for participation in three multisite studies of the National Drug Abuse Treatment Clinical Trials Network (CTN001-003), which studied the effectiveness of buprenorphine for opioid detoxification under varying treatment conditions. Patients were recruited from 23 addiction treatment programs across the US. Medical and psychiatric comorbidity were examined by past-month amphetamine use (current vs former) and route of administration. Five mutually exclusive groups were examined, ie, nonusers, current amphetamine injectors, current amphetamine noninjectors, former amphetamine injectors, and former amphetamine noninjectors. Of the sample (n = 1257), 22.3% had a history of regular amphetamine use. Of the 280 amphetamine users, 30.3% reported injection as their primary route. Amphetamine users were more likely than nonusers to be white and use more substances. Amphetamine users were as likely as nonusers to enroll in treatment trials. Bivariate analyses indicated elevated rates of psychiatric problems (depression, anxiety, hallucinations, cognitive impairment, violence, suicidal thoughts/attempts) and medical illnesses (dermatological, hepatic, cardiovascular, respiratory, neurological, seizure, allergy conditions) among amphetamine users. After adjusting for demographic variables and lifetime use of other substances: current amphetamine users and former injectors showed an increased likelihood of having medical illnesses and hospitalizations; current injectors had elevated odds of suicidal thoughts or attempts; current noninjectors exhibited elevated odds of anxiety, cognitive impairment, and violent behaviors; and former noninjectors had increased odds of depression. Treatment-seeking, amphetamine-using, opioid-dependent adults manifest greater levels of medical and psychiatric morbidity than treatment-seeking, opioid-dependent adults who have not used amphetamines, indicating a greater need for intensive clinical management. Pilowsky DJ, Wu LT, Burchett B, Blazer DG, Woody GE, Ling W. Co-occurring amphetamine use and associated medical and psychiatric comorbidity among opioid-dependent adults: results from the Clinical Trials Network. Subst Abuse and Rehab. 2011 July; 2011(2): 133-144.

Primary Outcome Indices In Illicit Drug Dependence Treatment Research: Systematic Approach To Selection and Measurement of Drug Use End-Points In Clinical Trials Clinical trials test the safety and efficacy of behavioral and pharmacological interventions in drug-dependent individuals. However, there is no consensus about the most appropriate outcome(s) to consider in determining treatment efficacy or on the most appropriate methods for assessing selected outcome(s). The authors summarize the discussion and recommendations of treatment and research experts, convened by the US National Institute on Drug Abuse, to select appropriate primary outcomes for drug dependence treatment clinical trials, and in particular the feasibility of selecting a common outcome to be included in all or most trials. A brief history of

outcomes employed in prior drug dependence treatment research, incorporating perspectives from tobacco and alcohol research, is included. The relative merits and limitations of focusing on drug-taking behavior, as measured by self-report and qualitative or quantitative biological markers, are evaluated. Drug-taking behavior, measured ideally by a combination of self-report and biological indicators, is seen as the most appropriate proximal primary outcome in drug dependence treatment clinical trials. The authors conclude that the most appropriate outcome will vary as a function of salient variables inherent in the clinical trial, such as the type of intervention, its target, treatment goals (e.g. abstinence or reduction of use) and the perspective being taken (e.g. researcher, clinical program, patient, society). It is recommended that a decision process, based on such trial variables, be developed to guide the selection of primary and secondary outcomes as well as the methods to assess them. Donovan DM, Bigelow GE, Brigham GS, Carroll KM, Cohen AJ, Gardin JG, Hamilton JA, Huestis MA, Hughes JR, Lindblad R, Marlatt GA, Preston KL, Selzer JA, Somoza EC, Wakim PG, Wells EA. Primary outcome indices in illicit drug dependence treatment research: systematic approach to selection and measurement of drug use end-points in clinical trials. Addiction. 2011 Jul 22. [Epub ahead of print]

Randomized Multi-Site Trial of the Job Seekers' Workshop In Patients With Substance Use Disorders Unemployment is associated with negative outcomes both during and after drug abuse treatment. Interventions designed to increase rates of employment may also improve drug abuse treatment outcomes. The purpose of this multi-site clinical trial was to evaluate the Job Seekers' Workshop (JSW), a three session, manualized program designed to train patients in the skills needed to find and secure a job. Study participants were recruited through the NIDA Clinical Trials Network (CTN) from six psychosocial counseling (n=327) and five methadone maintenance (n=301) drug treatment programs. Participants were randomly assigned to either standard care (program-specific services plus brochure with local employment resources) (SC) or standard care plus JSW. Three 4-h small group JSW sessions were offered weekly by trained JSW facilitators with ongoing fidelity monitoring. JSW and SC participants had similar 12- and 24-week results for the primary outcome measure (i.e., obtaining a new taxed job or enrollment in a training program). Specifically, one-fifth of participants at 12weeks (20.1-24.3%) and nearly one-third at 24weeks (31.4-31.9%) had positive outcomes, with "obtaining a new taxed job" accounting for the majority of cases. JSW group participants did not have higher rates of employment/training than SC controls. Rates of job acquisition were modest for both groups, suggesting more intensive interventions may be needed. Alternate targets (e.g., enhancing patient motivation, training in job-specific skills) warrant further study as well. Svikis DS, Keyser-Marcus L, Stitzer M, Rieckmann T, Safford L, Loeb P, Allen T, Luna-Anderson C, Back SE, Cohen J, Debernardi MA, Dillard B, Forcehimes A, Jaffee W, Killeen T, Kolodner K, Levy M, Pallas D, Perl HI, Potter JS, Provost S, Reese K, Sampson RR, Sepulveda A, Snead N, Wong CJ, Zweben J. Randomized multi-site trial of the Job Seekers' Workshop in patients with substance use disorders. Drug Alcohol Depend. 2011 Jul 27. [Epub ahead of print]

Cigarette and Cannabis Use Trajectories Among Adolescents In Treatment For Attention-Deficit/Hyperactivity Disorder and Substance Use Disorders Cigarette smoking is common in adolescents with attention-deficit/hyperactivity disorder (ADHD) and substance use disorders (SUD). However, little is known about the relationship between cigarette and cannabis use trajectories in the context of treatment for both ADHD and SUD. To address this research gap,

the authors report collateral analyses from a 16-week randomized, controlled trial (n=303) of osmotic-release methylphenidate (OROS-MPH) in adolescents with ADHD concurrently receiving cognitive behavioral therapy (CBT) targeting non-nicotine SUD. Participants completed cigarette and cannabis use self-report at baseline and throughout treatment. Analyses were performed to explore the relationships between cigarette smoking, cannabis use, and other factors, such as medication treatment assignment (OROS-MPH versus placebo). Baseline (pre-treatment) cigarette smoking was positively correlated with cannabis use. Negligible decline in cigarette smoking during treatment for non-nicotine SUD was observed in both medication groups. Regular cigarette and cannabis users at baseline who reduced their cannabis use by >50% also reduced cigarette smoking (from 10.8±1.1 to 6.2±1.1 cigarettes per day). Findings highlight the challenging nature of concurrent cannabis and cigarette use in adolescents with ADHD, but demonstrate that changes in use of these substances during treatment may occur in parallel. Gray KM, Riggs PD, Min SJ, Mikulich-Gilbertson SK, Bandyopadhyay D, Winhusen T. Cigarette and cannabis use trajectories among adolescents in treatment for attention-deficit/hyperactivity disorder and substance use disorders. Drug Alcohol Depend. 2011 Sep 1; 117(2-3): 242-247. Epub 2011 Mar 15.

INTERNATIONAL RESEARCH

HHH Fellow: Flavio Pechansky, Brazil, 1993-1994

De Boni R, Bozzetti MC, Hilgert J, Sousa T, Von Diemen L, Benzano D, Menegon G, Holmer B, Duarte Pdo C, Pechansky F. **Factors associated with alcohol and drug use among traffic crash victims in southern Brazil.** Accid Anal Prev. 2011 Jul; 43(4): 1408-1413. Epub 2011 Mar 15.

The objective of this study was to investigate the prevalence of and factors associated with alcohol- or drug-related traffic crashes (TC) in a sample of TC victims who were admitted to the two emergency rooms of Porto Alegre in southern Brazil. A cross-sectional study with consecutive samples was used. Victims of non-fatal TCs (as drivers, passengers or pedestrians) who had presented at emergency rooms during the 45days of data collection were selected. Subjects participated in a structured interview, were breathalyzed and underwent salivary drug testing. A multinomial logistic regression model was used to verify factors associated with alcohol or drug use. Of the 609 victims who participated in the interview, 72% were male, and the median age was 29 years (interquartile range 23.0-40.0years). The drivers were mostly men ($p<0.001$), with a higher binge drinking rate ($p=0.003$) and marijuana use ($p=0.005$) than seen in pedestrian and passengers. The prevalence of a positive blood alcohol concentration (BAC) ranged from 7.8% among the drivers to 9.2% among the pedestrians ($p=0.861$), and the cannabis prevalence was 13.3% among the drivers. The variables associated with an alcohol-related accident were binge drinking in the prior 12 months (OR 2.4; CI 95% 1.1-5.1) and coming from a party/bar (OR 8.7; CI 95% 2.8-26.7). Alcohol abuse or dependence increased by 5.2-fold the chance of another substance-related TC. The large number of individuals found in TC-related emergency room visits in a short time frame is evidence of the Brazilian epidemic of TC. The data showed that alcohol abuse or dependence also increases the risk of intoxication by other drugs, and they point to alcohol and drug use as a major problem requiring specific TC-related public policies and law enforcement.

Souza DZ, Boehl PO, Comiran E, Mariotti KC, Pechansky F, Duarte PC, De Boni R, Froehlich PE, Limberger RP. **Determination of amphetamine-type stimulants in oral fluid by solid-phase microextraction and gas chromatography-mass spectrometry.** Anal Chim Acta. 2011 Jun 24; 696(1-2): 67-76. Epub 2011 Apr 20.

A method for the simultaneous identification and quantification of amphetamine (AMP), methamphetamine (MET), fenproporex (FEN), diethylpropion (DIE) and methylphenidate (MPH) in oral fluid collected with Quantisal™ device has been developed and validated. Thereunto, in-matrix propylchloroformate derivatization followed by direct immersion solid-phase microextraction and gas chromatography-mass spectrometry were employed. Deuterium labeled AMP was used as internal standard for all the stimulants and analysis was performed using the selected ion monitoring mode. The detector response was linear for the studied drugs in the concentration range of 2-256ngmL(-1) (neat oral fluid), except for FEN, whereas the linear range was 4-256ngmL(-1). The detection limits were 0.5ngmL(-1) (MET), 1ngmL(-1) (MPH) and 2ngmL(-1) (DIE, AMP, FEN), respectively. Accuracy of quality control samples remained within 98.2-111.9% of the target concentrations, while precision has not exceeded 15% of the relative standard deviation. Recoveries with Quantisal™ device ranged from 77.2% to 112.1%. Also, the goodness-of-fit concerning the ordinary least squares model in the statistical inference of data has been tested through residual plotting and ANOVA. The validated method can be

easily automated and then used for screening and confirmation of amphetamine-type stimulants in drivers' oral fluid.

da Silva N Jr, Szobot CM, Anselmi CE, Jackowski AP, Chi SM, Hoexter MQ, Anselmi OE, Pechansky F, Bressan RA, Rohde LA. **Attention Deficit/Hyperactivity Disorder: Is There a Correlation Between Dopamine Transporter Density and Cerebral Blood Flow?** Clin Nucl Med. 2011 Aug;36(8):656-660. Attention deficit/hyperactivity disorder (ADHD) is one of the most frequent behavioral problems in school-age children. Although the etiology remains unclear, the involvement of the dopaminergic system has been suggested by genetic studies that report an overexpression of the dopamine transporter (DAT) gene. In spite of these abnormalities being directly related to the decrease of dopamine (DA) in the striatum (STR), abnormalities in brain perfusion have also been observed in cortical-subcortical structures. Functional neuroimaging studies have suggested that the DA concentration may cause changes in the cerebral blood flow (CBF). The objective of this study was to evaluate the relationship between DAT density in STR and cortical-subcortical impairment in CBF. Based on the hypothesis that there is a correlation between DA availability and brain perfusion, we postulated that individuals with ADHD, with a higher DAT density in the basal ganglia, will have lower perfusion in the fronto-striatal-cerebellar networks. We used Tc-99m TRODAT-1 SPECT to measure DAT density and Tc-99m ECD SPECT to assess brain perfusion. Ten adolescents diagnosed with ADHD by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria were investigated. Analysis with Statistical Parametric Mapping 5 corrected for multiple comparisons, using small volume correction, showed a significant negative correlation between the DAT density in the STR and CBF in the cingulate gyrus, frontal lobe, temporal lobe, and cerebellum (pFDR <0.01). Our findings suggest that higher DAT density in the STR was associated with a decrease in the regional CBF in the cortical and subcortical attention network.

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

Thomas DL, Leoutsakas D, Zabransky T, Kumar MS. **Hepatitis C in HIV-infected individuals: cure and control, right now.** J Int AIDS Soc. 2011 May 8;14(1):22. [Epub ahead of print] For persons living with HIV, hepatitis C is a major public health problem that must be controlled and could be eliminated. The challenge arises because the hepatitis C virus (HCV) is prevalent among HIV-infected persons in most parts of the world, because HIV worsens all HCV outcomes, and because HCV may add additional individual economic and psychosocial complications to HIV disease. Despite the major benefits of antiretroviral therapy on HIV outcomes, antiretroviral therapy is not sufficient to halt the complications of HCV. Nonetheless, HCV can be controlled at all stages, including prevention of infection and cure. Thus, HCV is an eradicable disease. There are significant inequalities worldwide in HCV control that could markedly constrain the impact of these measures.

INVEST Fellow: Min Zhao, China, 2001-2002

Min Z, Xu L, Chen H, Ding X, Yi Z, Mingyuang Z. **A pilot assessment of relapse prevention for heroin addicts in a Chinese rehabilitation center.** Am J Drug Alcohol Abuse. 2011 May; 37(3): 141-147. Epub 2011 Mar 28.

The objective of this study was to conduct a pilot assessment of relapse prevention (RP) group therapy for heroin-dependent patients in a drug rehabilitation center in China. A randomized

case-control study was conducted to assess the efficacy of RP delivered over a 2-month period to male heroin addicts (n = 50, RP group) in the Shanghai Labor Drug Rehabilitation Center (LDRC) compared with an equal number of participants (n = 50, labor rehabilitation (LR) group) in the LDRC program receiving standard-of-care treatment. Outcomes were assessed by the Beck Depression Inventory (BDI), the Self-Rating Anxiety Scale (SAS), the Self-Efficacy Scale (SE), and the Self-Esteem Scale (SES) after completion of RP, and by the Addiction Severity Index (ASI) and abstinence rates of heroin use at 3-month follow-up post release from the LDRC for both groups. Significant improvements in scores on SAS, SE, and SES were found in the RP group after completion of the 2-month RP group therapy compared with the LR group (SAS 7.85 ± 6.20 vs 1.07 ± 5.42, SE 3.88 ± 3.60 vs .08 ± 2.89, and SES 3.83 ± 3.31 vs .78 ± 2.55). At 3-month follow-up, the RP group participants had more improvements on ASI scores in most domains and had higher abstinence rates than that in the LR group (37.2% vs 16.7%). An RP component can be effective in increasing abstinence rates among post-program heroin-dependent individuals and may help reduce anxiety and improve self-esteem and self-efficacy during and following treatment. Scientific Significance: This study suggests RP as a potentially effective component of treatment for heroin addicts.

INVEST Fellow: Anton Bespalov, 1994-1995, Russia

Nikiforuk A, Kos T, Rafa D, Behl B, Bespalov A, Popik P. **lockade of glycine transporter 1 by SSR-504734 promotes cognitive flexibility in glycine/NMDA receptor-dependent manner.** Neuropharmacology. 2011 Apr 21. [Epub ahead of print]

Accumulating evidence suggests that cognitive processes may be regulated by glycine concentration in the local environment of glutamate N-methyl-d-aspartate receptor (NMDAR). The concentration of glycine is controlled, among other factors, by the glycine transporter 1 (GlyT1). While GlyT1 inhibitors are developed for a number of indications including cognitive improvement, little is known about their effects in tasks depending on prefrontal cortical function. The authors examined the effect of GlyT1 inhibitor SSR-504734 on cognitive flexibility assessed in the attentional set-shifting task in rats (ASST). The second goal was to elucidate whether SSR-504734 effect has been due to the compound's action at glycine/NMDAR site. Rats treated with SSR-504734 (3 and 10 mg/kg, IP) required significantly less trials to criteria during extra-dimensional shift (EDs) phase of the ASST. The effect of SSR-504734 (3 mg/kg) was completely prevented by the glycine/NMDAR site antagonist, L-687,414 (30 mg/kg, IP) that by itself exerted no effect on cognitive flexibility. Present study demonstrates that the elevation of glycine concentration through the blockade of its reuptake facilitates cognitive flexibility. As this effect was fully blocked by glycine/NMDAR antagonist, SSR-504734-induced cognitive improvement is likely mediated through glycine action at NMDAR. It is suggested that GlyT1 inhibitors like SSR-504734 may represent a useful pharmacological approach for cognitive enhancement, especially in domains critically affected in schizophrenia.

INVEST Fellow: Guilherme Borges, Mexico 1997-1998

Guilherme Borges, Joshua Breslau, Ricardo Orozco, Daniel J. Tancredi, Heather Anderson, Sergio Aguilar-Gaxiola, Maria-Elena Medina Mora
A cross-national study on Mexico-US migration, substance use and substance use disorders
Drug Alcohol Depend. 2011 Aug 1;117(1):16-23. Epub 2011 Feb 5.

Epidemiologic research has consistently found lower prevalence of alcohol and drug use disorders among Hispanic immigrants to the US than among US-born Hispanics. Recent research has begun to examine how this change occurs in the process of assimilation in the US. The authors aimed to study immigration, US nativity, and return migration as risk factors for alcohol and drug use among people of Mexican origin in both the US and Mexico. Data come from nationally representative surveys in the United States (2001–2003; n = 1208) and Mexico (2001–2002; n = 5782). They used discrete time event history models to account for time-varying and time-invariant characteristics. They found no evidence that current Mexican immigrants in the US have higher risk for alcohol or alcohol use disorders than Mexicans living in Mexico, but current immigrants were at higher risk for drug use and drug use disorders. Current Mexican immigrants were at lower risk for drug use and drug disorders than US-born Mexican-Americans. US nativity, regardless of parent nativity, is the main factor associated with increasing use of alcohol and drugs. Among families of migrants and among return migrants we found increased risk for alcohol use, drug use and alcohol and drug use disorders. Evidence of selective migration and return of immigrants with disorders was found regarding alcohol use disorders only. Research efforts that combine populations from sending and receiving countries are needed. This effort will require much more complex research designs that will call for true international collaboration.

INTRAMURAL RESEARCH

Cellular Neurobiology Research Branch Research

Electrophysiology Research Section

Decreased Parvalbumin Immunoreactivity In the Cortex and Striatum Of Mice Lacking The CB1 Receptor Cortical and striatal regions of the brain contain high levels of the cannabinoid-1 (CB1) receptor, the central neuronal mediator of activity-dependent synaptic plasticity evoked by endocannabinoids. The expression levels of parvalbumin, a calcium-binding protein found in fast-spiking interneurons of both regions, may be controlled in part by synaptic activity during critical periods of development. However, there is currently no evidence that CB1 receptor expression affects parvalbumin levels in either cortical or striatal interneurons. To assess this possibility, IRP scientists examined parvalbumin immunoreactivity in the dorsolateral striatum, primary motor cortex (M1), and prefrontal cortex (PFC) of CB1 knockout and wild-type C57/BL6 mice. Quantitative densitometry showed a significant decrease in parvalbumin immunoreactivity within individual neurons in each of these regions of CB1 knockout mice relative to controls. A significantly lower density (number of cells per unit area) of parvalbumin-labeled neurons was observed in the striatum, but not the cortical regions of CB1 knockout mice. These findings suggest that CB1 receptor deletion may elicit a compensatory mechanism for network homeostasis affecting parvalbumin-containing cortical and striatal interneurons. Fitzgerald ML, Lupica CR, Pickel VM.. Decreased parvalbumin immunoreactivity in the cortex and striatum of mice lacking the CB1 receptor. Synapse. 2011; 65(8): 827-831.

Molecular Neuropsychiatry Research Branch

Methamphetamine Preconditioning Causes Differential Changes In Striatal Transcriptional Responses To Large Doses of the Drug Methamphetamine (METH) is a toxic drug of abuse, which can cause significant decreases in the levels of monoamines in various brain regions. However, animals treated with progressively increasing doses of METH over several weeks are protected against the toxic effects of the drug. In the present study, IRP scientists tested the possibility that this pattern of METH injections might be associated with transcriptional changes in the rat striatum, an area of the brain which is known to be very sensitive to METH toxicity and which is protected by METH preconditioning. They found that the presence and absence of preconditioning followed by injection of large doses of METH caused differential expression in different sets of striatal genes. Quantitative PCR confirmed METH-induced changes in some genes of interest. These include small heat shock 27 kD proteins 1 and 2 (HspB1 and HspB2), brain derived neurotrophic factor (BDNF), and heme oxygenase-1 (Hmox-1). The authors'observations are consistent with previous studies which have reported that ischemic or pharmacological preconditioning can cause reprogramming of gene expression after lethal ischemic insults. These studies add to the growing literature on the effects of preconditioning on the brain transcriptome. Cadet JL, Brannock C, Ladenheim B, McCoy MT, Beauvais G, Hodges AB, Lehrmann E, Wood WH 3rd, Becker KG, Krasnova IN. Dose Response. 2011; 9(2): 165-181. Epub 2010 Jul 2.

Chronic Methamphetamine Administration Causes Differential Regulation Of Transcription Factors In the Rat Midbrain Methamphetamine (METH) is an addictive and neurotoxic psychostimulant widely abused in the USA and throughout the world. When administered in large doses, METH can cause depletion of striatal dopamine terminals, with preservation of midbrain dopaminergic neurons. Because alterations in the expression of transcription factors that regulate the development of dopaminergic neurons might be involved in protecting these neurons after toxic insults, IRP investigators tested the possibility that their expression might be affected by toxic doses of METH in the adult brain. Male Sprague-Dawley rats pretreated with saline or increasing doses of METH were challenged with toxic doses of the drug and euthanized two weeks later. Animals that received toxic METH challenges showed decreases in dopamine levels and reductions in tyrosine hydroxylase protein concentration in the striatum. METH pretreatment protected against loss of striatal dopamine and tyrosine hydroxylase. In contrast, METH challenges caused decreases in dopamine transporters in both saline- and METH-pretreated animals. Interestingly, METH challenges elicited increases in dopamine transporter mRNA levels in the midbrain in the presence but not in the absence of METH pretreatment. Moreover, toxic METH doses caused decreases in the expression of the dopamine developmental factors, Shh, Lmx1b, and Nurr1, but not in the levels of Otx2 and Pitx3, in saline-pretreated rats. METH pretreatment followed by METH challenges also decreased Nurr1 but increased Otx2 and Pitx3 expression in the midbrain. These findings suggest that, in adult animals, toxic doses of METH can differentially influence the expression of transcription factors involved in the developmental regulation of dopamine neurons. The combined increases in Otx2 and Pitx3 expression after METH preconditioning might represent, in part, some of the mechanisms that served to protect against METH-induced striatal dopamine depletion observed after METH preconditioning. Krasnova IN, Ladenheim B, Hodges AB, Volkow ND, Cadet JL. PLoS One. 2011 Apr 25; 6(4): e19179.

Clinical Pharmacology and Therapeutics Branch

Incubation of Cue-Induced Cigarette Craving During Abstinence In Human Smokers Abstinent drug users remain at risk for relapse long after withdrawal subsides. Animal studies indicate that responses to drug-related cues not only persist but increase with abstinence, a phenomenon termed "incubation of drug craving." It is unknown whether cue-induced craving increases, decreases, or remains constant with abstinence in humans. IRP scientists investigated effects of abstinence on cue-induced craving in cigarette smokers. Eighty-six non-treatment-seeking, adult smokers (≥10 cigarettes daily) were paid to abstain for 7 (Group 1), 14 (Group 2), or 35 (Groups 3 and 4) days. Abstinence was verified daily. Groups 1, 2, and 3 underwent a single cue session on the final abstinence day (7, 14, or 35). Group 4 viewed cues on Days 7, 14, and 35. Between and within groups, smoking-cue-induced craving increased with abstinence on some measures. Cue-induced craving was greater in Group 3 (35-day) compared with Group 1 (7-day). Within Group 4, cue-induced craving was greater at 35 than 14 days. Cue-induced craving did not decrease with abstinence on any measure. The authors present initial evidence of incubation of cue-induced craving in humans. The observation that cue-induced craving increases with abstinence, even as "background" craving and withdrawal symptoms subside, might have treatment implications. Bedi G, Preston KL, Epstein DH, Heishman SJ, Marrone GF, Shaham Y, de Wit H. Incubation of cue-induced cigarette craving during abstinence in human smokers. Biol Psychiatry. 2011 Apr 1; 69(7): 708-711.

Nicotine Psychopharmacology Section

Relative Performance of Common Biochemical Indicators In Detecting Cigarette Smoking Many cities have banned indoor smoking in public places. Thus, an updated recommendation for a breath carbon monoxide (CO) cut-off is needed that optimally determines smoking status. IRP scientists evaluated and compared the performance of breath CO and semiquantitative cotinine immunoassay test strips (urine and saliva NicAlert®) alone and in combination. This was a cross-sectional study carries out at an urban drug addiction research and treatment facility. Participants comprised ninety non-treatment-seeking smokers and 82 non-smokers. Participants completed smoking histories and provided breath CO, urine and saliva specimens. Urine and saliva specimens were assayed for cotinine by NicAlert® and liquid chromatography-tandem mass spectrometry (LCMSMS). An optimal breath CO cut-off was established using self-report and LCMSMS analysis of cotinine, an objective indicator, as reference measures. Performance of smoking indicators and combinations were compared to the reference measures. Breath CO ≥5 parts per million (p.p.m.) optimally discriminated smokers from non-smokers. Saliva NicAlert® performance was less effective than the other indicators. In surveys of smokers and non-smokers in areas with strong smoke-free laws, the breath carbon monoxide cut-off that discriminates most effectively appears to be ≥5 p.p.m. rather than the ≥10 p.p.m. cut-off often used. These findings may not generalize to clinical trials, regions with different carbon monoxide pollution levels or areas with less stringent smoke-free laws. Marrone GF, Shakleya DM, Scheidweiler KB, Singleton EG, Huestis MA, Heishman SJ. Relative performance of common biochemical indicators in detecting cigarette smoking. Addiction 2011; 106: 1325-1334.

Chemical Biology Research Branch

Serotonin (5-Hydroxytryptamine) 5-HT(2A) Receptor: Association with Inherent and Cocaine-Evoked Behavioral Disinhibition in Rats Alterations in the balance of functional activity within the serotonin [5-hydroxytryptamine (5-HT)] system are hypothesized to underlie impulse control. Cocaine-dependent subjects consistently show greater impulsivity relative to nondrug using control subjects. Preclinical studies suggest that the 5-HT(2A) receptor (5-HT(2A)R) contributes to the regulation of impulsive behavior and also mediates some of the behavioral effects of cocaine. IRP investigators hypothesized that the selective 5-HT(2A)R antagonist M100907 would reduce inherent levels of impulsivity and attenuate impulsive responding induced by cocaine in two animal models of impulsivity, the differential reinforcement of low rate (DRL) task and the one-choice serial reaction time (1-CSRT) task. M100907 reduced rates of responding in the DRL task and premature responding in the 1-CSRT task. Conversely, cocaine disrupted rates of responding in the DRL task and increased premature responding in the 1-CSRT task. M100907 attenuated cocaine-induced increases in specific markers of behavioral disinhibition in the DRL and 1-CSRT tasks. These results suggest that the 5-HT(2A)R regulates inherent impulsivity, and that blockade of the 5-HT(2A)R alleviates specific aspects of elevated levels of impulsivity induced by cocaine exposure. These data point to the 5-HT(2A)R as an important regulatory substrate in impulse control. Anastasio NC, Stoffel EC, Fox RG, Bubar MJ, Rice KC, Moeller FG, Cunningham KA. Behav Pharmacol. 2011 Jun; 22(3): 248-261.

Cannabinoid Potentiation of Glycine Receptors Contributes to Cannabis-Induced Analgesia Cannabinoids enhance the function of glycine receptors (GlyRs). However, little is known about the mechanisms and behavioral implication of cannabinoid-GlyR interaction. Using mutagenesis and NMR analysis, IRP investigators have identified a serine at 296 in the GlyR protein critical for the potentiation of I(Gly) by Δ(9)-tetrahydrocannabinol (THC), a major psychoactive component of marijuana. The polarity of the amino acid residue at 296 and the hydroxyl groups of THC are critical for THC potentiation. Removal of the hydroxyl groups of THC results in a compound that does not affect I(Gly) when applied alone but selectively antagonizes cannabinoid-induced potentiating effect on I(Gly) and analgesic effect in a tail-flick test in mice. The cannabinoid-induced analgesia is absent in mice lacking α3GlyRs but not in those lacking CB1 and CB2 receptors. These findings reveal a new mechanism underlying cannabinoid potentiation of GlyRs, which could contribute to some of the cannabis-induced analgesic and therapeutic effects. Xiong W, Cheng K, Cui T, Godlewski G, Rice KC, Xu Y, Zhang L. Nat Chem Biol. 2011 May;7(5): 296-303. Epub 2011 Apr 3.

Exploring the Neuroimmunopharmacology of Opioids: an Integrative Review of Mechanisms of Central Immune Signaling and Their Implications for Opioid Analgesia Vastly stimulated by the discovery of opioid receptors in the early 1970s, preclinical and clinical research was directed at the study of stereoselective neuronal actions of opioids, especially those played in their crucial analgesic role. However, during the past decade, a new appreciation of the non-neuronal actions of opioids has emerged from preclinical research, with specific appreciation for the nonclassic and nonstereoselective sites of action. Opioid activity at Toll-like receptors, newly recognized innate immune pattern recognition receptors, adds substantially to this unfolding story. It is now apparent from molecular and rodent data that these newly identified signaling events significantly modify the pharmacodynamics of opioids by eliciting proinflammatory reactivity from glia, the immunocompetent cells of the central nervous system. These central immune signaling events, including the release of cytokines and chemokines and the associated disruption of glutamate homeostasis, cause elevated neuronal excitability, which subsequently decreases opioid analgesic efficacy and leads to heightened pain states. This review examined the current preclinical literature of opioid-induced central immune signaling mediated by classic and nonclassic opioid receptors. A unification of the preclinical pharmacology, neuroscience, and immunology of opioids now provides new insights into common mechanisms of chronic pain, naive tolerance, analgesic tolerance, opioid-induced hyperalgesia, and allodynia. Novel pharmacological targets for future drug development are discussed in the hope that disease-modifying chronic pain treatments arising from the appreciation of opioid-induced central immune signaling may become practical. Hutchinson MR, Shavit Y, Grace PM, Rice KC, Maier SF, Watkins LR. Pharmacol Rev. 2011 Jul 13. [Epub ahead of print]

Patterns of Nicotinic Receptor Antagonism: Nicotine Discrimination Studies Evaluation of the discriminative stimulus effects of drugs is a useful procedure for identification of receptor mediation of in vivo drug effects. This assay can be enhanced when the stimulus effects of different doses of agonist are evaluated. In the present study, rats were trained to discriminate small or large doses of nicotine from saline, and interactions of these effects with nicotinic receptor antagonists and partial agonists were determined. The insurmountable nicotine antagonist mecamylamine blocked both the discriminative stimulus and response rate-reducing effects of nicotine, but was less effective against the large dose of nicotine. The α4β2*-selective,

competitive antagonist dihydro-beta-erythrodine (DHβE) antagonized the discriminative stimulus effects of both doses, but was less effective against the larger training dose of nicotine. Schild analyses of DHβE suggested that different nicotinic receptor populations may be mediating the stimulus effects of large and small doses of nicotine. This was supported by observations that the discriminative stimulus effects of the partial agonist cytisine were more like those of the large dose than of the small dose of nicotine, and that cytisine antagonized the effects of only the small nicotine dose. Varenicline produced nicotine-like effects in both training dose groups, but reduced the discriminative stimulus effects of intermediate doses of nicotine in the group trained to the small dose of nicotine. Overall, these results suggest that small doses of nicotine produce their stimulus effects via α4β2 nicotine receptors, whereas larger doses of nicotine recruit additional nicotine receptor subtypes, as revealed by drug discrimination assays in rats. Jutkiewicz EM, Brooks E, Kynaston A, Rice KC, Woods JH. J Pharmacol Exp Ther. 2011 Jul 5. [Epub ahead of print]

Probes for Narcotic Receptor Mediated Phenomena. 43. Synthesis of the Ortho-a and Para-a, and Improved Synthesis and Optical Resolution of the Ortho-b and Para-b Oxide-Bridged Phenylmorphans: Compounds with Moderate to Low Opioid-Receptor Affinity N-Phenethyl-substituted ortho-a and para-a oxide-bridged phenylmorphans have been obtained through an improved synthesis and their binding affinity examined at the various opioid receptors. Although the N-phenethyl substituent showed much greater affinity for μ- and κ-opioid receptors than their N-methyl relatives (e.g., K(i)=167nM and 171nM at μ- and κ-receptors vs >2800 and 7500nM for the N-methyl ortho-a oxide-bridged phenylmorphan), the a-isomers were not examined further because of their relatively low affinity. The N-phenethyl substituted ortho-b and para-b oxide-bridged phenylmorphans were also synthesized and their enantiomers were obtained using supercritical fluid chromatography. Of the four enantiomers, only the (+)-ortho-b isomer had moderate affinity for μ- and κ-receptors (K(i)=49 and 42nM, respectively, and it was found to also have moderate μ- and κ-opioid antagonist activity in the [(35)S]GTP-γ-S assay (K(e)=31 and 26nM). Li F, Folk JE, Cheng K, Kurimura M, Deck JA, Deschamps JR, Rothman RB, Dersch CM, Jacobson AE, Rice KC. Bioorg Med Chem. 2011 Jul 15; 19(14): 4330-4337. Epub 2011 May 24.

Stimulus Control by 5-Methoxy-N,N-Dimethyltryptamine in Wild-Type and CYP2D6-Humanized Mice In previous studies IRP scientists have observed that, in comparison with wild type mice, Tg-CYP2D6 mice have increased serum levels of bufotenine [5-hydroxy-N,N-dimethyltryptamine] following the administration of 5-MeO-DMT. Furthermore, following the injection of 5-MeO-DMT, harmaline was observed to increase serum levels of bufotenine and 5-MeO-DMT in both wild-type and Tg-CYP2D6 mice. In the present investigation, 5-MeO-DMT-induced stimulus control was established in wild-type and Tg-CYP2D6 mice. The two groups did not differ in their rate of acquisition of stimulus control. When tested with bufotenine, no 5-MeO-DMT-appropriate responding was observed. In contrast, the more lipid soluble analog of bufotenine, acetylbufotenine, was followed by an intermediate level of responding. The combination of harmaline with 5-MeO-DMT yielded a statistically significant increase in 5-MeO-DMT-appropriate responding in Tg-CYP2D6 mice; a comparable increase occurred in wild-type mice. In addition, it was noted that harmaline alone was followed by a significant degree of 5-MeO-DMT-appropriate responding in Tg-CYP2D6 mice. It is concluded that wild-type and Tg-CYPD2D6 mice do not differ in terms of acquisition of stimulus control by 5-MeO-

DMT or in their response to bufotenine and acetylbufotenine. In both groups of mice, harmaline was found to enhance the stimulus effects of 5-MeO-DMT. Winter JC, Amorosi DJ, Rice KC, Cheng K, Yu AM. Pharmacol Biochem Behav. 2011 Sep; 99(3): 311-315. Epub 2011 May 23.

Translational Pharmacology Research Section

Probes For Narcotic Receptor Mediated Phenomena. 43. Synthesis Of The Ortho-A and Para-A, and Improved Synthesis And Optical Resolution Of The Ortho-B And Para-B Oxide-Bridged Phenylmorphans: Compounds With Moderate To Low Opioid-Receptor Affinity N-Phenethyl-substituted ortho-a and para-a oxide-bridged phenylmorphans have been obtained through an improved synthesis and their binding affinity examined at the various opioid receptors. Although the N-phenethyl substituent showed much greater affinity for μ- and κ-opioid receptors than their N-methyl relatives (e.g., K(i)=167nM and 171nM at μ- and κ-receptors vs >2800 and 7500nM for the N-methyl ortho-a oxide-bridged phenylmorphan), the a-isomers were not examined further because of their relatively low affinity. The N-phenethyl substituted ortho-b and para-b oxide-bridged phenylmorphans were also synthesized and their enantiomers were obtained using supercritical fluid chromatography. Of the four enantiomers, only the (+)-ortho-b isomer had moderate affinity for μ- and κ-receptors (K(i)=49 and 42nM, respectively, and it was found to also have moderate μ- and κ-opioid antagonist activity in the [(35)S]GTP-γ-S assay (K(e)=31 and 26nM). Li F, Folk JE, Cheng K, Kurimura M, Deck JA, Deschamps JR, Rothman RB, Dersch CM, Jacobson AE, Rice KC. Bioorg Med Chem. 2011 Jul 15; 19(14): 4330-4337.

Probes For Narcotic Receptor Mediated Phenomena. Part 42: Synthesis And In Vitro Pharmacological Characterization Of The N-Methyl And N-Phenethyl Analogues Of The Racemic Ortho-C And Para-C Oxide-Bridged Phenylmorphans A new synthesis of N-methyl and N-phenethyl substituted ortho-c and para-c oxide-bridged phenylmorphans, using N-benzyl- rather than N-methyl-substituted intermediates, was used and the pharmacological properties of these compounds were determined. The N-phenethyl substituted ortho-c oxide-bridged phenylmorphan(rac-(3R,6aS,11aS)-2-phenethyl-2,3,4,5,6,11a-hexahydro-1H-3,6a-methanobenzofuro[2,3-c]azocin-10-ol (12)) was found to have the highest μ-opioid receptor affinity (K(i)=1.1 nM) of all of the a- through f-oxide-bridged phenylmorphans. Functional data ([^{35}S]GTP-γ-S) showed that the racemate 12 was more than three times more potent than naloxone as an μ-opioid antagonist. Bioorg Med Chem. 2011 Jun 1;19(11):3434-43. Epub 2011 Apr 22. Kim JH, Deschamps JR, Rothman RB, Dersch CM, Folk JE, Cheng K, Jacobson AE, Rice KC. Bioorg Med Chem. 2011 Jun 1; 19(11): 3434-3443.

Altered Gene Expression In Pulmonary Tissue Of Tryptophan Hydroxylase-1 Knockout Mice: Implications For Pulmonary Arterial Hypertension The use of fenfluramines can increase the risk of developing pulmonary arterial hypertension (PAH) in humans, but the mechanisms responsible are unresolved. A recent study reported that female mice lacking the gene for tryptophan hydroxylase-1 (Tph1(-/-) mice) were protected from PAH caused by chronic dexfenfluramine, suggesting a pivotal role for peripheral serotonin (5-HT) in the disease process. Here IRP scientists tested two alternative hypotheses which might explain the lack of dexfenfluramine-induced PAH in Tph1(-/-) mice. They postulated that: 1) Tph1(-/-) mice express lower levels of pulmonary 5-HT transporter (SERT) when compared to wild-type controls, and

2) Tph1(-/-) mice display adaptive changes in the expression of non-serotonergic pulmonary genes which are implicated in PAH. SERT was measured using radioligand binding methods, whereas gene expression was measured using microarrays followed by quantitative real time PCR (qRT-PCR). Contrary to the authors' first hypothesis, the number of pulmonary SERT sites was modestly up-regulated in female Tph1(-/-) mice. The expression of 51 distinct genes was significantly altered in the lungs of female Tph1(-/-) mice. Consistent with their second hypothesis, qRT-PCR confirmed that at least three genes implicated in the pathogenesis of PAH were markedly up-regulated: Has2, Hapln3 and Retlna. The finding that female Tph1(-/-) mice are protected from dexfenfluramine-induced PAH could be related to compensatory changes in pulmonary gene expression, in addition to reductions in peripheral 5-HT. These observations emphasize the intrinsic limitation of interpreting data from studies conducted in transgenic mice that are not fully characterized. Rothman RB, Cadet JL, Dersch CM, McCoy MT, Lehrmann E, Becker KG, Bader M, Alenina N, Baumann MH. PLoS One. 2011 Mar 25; 6(3): e17735**.**

Medications Discovery Research Branch

Medicinal Chemistry Section

Selective Dopamine D3 Receptor Ligands: Critical Role of the Carboxamide Linker for D3 Receptor Selectivity *N*-(3-fluoro-4-(4-(2,3-dichloro- or 2-methoxyphenyl)piperazine-1-yl)-butyl)-aryl carboxamides were prepared and evaluated for binding and function at dopamine D3 (D3R) and D2 receptors (D2R). In this series, IRP researchers discovered some of the most D3R selective compounds reported to date, (>1000-fold D3R-selective over D2R.) In addition, chimeric receptor studies further identified the second extracellular (E2) loop as an important contributor to D3R binding selectivity. Further, compounds lacking the carbonyl group in the amide linker were synthesized and while these amine-linked analogues bound with similar affinities to the amides at D2R, this modification dramatically reduced binding affinities at D3R by >100-fold resulting in compounds with significantly reduced D3R selectivity. This study supports a pivotal role for the D3R E2 loop and the carbonyl group in the 4-phenylpiperazine class of compounds and further reveals a point of separation between structure-activity relationships at D3R and D2R. Banala AK, Levy BA, Khatri SS, Mishra Y, Griffin SA, Luedtke RR, Newman AH. N-(3-Fluoro-4-(4-(2-methoxy or 2,3-dichlorophenyl) piperazine-1-yl)-butyl)-aryl carboxamides as Selective Dopamine D3 Receptor Ligands: Critical Role of the Carboxamide Linker for D3 Receptor Selectivity. J. Med. Chem. 2011; 54: 3581-3594.

Psychobiology Section

N-Substituted Benztropine Analogs: Selective Dopamine Transporter Ligands With A Fast Onset Of Action And Minimal Cocaine-Like Behavioral Effects Previous studies suggested that differences between the behavioral effects of cocaine and analogs of benztropine were related to the relatively slow onset of action of the latter compounds. Several N-substituted benztropine analogs with a relatively fast onset of effects were studied to assess whether a fast onset of effects would render the effects more similar to those of cocaine. Only one of the compounds increased locomotor activity, and the increases were modest compared to those of 10-20 mg/kg cocaine. In rats trained to discriminate 10 mg/kg cocaine from saline none of the compounds produced greater than 40% cocaine-like responding up to two hours after injection.

None of the compounds produced place-conditioning when examined up to 90 min after injection, indicating minimal abuse liability. The compounds had 5.6 to 30 nM affinities at the dopamine transporter (DAT), with uniformly lower affinities (from 490-4600 and 1420-7350 nM, respectively) at norepinephrine and serotonin transporters. Affinities at muscarinic M1 receptors were from 100- to 300-fold lower than DAT affinities, suggesting minimal contribution of those sites to the behavioral effects of the compounds. Affinities at histaminic H1 sites were from 11- to 43-fold lower than those for the DAT. The compounds also had affinity for sigma, 5-HT1 and 5-HT2 receptors that may have contributed to their behavioral effects. Together the results indicate that a slow onset of action is not a necessary condition for reduced cocaine-like effects of atypical DAT ligands, and suggests several mechanisms that may contribute to the reduced cocaine-like efficacy these compounds. Li SM., Kopajtic TA, O'Callaghan MJ, Agoston GE, Cao J, Newman AH, Katz JL Journal of Pharmacology and Experimental Therapeutics 2011; 336: 575-585.

Behavioral Economics Of Food Reinforcement And The Effects Of Prefeeding, Extinction, And Eticlopride In Dopamine D2 Receptor Mutant Mice Several studies have investigated the reinforcing effects of food in genetically-engineered mice lacking dopamine D2 receptors (DA D2Rs), however behavioral-economic analyses quantifying reinforcement have not been conducted. The role of DA D2Rs in food reinforcement was examined by comparing responding under various fixed-ratio (FR) schedules of reinforcement, and effects of extinction, satiation, and the DA D2R antagonist eticlopride, in mice with and without genetic deletions of the receptor. Response rates of DA D2R knockout (KO) mice were generally lower than those of littermate wild-type (WT) and heterozygous (HET) mice. The demand curve (consumption vs. FR value) for KO mice decreased more steeply than that of HET or WT mice, suggesting that reinforcing effectiveness is decreased with DA D2R deletion. Prefeeding decreased, whereas extinction increased overall response rates as a proportion of baseline, with no significant genotype differences. Both (+)- and (−)-eticlopride dose-dependently decreased responding in all genotypes with (−)-eticlopride more potent than (+)-eticlopride in all but KO mice. The enantiomers were equipotent in KO mice, and similar in potency to (+)-eticlopride in WT and HET mice. That prefeeding and extinction did not vary across genotypes indicates a lack of involvement of DA D2Rs in these processes. Differences between (-)-eticlopride effects and extinction indicate that DA D2R blockade does not mimic extinction. The maintenance of responding in KO mice indicates that the DA D2R is not necessary for reinforcement. However, the economic analysis indicates that the DA D2R contributes substantially to the effectiveness of food reinforcement. Soto PL, Grandy DK, Hursh SR, Katz JL. Psychopharmacology 2011; 215: 775–784.

Behavioral Neuroscience Branch

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. iRP scientists 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; 333: 353-357.

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. Differentiating the rapid actions of cocaine. Wise RA, Kiyatkin EA. Nat Rev Neurosci. 2011; 12: 479-484.

Dorsal As Well As Ventral Striatal Lesions Affect Levels Of Intravenous Cocaine And Morphine Self-Administration In Rats While the ventral striatum has long been implicated in the rewarding properties of psychomotor stimulants and opiates, little attention has been paid to the possible contribution of more dorsal regions of the striatum. IRP researchers have thus examined the effects of lesions in three different striatal subregions on cocaine and morphine self-administration. Different groups of rats were trained to self-administer intravenous cocaine (1.0mg/kg/infusion) or morphine (0.5mg/kg/infusion) first under fixed ratio (FR) and then under progressive ratio (PR) schedules of reinforcement. Upon completion of the training, independent groups received bilateral electrolytic or sham lesions of the dorsal portion of the caudate-putamen (dCPu), the ventral portion of the caudate-putamen (vCPu) or the more ventral nucleus accumbens (NAS). Following recovery, they were tested for self-administration of cocaine (0.25, 0.5, 1.0 and 1.5mg/kg/infusion) or morphine (0.125, 0.25, 0.5 and 0.75mg/kg/infusion) under the PR schedule. The PR responding for each drug was significantly reduced in a dose-dependent manner following lesions of dCPu, vCPu and NAS. While the relative effectiveness of these lesions is likely to be specific to the conditions of this experiment, NAS lesions reduced self-administration of each drug to a greater extent than did dCPu or vCPu lesions. Suto N, Wise RA, Vezina P. Dorsal as well as ventral striatal lesions affect levels of intravenous cocaine and morphine self-administration in rats. Neurosci Lett. 2011; 493: 29-32.

Preclinical Pharmacology Section

Blockade Of Nicotine Reward and Reinstatement By Activation Of Alpha-Type Peroxisome Proliferator-Activated Receptors Recent findings indicate that inhibitors of fatty acid amide hydrolase (FAAH) counteract the rewarding effects of nicotine in rats. Inhibition of FAAH increases levels of several endogenous substances in the brain, including the endocannabinoid anandamide and the noncannabinoid fatty acid ethanolamides oleoylethanolamide (OEA) and palmitoylethanolamide, which are ligands for alpha-type peroxisome proliferator-activated nuclear receptors (PPAR-α). Here, IRP scientists evaluated whether directly acting PPAR-α agonists can modulate reward-related effects of nicotine. The authors combined behavioral, neurochemical, and electrophysiological approaches to evaluate

effects of the PPAR-α agonists [[4-Chloro-6-[(2,3-dimethylphenyl)amino]-2-pyrimidinyl]thio] acetic acid (WY14643) and methyl oleoylethanolamide (methOEA; a long-lasting form of OEA) on 1) nicotine self-administration in rats and squirrel monkeys; 2) reinstatement of nicotine-seeking behavior in rats and monkeys; 3) nicotine discrimination in rats; 4) nicotine-induced electrophysiological activity of ventral tegmental area dopamine neurons in anesthetized rats; and 5) nicotine-induced elevation of dopamine levels in the nucleus accumbens shell of freely moving rats. The PPAR-α agonists dose-dependently decreased nicotine self-administration and nicotine-induced reinstatement in rats and monkeys but did not alter food- or cocaine-reinforced operant behavior or the interoceptive effects of nicotine. The PPAR-α agonists also dose-dependently decreased nicotine-induced excitation of dopamine neurons in the ventral tegmental area and nicotine-induced elevations of dopamine levels in the nucleus accumbens shell of rats. The ability of WY14643 and methOEA to counteract the behavioral, electrophysiological, and neurochemical effects of nicotine was reversed by the PPAR-α antagonist 1-[(4-Chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-a,a-dimethyl-5-(1-methylethyl)-1H-Indole-2-propanoic acid (MK886). These findings indicate that PPAR-α might provide a valuable new target for antismoking medications. Mascia P, Pistis M, Justinova Z, Panlilio LV, Luchicchi A, Lecca S, Scherma M, Fratta W, Fadda P, Barnes C, Redhi GH, Yasar S, Le Foll B, Tanda G, Piomelli D, Goldberg SR. Biological Psychiatry 2011; Apr;69: 633-641.

The Selective Anandamide Transport Inhibitor VDM11 Attenuates Reinstatement Of Nicotine Seeking Induced By Nicotine Associated Cues And Nicotine Priming, But Does Not Affect Nicotine-Intake The endocannabinoid system appears to play a pivotal role in mediating the rewarding and reinforcing effects of nicotine. Recent studies have shown that inhibition of fatty acid amide hydrolase (FAAH) enzyme attenuates reinstatement of nicotine seeking induced by nicotine priming and nicotine-associated cues. FAAH is responsible for the hydrolysis of the endogenous endocannabinoid anandamide, as well as other non cannabinoid ligands such as oleoylethanolamide (OEA) and palmitoylethanolamide (PEA). Since OEA/PEA can attenuate both nicotine-taking and nicotine-seeking behaviour, the specific role of anandamide remains unclear. Here, IRP scientists evaluated the impact of the selective anadamide uptake inhibitor, VDM11, which elevates anandamide levels without affecting levels of OEA/PEA, on nicotine-taking and nicotine-seeking behaviour. The authors used the nicotine intravenous self administration paradigm to assess the effect of intraperitoneal administration of 1,3 & 10 mg/kgVDM11 on nicotine taking using fixed and progressive ratio schedules of reinforcement as well as on reinstatement of nicotine seeking induced by nicotine priming and nicotine associated cues. VDM11 did not affect levels of responding for nicotine under fixed-ratio and progressive-ratio schedules of reinforcement. In contrast, VDM11 dose dependently attenuated reinstatement of nicotine-seeking behaviour induced by nicotine associated cues and nicotine priming. These results indicate that ligands elevating anandamide levels could have therapeutic value for preventing relapse to nicotine-seeking behavior and should be tested in human smokers trying to quit. Gamaleddin I, Guranda M, Goldberg SR, Lefoll B. Addiction Biology 2011; Apr; doi: 10.1111/j.1369-1600.2011.00314.x. (Epub ahead of print). PMID: 21521420.

The Endogenous Cannabinoid 2-Arachidonoylglycerol Is Intravenously Self-Administered By Squirrel Monkeys Two endogenous ligands for cannabinoid CB1 receptors, anandamide (N-arachidonoylethanolamine) and 2-arachidonoylglycerol (2-AG), have been identified and characterized. 2-AG is the most prevalent endogenous cannabinoid ligand in the brain, and electrophysiological studies suggest 2-AG, rather than anandamide, is the true natural ligand for cannabinoid receptors and the key endocannabinoid involved in retrograde signaling in the brain. Here, IRP researchers evaluated intravenously administered 2-AG for reinforcing effects in nonhuman primates. Squirrel monkeys that previously self-administered anandamide or nicotine under a fixed-ratio schedule with a 60 s timeout after each injection had their self-administration behavior extinguished by vehicle substitution and were then given the opportunity to self-administer 2-AG. Intravenous 2-AG was a very effective reinforcer of drug-taking behavior, maintaining higher numbers of self-administered injections per session and higher rates of responding than vehicle across a wide range of doses. To assess involvement of CB1 receptors in the reinforcing effects of 2-AG, we pretreated monkeys with the cannabinoid CB(1) receptor inverse agonist/antagonist rimonabant [N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide]. Rimonabant produced persistent blockade of 2-AG self-administration without affecting responding maintained by food under similar conditions. Thus, 2-AG was actively self-administered by monkeys with or without a history of cannabinoid self-administration, and the reinforcing effects of 2-AG were mediated by CB1 receptors. Self-administration of 2-AG by squirrel monkeys provides a valuable procedure for studying abuse liability of medications that interfere with 2-AG signaling within the brain and for investigating mechanisms involved in the reinforcing effects of endocannabinoids. Justinová Z, Yasar S, Redhi GH, Goldberg SR. Journal of Neuroscience. 2011; May; 31(19):7043-7048.

Combined Effects Of THC and Caffeine On Working Memory In Rats Cannabis and caffeine are two of the most widely used psychoactive substances. THC, the main psychoactive constituent of cannabis, is known to produce deficits in short term memory. Caffeine, a non-selective adenosine receptor antagonist, attenuates some kinds of memory deficits, but there have been few studies addressing the effects of caffeine and THC in combination. Here, IRP scientists evaluate the effects of these drugs using a rodent model of working memory. Rats were given THC (0, 1, and 3 mg/kg, i.p.) along with caffeine (0, 1, 3, and 10 mg/kg, i.p.), the selective adenosine A(1) -receptor antagonist CPT (0, 3, and 10 mg/kg), or the selective adenosine A(2A) -receptor antagonist SCH58261 (0 and 5 mg/kg), and tested with a delayed nonmatching-to-position procedure in which behavior during the delay is automatically recorded as a model of memory rehearsal. THC alone produced memory deficits at 3 mg/kg. The initial exposure to caffeine (10 mg/kg) disrupted the established pattern of rehearsal-like behavior, but tolerance developed rapidly to this effect. CPT and SCH58261 alone had no significant effects on rehearsal or memory. When a subthreshold dose of THC (1 mg/kg) was combined with caffeine (10 mg/kg) or CPT (10 mg/kg), memory performance was significantly impaired, even though performance of the rehearsal-like pattern was not significantly altered. Caffeine did not counteract memory deficits induced by THC, but in fact exacerbated them. These results are consistent with recent findings that adenosine A(1) receptors modulate cannabinoid signaling in the hippocampus. Panlilio LV, Ferré S, Yasar S, Thorndike EB, Schindler CW, Goldberg SR. British Journal of Pharmacology, 2011; June, doi: 10.1111/j.1476-5381.2011.01554.x (Epub ahead of print). PMID: 21699509.

PROGRAM ACTIVITIES

New NIDA PAs and RFAs

On June 16, 2011, NIDA issued a PA entitled **Epidemiology of Drug Abuse (R01) PA-11-230.** This Funding Opportunity Announcement (FOA) is intended to support research projects with the R01 mechanism to enhance our understanding of the nature, extent, distribution, etiology, and consequences of drug use, abuse, and addiction across individuals, families, communities, and diverse population groups. This Program strongly encourages applications that address multiple levels of causation, reflecting the breadth of epidemiology research, that are transdisciplinary in nature and apply novel methods that allow for the advancement of science (e.g., those that investigate interplay among genetic, environmental, and developmental factors, or those that examine how aspects of social environments affect health outcomes), as well as those that take advantage of the investments made by NIH and other funders by using existing data to inform our understanding of drug abuse epidemiology and etiology in a creative and cost efficient manner.

On June 16, 2011, NIDA issued a PA entitled **Epidemiology of Drug Abuse (R21) PA-11-231.** This Funding Opportunity Announcement (FOA) is intended to support research projects with the R21 mechanism to enhance our understanding of the nature, extent, distribution, etiology, and consequences of drug use, abuse, and addiction across individuals, families, communities, and diverse population groups. This Program strongly encourages applications that address multiple levels of causation, reflecting the breadth of epidemiology research, that are transdisciplinary in nature and apply novel methods that allow for the advancement of science (e.g., those that investigate interplay among genetic, environmental, and developmental factors, or those that examine how aspects of social environments affect health outcomes), as well as those that take advantage of the investments made by NIH and other funders by using existing data to inform our understanding of drug abuse epidemiology and etiology in a creative and cost efficient manner.

On June 16, 2011, NIDA issued a PA entitled **Epidemiology of Drug Abuse (R03) PA-11-232.** This Funding Opportunity Announcement (FOA) is intended to support research projects with the R03 mechanism to enhance our understanding of the nature, extent, distribution, etiology, and consequences of drug use, abuse, and addiction across individuals, families, communities, and diverse population groups. This Program strongly encourages applications that address multiple levels of causation, reflecting the breadth of epidemiology research, that are transdisciplinary in nature and apply novel methods that allow for the advancement of science (e.g., those that investigate interplay among genetic, environmental, and developmental factors, or those that examine how aspects of social environments affect health outcomes), as well as those that take advantage of the investments made by NIH and other funders by using existing data to inform our understanding of drug abuse epidemiology and etiology in a creative and cost efficient manner.

On July 29, 2011, NIDA issued a PA entitled **Pre-Application for the FY12 NIDA Avant-Garde Award Program for HIV/AIDS Research (X02) PAR-11-256.** The NIDA Avant-Garde Award Program for HIV/AIDS Research supports individual scientists of exceptional creativity who propose high-impact research that will open new areas of HIV/AIDS research and/or lead to new avenues for prevention and treatment of HIV/AIDS among drug abusers. The term "avant-garde" is used to describe highly innovative approaches that have the potential to be transformative. The proposed research should reflect approaches and ideas that are substantially different from those already being pursued by the investigator or others. The research proposed must be in an area described in the Trans – NIH Plan for HIV-Related Research http://www.oar.nih.gov/strategicplan/. Open date for this PA: October 30, 2011.

On July 29, 2011, NIDA issued an RFA entitled **FY12 NIDA Avant-Garde Award Program for HIV/AIDS Research (DP1) RFA-DA-12-011.** The NIDA Avant-Garde Award Program for HIV/AIDS Research supports individual scientists of exceptional creativity who propose high-impact research that will open new areas of HIV/AIDS research and/or lead to new avenues for prevention and treatment of HIV/AIDS among drug abusers. The term "avant-garde" is used to describe highly innovative approaches that have the potential to be transformative. The proposed research should reflect approaches and ideas that are substantially different from those already being pursued by the investigator or others. The research proposed must be in an area described in the Trans – NIH Plan for HIV-Related Research http://www.oar.nih.gov/strategicplan/

On July 29, 2011, NIDA issued a PA entitled **Pre-Application for the 2012 NIDA Translational Avant-Garde Award for Medication Development for the Treatment of Substance-Use Disorders (X02) PAR-11-269.** The purpose of this funding opportunity announcement (FOA) is to encourage pre-applications for the NIDA Translational Avant-Garde Award. The NIDA Translational Avant-Garde Award is designed to support dedicated and talented basic and/or clinical researchers with the vision, drive and expertise necessary to translate research discoveries into medications for the treatment of Substance-Use Disorders (SUDs). Through this FOA, NIDA is committed to making significant advances in the development of safe and efficacious medications for the treatment of SUDs stemming from tobacco, cannabis, cocaine, methamphetamine, heroin, or prescription opiate use or abuse. The 2012 Translational Avant-Garde Award competition will proceed in two phases. The X02 pre-application is the first phase. X02 pre-applications will be reviewed by external reviewers to identify the most outstanding applications. Those investigators whose submissions are judged to be the most outstanding will be notified of the opportunity to submit full DP1 grant applications under RFA-DA-12-010. All awards will be made under RFA-DA-12-010. No awards will be made under this announcement. Open date for this PA: September 20, 2011.

On July 29, 2011, NIDA issued an RFA entitled **2012 NIDA Translational Avant-Garde Award for Medication Development for the Treatment of Substance–Use Disorders (DP1) RFA-DA-12-010.** The NIDA Translational Avant-Garde Award is designed to support dedicated and talented basic and/or clinical researchers with the vision, drive and expertise necessary to translate research discoveries into medications for the treatment of Substance-Use Disorders (SUDs). Through this FOA, NIDA is committed to advancing the

development of safe and efficacious medications for the treatment of SUDs stemming from tobacco, cannabis, cocaine, methamphetamine, heroin, or prescription opiate use. Medications can be either small molecules or biologics. Biologics include vaccines and recombinant therapeutic proteins created by biological processes. Applications may focus on the treatment of substance use (i.e., abuse or dependence) disorders and specific clinical manifestations of these disorders such as withdrawal, craving, or relapse. Applications that focus on the development of new formulations of marketed medications that are available for other indications, or new combinations of existing medications that hold promise for the treatment of SUDs, are also within the scope of this RFA. The 2012 Translational Avant-Garde Award competition will proceed in two phases. The first phase is a pre-application phase in response to PAR-11-269. Pre-applications will be evaluated by a group of NIDA-assembled external reviewers. Those investigators whose submissions are judged to be the most outstanding will be notified in the summary statement of the X02 of the opportunity to submit full applications under this FOA, RFA-DA-12-010 (DP1). The 2012 Avant-Garde awardees will be selected from this group of applicants. Open Date for this RFA : January 21, 2011.

On May 20, 2011, NIDA issued an RFA entitled **Integration of Drug Abuse Prevention and Treatment in Primary Care Settings (R01) RFA-DA-12-008.** Efforts to prevent, detect, and treat drug abuse and addiction and its consequences can be improved by integrating existing evidence-based approaches into primary care settings. NIDA solicits translation and implementation research project applications to identify the most effective strategies and service delivery models for accomplishing this goal. Applicants should propose hypothesis-driven studies to achieve the integration of substance abuse prevention interventions and/or treatment services in public or private-sector settings where patients receive primary care services – including office-based practice settings, family practice, pediatric and adolescent medicine, obstetrics, general practice, and emergency departments. Letter of Intent Due Date for this RFA: September 30, 2011; Application Due Date: October 31, 2011.

On May 23, 2011, NIDA issued an RFA entitled **Remote Monitoring System for Detecting Cocaine Ingestion/Intoxication (R01) RFA-DA-12-007.** This Funding Opportunity Announcement (FOA) requests applications for funding to develop and validate a reliable remote real-time cocaine monitoring system for use by clinical trials researchers testing cocaine dependence treatments. Applications proposing validation of the monitoring system that do not include validation of the monitoring system in cocaine dependent subjects will not be considered responsive to this FOA. Systems will leverage developments in behavioral and/or biometric sensing, mobile and wireless technology (e.g., mHealth) and real time data analysis to detect cocaine use in vivo. Completed systems will include hardware, software, storage and analysis solutions to provide for secure encrypted storage on devices, secure encrypted transmission to a database, and secure researcher interfaces from which data may be aggregated to plot and display data demonstrating clinically meaningful changes in cocaine consumption patterns by individual participants. The system will include safeguards to ensure the behavioral and/or biological data gathered was sampled from the actual participant enrolled by including reliable identity verification measures and protection against tampering and hacking. It will also include “timestamp” information to ensure data sampled was sampled at the times and for the durations specified by researchers. All

hardware and software will be developed to ensure the system meets accepted standards for selectivity and specificity to identify cocaine. All hardware, software and databases will undergo sufficiently rigorous testing to be consistent with FDA medical device and software validation guidelines and the entire system will be Health Insurance Privacy and Portability Act (HIPPA) compliant. The purpose of this FOA is to notify qualified investigators of funding for research activities on the development and validation of a cocaine monitoring system which will provide for detection and measurement of cocaine ingestion in cocaine dependent people participating in clinical treatment trials. Ultimately the system may be used to monitor participants in clinical treatment or possibly judicial monitoring. Letter of Intent Receipt Date for this RFA: July 18, 2011; Application Due Date: August 18, 2011.

Additional PAs/RFAs Issued with Other NIH/HHS Components

On May 25, 2011, NIDA and NIAID issued a Program Announcement (PA) entitled **Mechanistic Studies of HIV-exposed Seronegative Individuals (HESN)(R21) PA-11-217.** The purpose of this initiative is to support mechanistic studies of individuals who are repeatedly exposed to HIV but remain seronegative (HESN), or demonstrate resistance to infection. The emphasis will be on demonstrating causality, and not simply association. Open date for this PA is August 7, 2011.

On May 25, 2011, NIDA and NIAID issued a Program Announcement (PA) entitled **Mechanistic Studies of HIV-exposed Seronegative Individuals (HESN)(R01) PA-11-218.** The purpose of this initiative is to support mechanistic studies of individuals who are repeatedly exposed to HIV but remain seronegative (HESN), or demonstrate resistance to infection. The emphasis will be on demonstrating causality, and not simply association. Open date for this PA is August 7, 2011.

On June 17, 2011, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Spatial Uncertainty: Data, Modeling, and Communication (R01) PA-11-238.** The purpose of this funding opportunity announcement (FOA) is to support innovative research that identifies sources of spatial uncertainty (i.e., inaccuracy or instability of spatial or geographic information) in public health data, incorporates the inaccuracy or instability into statistical methods, and develops novel tools to visualize the nature and consequences of spatial uncertainty.

On June 17, 2011, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Spatial Uncertainty: Data, Modeling, and Communication (R21) PA-11-239.** The purpose of this funding opportunity announcement (FOA) is to support innovative research that identifies sources of spatial uncertainty (i.e., inaccuracy or instability of spatial or geographic information) in public health data, incorporates the inaccuracy or instability into statistical methods, and develops novel tools to visualize the nature and consequences of spatial uncertainty.

On June 17, 2011, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Spatial Uncertainty: Data, Modeling, and Communication (R03) PA-11-240.** The purpose of this funding opportunity announcement (FOA) is to support innovative research that identifies sources of spatial uncertainty (i.e., inaccuracy or instability of spatial or geographic information) in public health data, incorporates the inaccuracy or instability into statistical methods, and develops novel tools to visualize the nature and consequences of spatial uncertainty.

On July 19, 2011, NIDA and NIAAA cosponsored a PA entitled **Gene-Environment Interplay in Substance Use Disorders (R01) PA-11-235.** The National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism seek to stimulate and expand research on the interplay of genetic and environmental factors in the genesis, course, and outcomes of substance and alcohol use disorders (SUDs). Previous work in genetic epidemiology and molecular genetics has established that SUDs are highly heritable, developmental disorders with important genetic substrates. Building on these findings, new studies using genetically informative approaches are needed to elucidate the complex interplay of genetic and environmental factors in developmental trajectories of SUDs and comorbid conditions, deepen and refine phenotypic definitions of SUDs, and meet the methodologic challenges of the field. Such studies hold great potential to promote understanding of the true contributions of both genetic and environmental factors to initiation, progression, comorbidity, adverse outcomes, and desistance of SUDs; to elucidate mechanisms of risk; and to enhance opportunities for translation to treatment, prevention, gene-finding and molecular studies.

On July 19, 2011, NIDA and NIAAA cosponsored a PA entitled **Gene-Environment Interplay in Substance Use Disorders (R21) PA-11-236.** The National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism seek to stimulate and expand research on the interplay of genetic and environmental factors in the genesis, course, and outcomes of substance and alcohol use disorders (SUDs). Previous work in genetic epidemiology and molecular genetics has established that SUDs are highly heritable, developmental disorders with important genetic substrates. Building on these findings, new studies using genetically informative approaches are needed to elucidate the complex interplay of genetic and environmental factors in developmental trajectories of SUDs and comorbid conditions, deepen and refine phenotypic definitions of SUDs, and meet the methodologic challenges of the field. Such studies hold great potential to promote understanding of the true contributions of both genetic and environmental factors to initiation, progression, comorbidity, adverse outcomes, and desistance of SUDs; to elucidate mechanisms of risk; and to enhance opportunities for translation to treatment, prevention, gene-finding and molecular studies.

On July 19, 2011, NIDA and NIAAA cosponsored a PA entitled **Gene-Environment Interplay in Substance Use Disorders (R03) PA-11-237.** The National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism seek to stimulate and expand research on the interplay of genetic and environmental factors in the genesis, course, and outcomes of substance and alcohol use disorders (SUDs). Previous work in genetic epidemiology and molecular genetics has established that SUDs are highly heritable,

developmental disorders with important genetic substrates. Building on these findings, new studies using genetically informative approaches are needed to elucidate the complex interplay of genetic and environmental factors in developmental trajectories of SUDs and comorbid conditions, deepen and refine phenotypic definitions of SUDs, and meet the methodologic challenges of the field. Such studies hold great potential to promote understanding of the true contributions of both genetic and environmental factors to initiation, progression, comorbidity, adverse outcomes, and desistance of SUDs; to elucidate mechanisms of risk; and to enhance opportunities for translation to treatment, prevention, gene-finding and molecular studies.

On August 24, 2011, NIDA, in collaboration with NIMH, NIAAA and NINDS, issued a PA entitled **Scalable Assays for Unbiased In Vitro Analysis of Neurobiological Function (R21/R33). PAR-11-319.** This Funding Opportunity Announcement (FOA) encourages research grant applications from institutions/organizations to develop novel, robust analytical platforms using in vitro assays to reveal changes in neuronal and/or glial function. The goal is to adapt state-of-the-art measures of basic cellular processes or molecular events that are key mediators of nervous system function with the intent to probe mechanisms and/or perturbations in an unbiased and efficient manner. The novel assay platforms would provide opportunities to measure neurobiological endpoints and build a pipeline to be used in the context of target identification and drug discovery. Open date for this PA: September 16, 2011.

On June 2, 2011, NIDA, NIMH and NIAID jointly issued an RFA entitled **Promoting Engagement in Care and Timely Antiretroviral Initiation Following HIV Diagnosis (R01) RFA-MH-12-060.** This Funding Opportunity Announcement (FOA) seeks research to improve medical care engagement and treatment adherence among HIV infected individuals in the first twelve months following HIV diagnosis, enrollment in HIV primary care, or initiation of antiretroviral treatment (ART). In targeting these periods, this FOA invites applications to address the need for efficacious interventions to promote rapid linkage to medical care following HIV diagnosis, enhance retention in early HIV primary care, and improve readiness to voluntarily initiate and adhere to antiretroviral medications. The overarching aims of this initiative are to develop and test interventions to reduce the time between HIV diagnosis and achievement of first undetectable viral load among patients for whom ART is indicated, as well as to reduce racial/ethnic disparities in HIV treatment outcomes. The initiative invites interventions targeting patients in care or those recently diagnosed but not yet in care, as well as interventions that target care providers and/or care systems.

On June 2, 2011, NIDA and NIMH jointly issued an RFA entitled **Promoting Engagement in Care and Timely Antiretroviral Initiation Following HIV Diagnosis (R34) RFA-MH-12-061.** This Funding Opportunity Announcement (FOA) seeks research to improve medical care engagement and treatment adherence among HIV infected individuals in the first twelve months following HIV diagnosis, enrollment in HIV primary care, or initiation of antiretroviral treatment (ART). In targeting these periods, this FOA invites applications to address the need for efficacious interventions to promote rapid linkage to medical care following HIV diagnosis, enhance retention in early HIV primary care, and improve

readiness to voluntarily initiate and adhere to antiretroviral medications. The overarching aims of this initiative are to develop and test interventions to reduce the time between HIV diagnosis and achievement of first undetectable viral load among patients for whom ART is indicated, as well as to reduce racial/ethnic disparities in HIV treatment outcomes. The initiative invites interventions targeting patients in care or those recently diagnosed but not yet in care, as well as interventions that target care providers and/or care systems. Letter of Intent Due Date for this RFA: August 9, 2011; Application Due Date: September 9, 2011.

On June 21, 2011, NIDA, in collaboration with a number of other NIH components, issued an RFA entitled **Advancing HIV Prevention through Transformative Behavioral and Social Science Research (R01) RFA-MH-12-080.** This Funding Opportunity Announcement (FOA) encourages applications that will advance generalizable knowledge about HIV prevention through transformative behavioral and social science research. An underlying assumption for this funding opportunity is that methods of and findings from social and behavioral studies can make essential contributions to research that utilizes biomedical modalities. In addition, biomedical perspectives are essential for the advancement of social and behavioral HIV research on HIV prevention. Therefore, this FOA invites studies that are comprehensive in the sense that the reciprocal influences of relevant variables, whether social, behavioral, or biomedical are included in study design and interpretation. This FOA is intended to address the goals of the National HIV AIDS Strategy, and therefore studies should address issues that are highly relevant to the domestic (i.e., United States) HIV problem. Letter of Intent Receipt Date for this RFA: December 6, 2011; Application Due Date: January 6, 2012.

On June 30, 2011, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **NIH Blueprint for Neuroscience Research Grand Challenge on the Transition from Acute to Chronic Neuropathic Pain (R01) RFA-DE-12-008.** This FOA is issued as an initiative of the NIH Blueprint for Neuroscience Research. The Neuroscience Blueprint is a collaborative framework through which 16 NIH Institutes, Centers and Offices jointly support neuroscience-related research, with the aim of accelerating discoveries and reducing the burden of nervous system disorders (for further information, see http://neuroscienceblueprint.nih.gov/).The goal of this FOA is to facilitate research collaborations between pain scientists and neuroscientists with expertise in neuroplasticity who have not previously studied the pain system in order to expand the understanding of biological mechanisms underlying the transition from acute to chronic pain. These collaborations should capture insights and expertise from neurobiological approaches. The purpose of this FOA is to encourage submission of multi-PI grant applications that propose highly collaborative, multidisciplinary research projects addressing the development of neuropathic pain conditions. The expected outcome of this FOA will be the formation of partnerships between pain researchers and non-pain neuroscientists with expertise in neuroplasticity to elucidate the maladaptive neuroplastic changes that occur during the transition from acute to chronic neuropathic pain. Letter of Intent Receipt Date for this RFA: September 4, 2011; Application Due Date: October 4, 2011.

On June 28, 2011, NIDA, in collaboration with several other NIH components, issued an RFA entitled **Specialized Centers of Research (SCOR) on Sex Differences (P50) RFA-OD-11-003.** The ORWH and participating organizations and institutes seek to expand the Specialized Centers of Interdisciplinary Research (SCOR) on Sex Differences. These centers will provide opportunities for interdisciplinary approaches to advancing studies in sex differences research. Each SCOR should develop a research agenda bridging basic and clinical research underlying a health issue that affects women. Letter of Intent Receipt Date for this RFA: September 4, 2011; Application Due Date: October 4, 2011.

On July 12, 2011, NIDA, in collaboration with the Fogarty International Center and the NCI, issued an RFA entitled **International Tobacco and Health Research and Capacity Building Program (R01) RFA-TW-11-003.** This Funding Opportunity Announcement (FOA) solicits collaborative research and capacity building projects that address the burden of tobacco use in low-and middle-income countries (LMIC) by (1) pursuing observational, intervention and policy research of LMIC relevance and (2) building capacity in epidemiological and behavioral research, prevention, treatment, communications, implementation, health services and policy research. The level of research and research training specialization in any given project will vary based on the strengths of the particular investigators and institutions and the specific need to build capacity to support locally relevant research on tobacco control interventions. The overall intent of the program is to encourage trans-disciplinary research to the international tobacco epidemic and to reduce the global burden of morbidity and mortality caused by tobacco use. Letter of Intent Receipt Date for this RFA: August 15, 2011; Application Due Date: September 15, 2011.

On July 18, 2011, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Sleep and Social Environment: Basic Biopsychosocial Processes (R21) RFA-HD-12-204.** This funding opportunity announcement (FOA) issued by the Basic Behavioral and Social Sciences Research Opportunity Network (OppNet), National Institutes of Health (NIH), solicits Research Project Grant (R21) applications from institutions/organizations that propose to investigate the reciprocal interactions of the processes of sleep and circadian regulation and function with behavioral and social environment processes. Sleep is a complex biological phenomenon that is essential to normal behavioral and social functioning, as well as optimal health. In spite of its vital nature, the mechanisms by which social environment factors affect sleep behavior patterns have not been studied systematically, especially within the context of individual vulnerabilities and resilience. There is a need for greater understanding of the dynamic relationships between behavioral and social environment factors on the one hand and the basic mechanisms of sleep-wake and circadian regulation and function on the other. This FOA is not intended to support research on or development of treatments or interventions for disorders of sleep or circadian rhythms. Letter of Intent Receipt Date for this RFA: August 30, 2011; Application Due Date: September 30, 2011.

On July 21, 2011, NIDA, in collaboration with a number of other NIH components, issued an RFA entitled **Building Interdisciplinary Research Careers in Women's Health (K12) RFA-OD-11-002.** The NIH Office of Research on Women's Health (ORWH) and its cosponsors invite institutional career development award applications for Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Career Development Programs, hereafter termed "Programs." Programs will support mentored research career development of junior faculty members, known as BIRCWH Scholars, who have recently completed clinical training or postdoctoral fellowships, and who will be engaged in interdisciplinary basic, translational, behavioral, clinical, and/or health services research relevant to women's health or sex differences research. Letter of Intent Receipt Date for this RFA: September 22, 2011; Application Due Date: October 21, 2011.

On August 23, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Human Heredity and Health in Africa (H3Africa): Collaborative Centers (U54) RFA-RM-11-008.** This NIH Funding Opportunity Announcement (FOA), supported by funds from the NIH Common Fund (Common Fund) and participating NIH Institute(s) and Center(s), invites applications from foreign Institutions in African countries who wish to develop the study of genomic/genetic/environmental contributors of human health and disease within Africa, using cutting edge research tools to understand health and diseases affecting African populations more completely and increase capacity for biomedical research, in terms of building infrastructure (including data and research resources), genomic proficiency of researchers and numbers of trainees. In partnership with the Wellcome Trust, the H3Africa initiative is focused on supporting these efforts as part of an effort to promote sustainable research in Africa that will promote health and combat disease.
Letter of Intent Receipt Date for this RFA: September 30, 2011; Application Due Date: December 2, 2011.

On August 23, 2011, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Human Health and Heredity in Africa (H3Africa): Research Grants (U01) RFA-RM-11-009.** This NIH Funding Opportunity Announcement (FOA), supported by funds from the NIH Common Fund (Common Fund) and participating NIH Institute(s) and Center(s), invites applications from foreign Institutions in African countries who wish to develop the study of genomic/genetic/environmental contributors of human health and disease within Africa, using cutting edge research tools to understand health and diseases affecting African populations more completely and increase capacity for biomedical research, in terms of building infrastructure (including data and research resources), genomic proficiency of researchers and numbers of trainees. In partnership with the Wellcome Trust, the H3Africa initiative is focused on supporting these efforts as part of an effort to promote sustainable research in Africa that will promote health and combat disease.
Letter of Intent Receipt Date for this RFA: November 2, 2011; Application Due Date: December 2, 2011.

Other 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, 25 ancillary studies have been supported by CTN and non-CTN funds. Over 13,000 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 0032, HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the U.S.
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 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 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

[1] The letter "A" is used to indicate an ancillary study attached to a clinical trial. The number after the "A" indicates the number of ancillary studies.

Increasing 12-Step Involvement. Recruitment was completed on September 30, 2009, yielding a total of 471 randomized participants across 10 sites. The study is now in the data analysis phase.
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 study is now in the data analysis phase.
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 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 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 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.

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 August 4, 2011, 169 participants have been randomized at nine sites.

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. As of August 4, 2011, 477 participants have been randomized at 10 sites.

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. As of August 4, 2011, 415 participants have been randomized at 12 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. As of August 4, 2011 783 participants have been randomized at all six participating sites.

The following protocols are in the implementation/development phase:

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 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 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.

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.

In addition to the primary CTN trials, there are currently five secondary analyses underway using data across several of the completed trials. Manuscripts have been published or being prepared by the investigators. Posters are being presented at scientific meetings for several of the trials.

There are also close to 50 funded studies supported by independent grants that use CTN studies as a platform.

NIDA's New and Competing Continuation Grants Awarded Since May 2011

Akbarali, Hamid I. – Virginia Commonwealth University
Opioid Tolerance and Bowel Dysfunction

Alessi, Sheila M. – University of Connecticut School of Medicine/DNT
IVR Technology to Mobilize Contingency Management for Smoking Cessation

Audrain-McGgovern, Janet E. – University of Pennsylvania
Smoking's Role in Positive Affect & Reward Regulation in Depression-Prone Smokers

Basbaum, Allan I. – University of California San Francisco
Multiple Opioid Receptors and the Control of Pain

Bates, Marsha E. – Rutgers The State University of New Jersey New Brunswick
Marijuana Cues, Arousal and the Central Autonomic Network

Benamar, Khalid – Temple University
Chemokine Antagonist, Opioid Medication and HIV gp120

Benner, Aprile Dawn – University of Texas at Austin
Social Demographics, Marginalization, and Adolescent Substance Use

Bergman, Jack – McLean Hospital (Belmont, MA)
Alpha Adrenergic Pharmacotherapy for Polydrug (Stimulant/Opiate) Abuse

Berke, Joshua D. – University of Michigan at Ann Arbor
Reinforcement Learning and Striatal Patch/Matrix Architecture

Blondell, Richard D. – State University of New York at Buffalo
Medical Strategies for the Management of Pain in the Addicted Patient

Bohn, Laura M. – Scripps Florida
Novel Probes of the Kappa Opioid Receptor: Chemistry, Pharmacology, and Biology

Booth, Robert Edwin – University of Colorado Denver
The Impact of Medical Marijuana in Metropolitan Denver

Borckardt, Jeffrey J. – Medical University of South Carolina
Opioid Abuse and Chronic Pain: An fMRI Model of Negative Reinforcement

Bradshaw, Heather Bryte – Indiana University Bloomington
Microglial Activation by N-arachidonoyl Glycine

Braverman, Julia – Cambridge Health Alliance
Matching Graphical Data Display to Regulatory Focus to Motivate Smoking Cessation

Bricker, Jonathan B. – Fred Hutchinson Cancer Research Center
Improving Smoking Cessation Quitlines: Pilot Study of Acceptance Therapy

Brunzell, Darlene H. – Virginia Commonwealth University
Nicotinic Contributions to Affective Behavior

Buck, Kari J. – Oregon Health and Science University
Genetic Vulnerability to Drugs of Abuse

Bumbarger, Brian – Pennsylvania State University-University Park
Integrated System for Prevention Implementation & Real-time Evaluation (INSPIRE)

Burrell, Brian Donald – University of South Dakota
Differential Modulation of Nociceptive versus Non-Nociceptive Synapses by Endocan

Carrano, Jennifer Lynn – Boston College
Cumulative Genetic and Environmental Predictors of Youth Substance Use

Cederbaum, Julie Anne – University of Southern California
Maternal Influences of Substance Use Among Urban Black Male Adolescents

Cicero, Theodore J. – Washington University
Paternal Opioid Exposure Imparts Biobehavioral Deficits in their Offspring

Clark, Karl J. – Mayo Clinic
Developing Zebra Fish Models to Reveal Interactions Between Stress and Addiction

Cleveland, Hobart Harrington – Pennsylvania State University-University Park
Implications of Genetic Variance for Substance Use Interventions in Adolescence

Colfax, Grant Nash – Public Health Foundation Enterprises
Naltrexone for the Treatment of Actively-Using Met-Dependent MSM with High-Risk B

Colon, Vivian – University of Puerto Rico Medical Sciences
Oral HPV Infection Among HIV+/HIV- Male Drug Users in Puerto Rico

Costello, Elizabeth J. – Duke University
Vulnerability to Drug Abuse: Pathways to Recovery

Cunningham, Chinazo – Albert Einstein College of Medicine Yeshiva University
Abstinence Reinforcing Contingency Management to Suppress HIV Viral Load

Daniulaityte, Raminta – Wright State University
A Study of Social Web Data on Buprenorphine Abuse Using Semantic Web Technology

Datta, Prasun K. – Temple University
Role of Epigenetics in Glutamate Transporter EAAT2 Regulation in NeuroAIDS

Daughters, Stacey B. – University of Maryland College Park Campus
Identification of Neural Indices of Distress Tolerance Using fMRI

De La Garza, Richard – Baylor College of Medicine
Exercise as a Behavioral Treatment for Cocaine Dependence

Deth, Richard C. – Northeastern University
Effect of Drugs of Abuse on Neuronal Redox and Methylation Status

De Wit, Harriet – University of Chicago
The Genetic Basis of Impulsive Behavior in Humans

D'Souza, Deepak Cyril – Yale University
Imaging Brain Cannabinoid Receptors in Cannabis Dependence, Withdrawal and Abstinence

Du, Jiang – Shanghai Mental Health Center
Reducing HCV/HIV Risk Behaviors among Injection Drug Users in China

Duerr, Ann C. – Fred Hutchinson Cancer Research Center
HIV Testing and Treatment to Prevent Onward HIV Transmission among High-risk MSM

El-Sadr, Wafaa M. – Columbia University Health Sciences
STAR-Seek, Test and Retain. Linkages for Black HIV+, Substance Using MSM

Engert, Florian – Harvard University
Monitoring Neural Activity in Freely Behaving Zebrafish Larvae with Bioluminescence

Evins, A. Eden – Massachusetts General Hospital
Enhancing Self-Control of Cigarette Craving with Real-Time fMRI

Finch, Andrew J. – Vanderbilt University
Effectiveness of Recovery High Schools as Continuing Care

Forster, Gina L. – University of South Dakota
Neural Sensitivity to Stress During Drug Withdrawal

Fox, Howard S. – University of Nebraska Medical Center
Methamphetamine and HIV: Defective Immunity with CD8 T Cell Dysfunction

Friedman, Samuel R. – National Development and Research Institutes
Developing Measures to Study how Structural Iinterventions May Affect HIV Risk

Fu, Eugene S. – University of Miami School of Medicine
Carbonic Anhydrase 8 and Susceptibility to the Acute to Chronic Pain Transition

Garfein, Richard S. – University of California San Diego
Drug Tourism to Mexico: Impact of Mexico's New Drug Law on HIV-HCV-TB in US IDUs

Gentry, W Brooks – University of Arkansas Medical Sciences Little Rock
First Human Studies of a Chimeric Anti-Methamphetamine Monoclonal Antibody

Gilbert, Louisa -- Columbia University New York Morningside
A Computerized Service Tool to Address Partner Abuse among Women in Drug Court

Grasing, Kenneth W. – Midwest Biomedical Research Foundation
Tacrine Effects on Cocaine Self-Administration and Pharmacokinetic Measures

Guthrie, Sally K. – University of Michigan at Ann Arbor
Exploring Tobacco Effects on Attention in Schizophrenics and Controls Using fMRI

Gwadz, Marya – New York University
Peer-Driven Intervention to Seek, Test & Treat Heterosexuals at High Risk for HIV

Heil, Sarah H. – University of Vermont and State Agriculture College
Improving Effective Contraceptive Use Among Opioid-Maintained Women

Hendricks, Peter S. – University of Alabama at Birmingham
Withdrawal Exposure with Withdrawal Regulation Training for Smoking Cessation

Hogg, Robert Stephen – Simon Fraser University
HAART Optimism, Drug Use and Risky Sexual Behavior among MSM in British Columbia

Hogue, Aaron – National Center on Addiction and Substance Abuse
Family-Based Protocol for Medication Integration in Treatment of Comorbid ASU/ADH

Hops, Hyman – Oregon Research Institute
Early Intervention for Minors in Possession of Alcohol/Drugs: A Feasibility Study

Houghten, Richard A. – Torrey Pines Institute for Molecular Studies
High Throughput In Vivo Screening: Translational Generation of Novel Analgesics

Jansson, Lauren M. – Johns Hopkins University
Fetal and Infant Neurobehavioral Effects of maternal Buprenorphine Treatment

Johnson, Matthew Wayne – Johns Hopkins University
Pharmacotherapy for Cocaine Dependence: d-cycloserine with Contingency Management

Kaczocha, Martin – State University New York Stony Brook
FABPs Mediate Activation of PPAR Alpha Receptors by N-Acylethanolamines

Kahn, James O. – University of California San Francisco
Seek, Test, Treat and Retain Strategies Leveraging Mobile Health Technologies

Koller, Beverly H. – University of North Carolina Chapel Hill
Models for Functional Evaluation of CHRN Polymorphisms

Kong, Jian – Massachusetts General Hospital
A PET & fMRI Study on Opioid Conditioning (placebo) Effects

Kumar, Santosh – University of Missouri Kansas City
Tobacco/Nicotine, Cytochrome P450, and HIV-1

Kurth, Ann E. – New York University
Test and Linkage to Care (TLC_IDU) Kenya

Li, Guigen – Texas Tech University
GAP Chemistry Approaches to Chiral Amino Acids, Peptides and Peptidomimetics

Lu, Bo – Ohio State University
Causal Inference in Repeated Observational Studies

Mackesy-Amiti, **Mary E.** – University of Illinois at Chicago
Patterns of Changing Risk Behavior in the CIDUS-3 Drug Users Intervention Trial

Magura, Stephen – Western Michigan University
Critical Review of Evidence-Based Program Repositories for Behavioral Health Treatment

Marinelli, Michela – Rosalind Franklin University of Medicine and Science
Afferents modulating VTA activity and their plasticity after self-administration

Matell, Matthew S. – Villanova University
Synthesis of Incongruent Temporal Information

Mccarty, Dennis – Oregon Health and Science University
Integrating Addiction Treatment and Medical Care in a Commercial Health Plan

McCloskey, Michael S. – National Opinion Research Center
Prevention of Substance Abuse and Problem Behaviors in High-Risk Adolescents

McCollister, Kathryn E. – University of Miami School of Medicine
Economic Evaluation of Recovery Management Checkups for Women Offenders (RMC-WO)

Mcgaugh, Janette D. – University of Arkansas Medical Sciences Little Rock
Clinical Efficacy of Atomoxetine for Methamphetamine Dependence

Meara, Ellen R. – Dartmouth College
Depression Treatment and Substance Abuse

Mendelson, Tamar – Johns Hopkins University
School-Based Mindfulness Intervention to Prevent Substance Use Among Urban Youth

Metsch, Lisa R. – University of Miami School of Medicine
Project RETAIN: Providing Integrated Care for HIV-Infected Crack Cocaine Users

Miczek, Klaus A. – Tufts University Medford
Neuropeptides, Social Stress and Drugs of Abuse

Miesenboeck, Gero – University of Oxford
Neural Circuits Underlying Adaptive Behavior and Addiction

Miller, Richard J. – Northwestern University
Chemokine Receptor Function in the Nervous System

Mitchell, John – Duke University
Ecological Momentary Assessment of Ad Lib Smoking in ADHD Smokers

Mong, Jessica – University of Maryland Baltimore
Methamphetamine Induced Neuroplasticity and Female Reproductive Health

Moorman, David E. – Medical University of South Carolina
Role of Prefrontal Networks in Addiction Endophenotypes

Mumford, Elizabeth A. – National Opinion Research Center
Social Ecology of Maternal Substance Use

Nosyk, Bohdan – University of California Los Angeles
A Comparison of Methadone Treatment Systems in California and British Columbia

O'Cleirigh, Conall Michael – Massachusetts General Hospital
Integrated Treatment for Smoking Cessation & Anxiety in People with HIV

Padilla, Mark B. – University of Michigan at Ann Arbor
Injection Practices and HIV Risk Behavior among Transgendered Persons in Puerto Rico

Page, Kimberly – University of California San Francisco
International Collaborative of Prospective Studies of HIV and Hepatitis in IDU

Paladini, Carlos Antonio – University of Texas San Antonio
The Synaptic Origin of Reward Prediction Error Signal in Dopaminergic Neurons

Palmer, Abraham A. – University of Chicago
Systems Genetic Analysis of Methamphetamine's Motivational Effects in a Mouse AIL

Pan, Yingtian – State University New York Stony Brook
Ultrahigh-Resolution Optical Tomography of Cocaine-Induced Neurovascular Toxicity

Paudel, Kalpana – University of Kentucky
Transdermal delivery of 2-Arachidonoyl glycerol (2-AG) for the Treatment of Arthritis

Pechmann, Cornelia – University of California Irvine
Twitter-enabled Mobile Messaging for Smoking Relapse Prevention

Perkins, Kenneth Alan – University of Pittsburgh
Reinforcement-Enhancing Effects of Nicotine

Portoghese, Philip S. – University of Minnesota Twin Cities
Ligands that Target Opioid-Chemokine and Opioid-mGlu5 Heteromers

Read, Stephen J. – University of Southern California
Neural Mechanisms of Risky Sexual Decision-Making in METH and non-METH Using MSM

Roberts, David Charles Stephen – Wake Forest University Health Sciences
Animal Models of Cocaine Addiction

Robertson, Angela M. – University of California San Diego
Concurrent Partnerships Among High-Risk Couples in the U.S.-Mexico Border Region

Roesch, Matthew R. – University of Maryland College Park Campus
Impact of Cocaine on the Actor/Critic Circuit

Ruiz, Monica S. – George Washington University
Impact Evaluation of a Policy Intervention for HIV Prevention in Washington, DC

Sanders-Phillips, Kathy – Howard University
Violence, Drug Use & AIDS in South African Youth: A U.S./South Africa Research Co

Sevak, Rajkumar Jyotishchandra – University of California Los Angeles
Human Methamphetamine Self-Administration in a Progressive-Ratio Paradigm

Shoptaw, Steven – University of California Los Angeles
Varenicline for Methamphetamine Dependence

Smith, Philip H. – State University of New York at Buffalo
Intimate Partner Violence in Newly Married Couples: The Role of Illicit Drug Use

Sorkin, Alexander D. – University of Pittsburgh at Pittsburgh
Dopamine Transporter Regulation by Endocytosis

Sullivan, Maria A. – New York State Psychiatric Institute
Improved Strategies for Outpatient Opioid Detoxification

Sullivan, Tami P. – Yale University
Racial/ethnic Differences in Daily Dynamics of PTSD, Sexual-Risk & Substance Use

Sunahara, Roger K. – University of Michigan at Ann Arbor
Crystallization and Structure Determination of the Mu-Opioid Receptor

Tangney, June P. – George Mason University
Jail-Based Treatment to Reduce Substance Abuse, Recidivism and Risky Behavior

Tiburcio, Nelson Jose – National Development & Research Institutes
The Process of Long-Term Abstinence From Opioid Use Among HIV+ Respondents

Tucker, Joan S. – Rand Corporation
Family Mediation Program for At-Risk Youth

Tull, Matthew T. – University of Mississippi Medical Center
Risk-Taking Following Trauma Cue Exposure in Substance Users with PTSD

Valdez, Avelardo – University of Houston
Emergence and Diffusion of Crack and Related Health Risk Behaviors in Mexico City

Vann, Robert E. – Virginia Commonwealth University
Endocannabinoid Modulation of Pain-Depre

Van Voorhees, Elizabeth – Duke University
Sensitivity to Smoking Reinforcement in Women: Menstrual Cycle Effects

Vatakis, Dimitrios N. – University of California Los Angeles
Effects of Cocaine on HIV Infection of Quiescent T Cells

Von Zastrow, Mark E. – University of California San Francisco
Mechanisms Regulating Endocytosis of Opioid Receptors

Wakeland, Wayne William – Portland State University
The System Dynamics of Pharmaceutical Opioid Misuse

Wechsberg, Wendee M. – Research Triangle Institute
Combination Prevention for Vulnerable Women in South Africa.

West, Mark O. – Rutgers the State University of New Jersey New Brunswick
Changes in Firing in Striatal Circuits During Chronic Cocaine Self-Administration

White, Shane Newport – University of California Los Angeles
Stress History is Recorded in Tooth Enamel

White, Tara L. – Brown University
Imaging Individual Differences in Methamphetamine Effects

Whiteaker, Paul – St. Joseph's Hospital and Medical Center.
HTS Assay Development for alpha6/3beta2beta3 Subtype Nicotinic Receptors

Wiley, Jenny L. – Research Triangle Institute
Behavioral Pharmacology of Synthetic Cannabinoids

Wood, Marcelo Andres – University of California Irvine
Histone Deacetylases: Regulators of Cocaine Reward and Targets for Therapeutics

Xiao, Yingxian – Georgetown University
High Throughput Screening for nAChRs: Cell Lines and Assay Development

Yao, Wei-Dong – Harvard University (Medical School)
Dopaminergic Enabling of Synaptic Plasticity in Prefrontal Circuits

Yu, Angela Jie – University of California San Diego
A Neurocognitive and Computational Study of Inhibitory Control in Substance Use

Zheng, Guangrong – University of Kentucky
Development of M5 Selective Muscarinic Antagonists

Zjawiony, Jordan K. – University of Mississippi
Psychopharmacology of Plants and their Metabolites used as Marijuana Substitutes

Zlotnick, Caron – Women and Infants Hospital – Rhode Island
Sober Network IPT for Perinatal Women with Comorbid Substance Use and Depression

Zuo, Yantao – Duke University
Effects of Cigarette Mentholation on Brain Nicotine Accumulation During Smoking

EXTRAMURAL POLICY AND REVIEW ACTIVITIES

Receipt, Referral, and Review

NIDA received 1,838 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 1,151 applications. OEA arranged and managed 19 grant review meetings in which 323 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 21 contract proposal and concept review meetings. NIDA has one standing chartered committee, NIDA-K, which reviews Career Development applications and Institutional Training Grant applications (T32). There were also 18 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)
- Mechanism for Time-Sensitive Drug Abuse Research (R01)
- Conference Grants (R13)
- Multi-site Clinical Trials (R01)
- Loan Repayment Program
- Requests for Applications (RFAs)

OEA managed the following RFA reviews:

DA11-002	2011 Avant-Garde Award Program for HIV/AIDS Research (DP1)
DA11-008	Medical Marijuana Policy Research: Exploring Trends and Impacts (R01)
DA11-009	2011 NIDA Translational Avant-Garde Award for Medication Development for Diseases of Addiction (DP1)
DA11-012	Exploring Human Induced Pluripotent Stem Cells for Substance Abuse Research (R21)
DA11-013	Blueprint for Neuroscience Research Education Award (R25)
DA11-014	Predictive Animal Models for Smoking Cessation Medications (U54)
DA11-015	Medication Initiative for Tobacco Dependence (MITD): A New Product Development Partnership (PDP)(UH2/UH3)
DA12-001	New Molecular Entities to Treat Substance Use Disorders (R01)

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

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

N43DA-12-2227	Confirming Compliance with Experimental Pharmacotherapy Treatment of Drug Abuse
N43DA-12-5569	Drugged Driving: Future Research Directions

N43DA-12-8906	Development of a Solid Dosage Form for Fenobam
N43DA-12-2228	Feedback-regulated Naloxone Delivery Device to Prevent Opiate Overdose Deaths
N43DA-12-7782	Highly Effective Methods for Systemic In Vivo Targeted Delivery of shRNAi to the Brain for Treatment of Substance Use Disorders
N43DA-12-8907	Feasibility of Development of RNAi-based Therapeutics for Treatment of HIV and HCV Infections in Drug Abusing Populations
N43DA-12-4415	Recovery Warrior: Behavioral Activation Video Game for Substance Abuse
N43DA-12-7783	Smokescreen: Genetic Screening Tool for Tobacco Dependence and Treatment Approaches

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

NO1DA-11-1144	NIDA's Science Meetings Logistical Support
NO1DA-11-8899	Development and Manufacture of Pharmaceutical Products
NO1DA-11-1207	Research Support Services for NIDA AIDS Research Program
NO1DA-11-5565	MTA Data Coordination and Quality Control
NO1DA-11-7777	Synthesis and Distribution of Opioid and Related Peptides
NO1DA-11-5568	Family Smoking Prevention and Tobacco Control Act National Longitudinal Study
NO1DA-11-8901	Technical and Conference Support for DPMC
NO1DA-11-1147	Physician Outreach and Education: Development of E-Tools, E-Learning, and CME Course on Prescription Drug Abuse and Treatment
N01DA-11-1145	NIDA Blending Research and Practice

SBIR Phase II Contract Reviews

N44DA-11-2219	Research Works: Enrollment Workflow
N44DA-11-5558	GISTE: The Geospatial Information Systems Tool
N44DA-11-5560	SecuRX: Preventing Prescription Drug Diversion
N44DA-11-5569	State & Local Epidemiology Planning & Information Development

Certificates of Confidentiality

Between March 19, 2011 and August 6, 2011 OEA processed 95 Certificate of Confidentiality applications, including 22 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 about revised applications, presented by Chair of the Center for Scientific Review (CSR) Scientific Oversight Committee.

CONGRESSIONAL AFFAIRS SECTION
(Prepared September 1, 2011)

APPROPRIATIONS/BUDGET

After significant negotiations, the Budget Control Act of 2011 was passed by the Congress and signed by the President in early August. For those interested in details, a helpful section-by-section analysis is provided by the House at http://rules.house.gov/Media/file/PDF_112_1/legislativetext/731%20CBAsbs%20v2.pdf. Separately, we await further Congressional action on the proposed HHS and NIH budgets for FY 2012.

CONGRESSIONAL BRIEFINGS OF INTEREST

APA Showcase – Research to Improve the Lives of Veterans and Returning Military -- On May 3, the American Psychiatric Association sponsored a congressional briefing showcasing research developments in substance abuse and mental health. NIDA's Dr. Wilson Compton gave a very well received presentation on substance use disorders among returning military populations, and what we know about addressing those issues.

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).

H.R. 1425 – On May 11, 2011, the House Committee on Small Business marked up and reported out H.R. 1425 as amended, the Creating Jobs Through Small Business Innovation Act of 2011. Among the many provisions, the bill would reauthorize the SBIR/STTR programs for 3 more years. The bill would maintain the current set-aside requirements, but allow up to 45 percent of the SBIR/STTR monies to fund venture capital backed small businesses. Several amendments passed that are relevant to NIH. The amendments include: language requiring pilot programs to be carried out no longer than 3 years after enactment of H.R. 1425; an amendment addressing the "mill runner" problem that will prohibit a small business from receiving an award if that company receives an aggregate amount of awards that exceeds 50 percent of the aggregate amount received by the median State in the prior fiscal year; an amendment requiring agencies to shorten the amount of time between award and funding (provision contains no enforcement mechanism); an amendment struck the "shall" language and inserted "may" language for Section 207 "Phase 0 Proof of Concept Partnership Pilot Program at NIH" (Lipinski Amendment); and an amendment allowing agencies to develop a "fast track" program to eliminate the delay

between the Phase I award and Phase II. The committee passed H.R. 1425 as amended by voice vote. See also S. 493

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 and Judiciary Committees.

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. See also S. 507.

H.R. 1983 – On May 25, 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.

H.R. 2119 – On June 3, 2011, Representative Mary Bono Mack (R-CA) introduced the Ryan Creedon Act of 2011, to amend the Controlled Substance 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 and House Energy and Commerce Committee.

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.

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.

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.

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. See also S. 1447.

S. 493 -- On March 4, 2011, Senator Mary Landrieu (D-LA) introduced S. 493, the SBIR/STTR Reauthorization Act of 2011. Similar to the compromise bill (S. 4053/S. 1233) passed by the Senate at the close of the 111th Congress, S. 493 would reauthorize the Small Business Innovation Research (SBIR) and Small Business Technology Transfer Programs (STTR) for 8 years; increase the SBIR set aside to 3.5 percent over 10 years and increase the STTR set aside to 0.6 percent over six years; and allow small business concerns majority-owned and controlled by venture capital firms to be eligible for up to 25 percent of the SBIR funds. In addition, the bill would increase SBIR/STTR awards to $150,000 for Phase I and $1 million for Phase II awards; limit award increases to 50 percent according to the guidelines for Phase I and Phase II awards; and require that federal agencies shorten the time span for final decisions to not more than 90 days after the date a solicitation closes.

On March 9, 2011, the Senate Committee on Small Business and Entrepreneurship marked up and reported out an amended version of the bill. While most of the amendments were minor, one amendment is of particular interest to NIH. Section 108, Participation by Firms with Substantial Investment From Multiple Venture Capital Operating Companies in a Portion of the SBIR Program, is amended to require that for 'covered small business concerns' and the award was not made within 9 months of the application date, a federal agency shall transfer an amount equal to any amount awarded to the company from non-SBIR and non-STTR funds of the federal agency not later than 90 days after the date on which the federal agency makes the award. The term 'covered small business concerns' is defined as companies that were not majority-owned venture capital companies at the date of their SBIR application, but whose status changed to majority-owned venture capital companies by the time of award). The bill has attracted a very large volume of amendments, and its path on the floor of the Senate is unclear at this time.

> **UPDATE:** S. 493 was abandoned after being brought up on the Senate floor (it attracted a large volume of non-germane amendments) after a cloture motion was unsuccessful. See H.R. 1425

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 HR 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. See also H.R. 2689.

INTERNATIONAL ACTIVITIES

Binational Agreements

NIDA, Italian Officials Agree to Cooperate on Drug Abuse Research and Training

NIDA Director Nora Volkow, M.D., and Giovanni Serpelloni, M.D., Department for Anti-drug Policies (DAP), Presidency of the Council of Ministers, Italy, agreed July 25, 2011, to foster the conduct of mutually beneficial research and research training to improve the diagnoses and treatment of drug abuse and addiction. The Memorandum of Understanding cited three areas of particular interest for the two agencies, including research to: develop new treatment medications; improve early detection, screening, referral to treatment and brief interventions (SBIRT), particularly among adolescents and young adults; and to increase the number of HIV-infected drug users who seek treatment for HIV infection and addiction (the Seek, Test, Treat, and Retain strategy). The agreement establishes a binational working group to coordinate future collaborative activities. Priorities include partnerships between the NIDA Clinical Trials Network and DAP, as well as cross-national training activities such as: short-term visits by Italian scientists to NIDA-supported research labs and visits by U.S. scientists to Italy; participation by U.S. scientists in Italian training programs such as the National School on Addiction at the Scuola Superiore di Formazione della Pubblica Amministrazione in Rome; and improving medical education following the NIDA Centers of Excellence for Physician Education model. NIDA staff serving on the binational working committee include: Dr. Volkow; Betty Tai, Ph.D., CTN; and Antonello Bonci, M.D., IRP. The NIDA-DAP agreement follows a July 11, 2011, agreement between the White House Office of National Drug Control Policy (ONDCP) and the Italian Ministry for Family, Drugs, and Civil Service to provide a foundation for increased collaboration, cooperation, and partnership between the two nations in the fields of addiction research, clinical best practices, and drug policies. The ONDCP agreement specifically called for increased cooperation between U.S. and Italian public health research institutes and clinical centers on prevention, early intervention, treatment, rehabilitation, recovery, and reintegration of drug abusers.

NIDA and Mexico Launch Prevention Research Fellowship

NIDA and the Mexican National Institute of Psychiatry Ramón de la Fuente Muñiz (NIP), along with the Mexican National Commission Against Addictions (CONADIC) and the Society for Prevention Research, have established the United States –Mexico Drug Abuse Prevention Research Fellowship. The fellowship is part of the ongoing collaborative efforts between the United States and Mexico to reduce initiation and use of drugs, the progression from abuse to dependence, and drug abuse-related HIV transmission. NIDA Director Nora Volkow, M.D., NIP Director María Elena Medina-Mora Icaza, Ph.D., and CONADIC Commissioner Carlos Tena Tamayo, M.D., signed the memorandum of understanding creating the fellowship on June 23, 2011, during the 9th Binational U.S. – Mexico Demand Reduction Conference in Mexico. Modeled after the successful NIDA INVEST Drug AbuseResearch Fellowship, the Prevention Research Fellowship will provide Mexican postdoctoral scientists with 12 months of research training with a NIDA grantee in the United States, along with professional development and grant writing activities. Fellows may investigate any area of drug abuse prevention research, such as prevention intervention research, prevention services research, prevention methodology, or drug abuse prevention as

HIV/AIDS prevention. NIDA IP will administer the Prevention Research Fellowship with assistance from DESPR. More information and application details are available through the NIDA IP Web site, www.international.drugabuse.gov.

Spanish Drug Abuse Agency Supports Research Visits to NIDA Grantees

As part of the ongoing binational collaboration on drug abuse research between NIDA and the Spanish Plan Nacional sobre Drogas (PNSD), Spanish researchers may apply for funding from PNSD to support brief research visits with NIDA-funded investigators. The Spanish researchers will learn new research methods, promote awareness of Spain's academic and scientific research environment, advance collaboration between Spanish and U.S. institutions and researchers, and increase the qualifications and visibility of Spanish scientists as potential research partners. DPMCDA Acting Deputy Director Ivan Montoya, M.D., M.P.H., is the NIDA liaison to PNSD for this project, with support from NIDA IP Director Steven W. Gust, Ph.D. NIDA and PNSD first signed agreements to cooperate on drug abuse and addiction research in 1997.

NIDA International Forum

NIDA International Forum Focuses on Collaboration Among Research Organizations and Binational Scientific Teams

"Find good partners, start small, and take advantage of every research training and funding opportunity available." That was the theme of presenters at the 16th NIDA International Forum, which featured reports on U.S. initiatives to improve evidence-based drug treatment, research training, and policy implementation around the world. IP Director Steven W. Gust, Ph.D., chaired the meeting, which was held June 17–20, 2011, in Hollywood, Florida, as a satellite to the Annual Scientific Meeting of the College on Problems of Drug Dependence (CPDD). More than 255 participants from 51 countries participated in the plenary session, workshops, and networking activities. A joint CPDD/NIDA International Forum poster session featured presentations by 146 U.S. and international researchers. Plenary Session speakers included NIDA Deputy Director David Shurtleff, Ph.D., as well as James E. Herrington, Ph.D., M.P.H, Fogarty International Center, and Richard H. Needle, Ph.D., M.P.H., U.S. President's Emergency Plan for AIDS Relief (PEPFAR). A panel of NIDA grantees organized by DPMCDA Acting Deputy Director Ivan Montoya, M.D., M.P.H., described recent progress in developing pharmacotherapies to treat addiction. Another panel of NIDA grantees offered advice on building international research collaborations that could compete for funding, and a group of former IP fellows reviewed the challenges of collecting and publishing reliable youth risk behavior data in Muslim-majority countries. NIDA staff chaired sessions where international scientists presented research reports in basic science (Joni L. Rutter, Ph.D., DBNBR), HIV/AIDS (Marsha F. Lopez, Ph.D., M.H.S., DESPR), and epidemiology, prevention, and treatment (Betty C. Tai, Ph.D., CCTN).

IP Presents Awards of Excellence

During the 2011 NIDA International Forum, NIDA IP presented Awards of Excellence to honor mentors and researchers whose efforts support the International Program mission, including the following:

- Excellence in Mentoring: Jeffery H. Samet, M.D., Boston University School of Medicine.
- Excellence in International Leadership: María Elena Medina-Mora Icaza, Ph.D., Instituto

Nacional de Psiquiatria Ramón de la Fuente, Mexico.
- Excellence in International Collaborative Research: Richard A. Rawson, Ph.D., University of California, Los Angeles.
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International Traveling Fellows Participate in NIDA International Forum and CPDD

Researchers from Russia and South Africa were selected as the 2011 WHO/NIDA/CPDD International Traveling Fellows. NIDA partners with the World Health Organization (WHO) and the College on Problems of Drug Dependence (CPDD) to provide support for a 1-week research visit with a NIDA grantee and participation in the NIDA International Forum and the CPDD Annual Scientific Meeting. The 2011 International Traveling Fellows are:

- Elena Blokhina, M.D., Ph.D., is a research scientist at Pavlov State Medical University in St. Petersburg, Russia, and an experienced international researcher in the area of substance dependence and HIV prevention. She currently is the project coordinator for a NIDA binational grant to the University of Pennsylvania and Pavlov State Medical University to compare an implantable formulation of naltrexone vs. 50 mg/day oral naltrexone for improving anti-retroviral therapy (ART) adherence and treatment outcome in HIV-positive opioid-addicted patients who are beginning their first episode of ART. She is also a project coordinator for a binational grant to Boston University and Pavlov from the National Institute on Alcohol Abuse and Alcoholism that focuses on HIV prevention among Russian drinkers, and has been a valuable member of the research teams for several NIDA clinical trials supported in Russia. She spent her research visit with Jeffery H. Samet, M.D., Boston University School of Medicine to complete a scientific article on HIV prevention among polysubstance abusers and discuss the development of additional collaborative research projects on drug abuse and HIV prevention, including the "seek, test, treat" protocol.
- Tara Carney, M.A., is the senior scientist at the Alcohol and Drug Abuse Research Unit of the South African Medical Research Council and an experienced international researcher in the area of alcohol and drug intervention projects. Ms. Carney focuses on the development and testing of brief interventions for substance use, HIV risk behaviors, and delinquent behaviors among adolescents, and has collaborated with grantees from NIDA, the National Institute on Alcohol Abuse and Alcoholism, and the Centers for Disease Control and Prevention. She spent her research visit with Dr. Ken Winters at the University of Minnesota, to begin adapting for use in South Africa the evidence-based early intervention program that he has developed to reduce substance use and associated harms among adolescents.

NIDA-Supported Meetings

NIDA Supports Poster Session at Society for Prevention Research Meeting

NIDA IP, DESPR, and the National Cancer Institute cosponsored the fourth International Poster Session at the 19th Society for Prevention Research (SPR) meeting, held May 31 – June 3, 2011, in Washington, D.C. More than 25 early career scientists presented their research, which featured remarks by SPR president Linda M. Collins, Ph.D., Pennsylvania State University; DESPR Director Wilson M. Compton, M.D., M.P.E.; and IP director Steven W. Gust, Ph.D. The theme of the SPR meeting was "Prevention Scientists Promoting Global Health: Emerging Visions for Today and Tomorrow," and two sessions explored how to form and maintain international collaborations. Jacqueline Lloyd, Ph.D., DESPR, and Susannah Allison, Ph.D., National Institute of Mental Health, co-chaired a roundtable highlighting successful international collaborations

that have conducted HIV prevention research with diverse populations around the globe. A session co-chaired by Marie-Héléne Véronneau, Ph.D., University of Oregon, and Kerry Green, Ph.D., University of Maryland, focused on initiating international collaborations, keys to success, and common pitfalls. Now in its third year, the International Networking Forum at SPR, composed of scientists, policymakers, and community representatives, gathered to discuss ways to increase international involvement in SPR activities; share knowledge about prevention strategies; and support ongoing networking and collaboration. Brenda Miller, Ph.D., Prevention Research Center, Berkeley, California, chaired both the SPR meeting and the International Networking Forum at SPR. NIDA provided travel awards for 13 researchers who presented the results of drug abuse prevention research completed in international settings during the International Poster Session, including:

- Josipa Basic, Ph.D., University of Zagreb, Zagreb, Croatia.
- Meen Poudyal Chhetri, Ph.D., Disaster Preparedness Network-Nepal, Kathmandu, Nepal.
- Helga S. Fridjonsdottir, Ph.D., University of Iceland, Reykjavik, Iceland.
- Fabrizia Giannotta, Ph.D., Orebro University, Orebro, Sweden.
- Olga Levina, NGO "Stellit," St. Petersburg, Russia.
- Gustavo Martinez, M.D., Salud y Desarollo Comunitario de Ciudad Juarez, Juarez, Mexico.
- Boladale M. Mapayi, MBChB, Obafemi Awolowo University, Osun, Nigeria.
- Carmen Orte, Universitat Illes Balears, Palma, Spain.
- Zila M. Sanchez, Ph.D., Universidade Federal de Brazil, Sao Paulo, Brazil.
- Eva Skarstrand, Karolinska Institute, Stockholm, Sweden.
- Tasanai Vongchak, Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand.
- Trecia A. Wouldes, University of Auckland, Auckland, New Zealand.
- Matthew M. Young, Ph.D., Canadian Centre on Substance Abuse, Ottawa, Canada.

ASAM Focuses on International Addiction Treatment and Changing Views of Cannabis

NIDA supported a symposium on innovative international models of addiction treatment at the 42nd American Society of Addiction Medicine, held April 14–17, 2011, in Washington, D.C. Jag Khalsa, Ph.D., DPMDCA, organized the symposium along with Marc Galanter, M.D., New York University, and Petros Levounis, M.D., M.A., Addiction Institute of New York. IP director Steven W. Gust, Ph.D., reviewed the worldwide situation on drug abuse and presented IP research activities, funding opportunities, and training programs available to support international collaboration. Other speakers in the session discussed heroin maintenance treatment for opioid dependence in the Netherlands; integration of Indian culture, yoga, and meditation in addiction treatment; and new Brazilian treatments for crack smoking. A second symposium reviewed research, clinical data, and evolving public perceptions and policies related to marijuana. Dr. Gust presented prevalence statistics on marijuana and participated in discussions of the clinical consequences and sequelae of cannabis use and the diverse viewpoints on the topic. Elliot Gardner, Ph.D., IRP, discussed research on endocannabinoid brain mechanisms.

Fellowships

International AIDS Society, NIDA Select New Postdoctoral Fellows

The International AIDS Society (IAS) and NIDA have awarded postdoctoral fellowships to scientists from China and Indonesia. IAS and NIDA cosponsor the fellowships, which provide 18 months of training with an expert in drug abuse-related HIV, to advance scientific understanding of the linkages between drug use and HIV while fostering multinational research. The 2011 fellows are:

- Former NIDA INVEST Fellow Huaihui Zhang, M.D., Ph.D., a psychiatrist at the Shanghai Yangpu District Mental Health Center, China, will carry out a brief assessment and a modular, education-based intervention for methadone maintenance treatment patients who are at risk of HIV infection in Shanghai, China. Her INVEST fellowship mentor, Richard S. Schottenfeld, M.D., Yale University School of Medicine, also will serve as her mentor for the IAS/NIDA fellowship.
- Working with Scott Burris, J.D., Temple University School of Law, Jinmei Meng of China will work on HIV, drug use, and the law in China, investigating the penalization of drug use and HIV risks of injecting drug users.
- Iko Safika, Ph.D., M.P.H., of the South East Asia Infectious Disease Clinical Research Unit in Indonesia, will study depression, drug use and high-risk sexual behaviors among men who have sex with men and transgendered individuals in Jakarta, Indonesia. Timothy Johnson, Ph.D., University of Illinois at Chicago (UIC), will be her mentor. Dr. Safika received her doctorate from UIC as a Fogarty International Center AIDS International Training and Research Program (AITRP) trainee.

Chinese Researcher Named INVEST Fellow

Sun Hongqiang, M.D., Ph.D., China, has been selected as a 2010–2011 NIDA INVEST Drug Abuse Research Fellow. He will be working with mentor Thomas R. Kosten, M.D., at the Baylor College of Medicine and DeBakey Veterans Administration Medical Center in Houston, Texas, to investigate the effectiveness of pharmaceutical interventions for smoking cessation. As a 2010 WHO/NIDA/CPDD International Traveling Fellow, Dr. Sun spent the 1-week traveling fellowship research visit with Dr. Kosten to learn more about clinical trials in smoking cessation, detoxification and relapse prevention. INVEST Fellows conduct 12 months of postdoctoral research with a NIDA grantee in the United States and participate in professional development and grant-writing activities.

INVEST/CTN Fellowships Contribute to Clinical Research Advances

The 2010 INVEST/CTN Drug Abuse Research Fellows have ended their 12-month postdoctoral fellowships, having acquired significant experience in conducting clinical trials and genotyping:

- Suzanne Nielsen, Ph.D., Turning Point Alcohol and Drug Centre, Australia, spent her INVEST/CTN Fellowship with Walter L. Ling, M.D., University of California, Los Angeles (UCLA), conducting secondary data analysis examining differences between prescription opioid and heroin users in two buprenorphine treatment studies, and supporting the multisite clinical trial "Cocaine Use Reduction with Buprenorphine" (CURB) study (CTN-0048). CURB is a complex protocol involving multiple medications designed to reduce cocaine use in cocaine-dependent individuals with a history of opioid abuse or dependence. Dr. Nielsen wrote the operations manual for the study, developed training materials, and helped run the

national training for the study. She has completed two papers, presented her work at several scientific meetings, and served as guest editor of a special issue of *Drug and Alcohol Review* on pharmaceuticals. She will spend a second year at UCLA before returning to Australia to develop a network of clinical treatment providers in Australia, where multisite studies examining treatments for substance dependence do not currently exist.

- Meera Vaswani, Ph.D., All India Institute of Medical Sciences, spent her INVEST/CTN fellowship with Wade Berrettini, M.D., Ph.D., University of Pennsylvania, identifying variants in known and novel mu-opioid receptor interacting proteins (MORIPs), genotyping 8 genes for both opioid and cocaine addiction. Dr. Vaswani presented the work at several scientific meetings and completed two papers.

Travel Support

NIDA Awards Tuition Waiver for Intensive Summer Institute in Addiction

NIDA IP supported tuition costs for Cendrine Danae Robinson, a doctoral student at the Uniformed Services University of the Health Sciences (USU), to attend the 2011 Dutch Summer Institute on Alcohol, Drugs and Addiction in July. The Summer Institute, a joint initiative of the Netherlands Organisation for Health Research and Development (ZonMw) and the University of Amsterdam Graduate School of Social Sciences, is a 2-week, intensive multidisciplinary program offering graduate-level and continuing professional development training in addiction, while promoting opportunities for international networking. In addition to studying cognition as it relates to addiction and loss of control, the genetic basis for addiction, and new approaches to treatment, Ms. Robinson planned to visit the laboratory of Dutch scientist Ingmar Franken, Ph.D., Erasmus University, who has collaborated with her USU mentor Andrew J. Waters, Ph.D., under the NIDA IP binational funding agreement with ZonMw.

NIDA Supports Hispanic Drug Abuse Research Training Institute

NIDA IP supported the participation of Maurice Reuven Samolski Klein, M.D., Michigan State University, in the 2011 National Hispanic Science Network on Drug Abuse (NHSN) Interdisciplinary Research Training Institute on Hispanic Drug Abuse, held June 1-11, 2011, at the University of Houston, Texas. NHSN conducts the institute to help predoctoral, postdoctoral, and early career scientists develop a broad-based set of scientific knowledge and research skills that will equip them to conduct interdisciplinary research on drug abuse issues among Hispanics. In addition to the 11-day training institute, participants receive two years of mentoring and networking assistance to help them meet career development goals. Dr. Klein will continue to work with his mentor, James C. Anthony, Ph.D., M.Sc., Michigan State University, to conduct research, prepare publications, present his research at scientific meetings, and apply for National Institutes of Health funding.

International Visitors

Dr. José Luis Vázquez the Mexican Under Director of the General Direction of Coordination and Cooperation on Addictions of CONADIC (Comisión Nacional contra las Adicciones) visited NIDA on July 27, 2011. The purpose of the visit was for Dr. Vázquez to learn more about NIDA's communication efforts for prevention and the NIDAMed program. While at NIDA Dr. Vázquez met with Drs. Jacqueline Lloyd and Belinda Sims, DESPR, Ms. Ana Anders, Special Populations Office, Ms. Carol Krause, OSPC and Ms. Dale Weiss, IP.

As part of the U.S. Department of State International Visitor Leadership Program a group of visitors from Brazil came to NIDA on August 4, 2011. The objectives of the program were to explain the overall U.S. strategy to address the problem of illicit drug use in the U.S. including prevention efforts to combat drug use in schools, workplaces and communities, highlight education strategies and treatment programs at the national, state and local levels and promote the establishment of cooperation with counterpart institutions to share information on the development of anti-drug measures. NIDA staff that met with the group were Ms. Jan Lipkin, OSPC, Augie Diana, Ph.D., DESPR and Steve Gust, Ph.D., IP.

Other International Activities

Dr. Susan R.B. Weiss, Acting Director, Office of Science Policy and Communications, presented on NIDA's Research Priorities, Policies and Opportunities to the Independent Scientific Committee on Drugs (ISCD) in London, England on June 29, 2011.

Dr. Cora Lee Wetherington, DBNBR, 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 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. Speakers were Sakire Pogun (Ege University, Turkey), Wendy Lynch (University of Virginia), Kevin Gray (Medical University of South Carolina), Caryn Lerman (University of Pennsylvania), and Sherry McKee (Yale University School of Medicine).

Dr. Samia Noursi, Deputy Coordinator, Women and Sex/Gender Differences Research 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, at the invitation of Dr. Tyrfingsson, the Director of Drug Abuse Treatment Center (SAA) in Reykjavik, Iceland, led a team of NIDA/NIH-funded researchers (Drs. Emmalee Bandstra [Umiami], Igor Grant [UCSD], Shenghan Lai [JHU], Glenn Treisman [JHU], and George Woody [Upenn]) to present a symposium and participate in their International Conference on Drug Abuse Treatment. Dr. Khalsa and the visiting team were given a special reception by the President of Iceland where he thanked Dr. Khalsa for developing collaborations between the US and Icelandic researchers. Dr. Khalsa also gave two interviews in the Reykjavik newspapers.

Dr. Wilson M. Compton chaired a panel on "Policy Approaches to Improving Substance Abuse and Mental Health Treatment" at the World Psychiatric Association Meeting, Istanbul, Turkey, June 10, 2011.

Dr. Wilson M. Compton presented a plenary on "Addressing Addiction Using an Integrated Public Health and Public Safety Approach" at the International Conference on Security and Justice in Democracy: Towards a State Policy at the Dawn of the Third Millennium, National Autonomous University, Mexico City, Mexico, June 6, 2011.
Dr. Wilson M. Compton presented on "United States-Mexico Prevention Research Collaborative Initiative" at the annual meeting of the Society for Prevention Research, Washington, District of Columbia, June 3, 2011.

Dr. Ivan Montoya, DPMCDA, was invited to present at the biannual meeting of the Spanish Society of Addictions in Bilbao (Spain) on June 1, 2011. The title of his presentation was "Scientific Advances in the Treatment of Drug Addictions".

Dr. Meyer Glantz, Ph.D., DESPR, attended the 2011 World Mental Health Consortium meeting as NIDA's representative and scientific collaborator. The WHO meeting was held in Providence, Rhode Island from June 28 through July 2, 2011. Dr. Glantz collaborates with the Drug Dependence, Nosology, and Primary Care Screening analysis workgroups. The WMH Consortium is a multinational set of coordinated community psychiatric epidemiology surveys. The U.S. implementation was the National Comorbidity Survey Replication Survey. Dr. Glantz led discussions on the relationship of the consequences of psychiatric disorders to the symptoms identifying those disorders.

Dr. Eve Reider, DESPR, was an organizer and theme reviewer for the 4th Annual NIDA International Poster Session, held May 31, 2011 at the 19th Annual Society for Prevention Research Annual Meeting, Washington, D.C.

Dr. Peter Hartsock, DESPR, met with representatives of the African Union and academia in a planning meeting for an autumn 2011 pan-African conference dealing with pressing social and health problems, including increasing drug abuse, on the continent, Washington, D.C., May 17, 2011.

Dr. Peter Hartsock represented NIH at the Carnegie Endowment for International Peace's Russia-Eurasia Program's conference on health cooperation with Russia, Washington, D.C., May 6, 2011. Dr. Hartsock reported on NIDA/DESPR's Russian research portfolio extending over 20 years and dealing with drug abuse, HIV, and associated problems. Planning is underway for escalated Carnegie and NIH efforts with Russia.

Dr. George Uhl, IRP, is aiding in recovery of mouse strains/fellows from Tohoku University, Sendai Japan.

MEETINGS/CONFERENCES

The National Institute on Drug Abuse (NIDA) organized a program at the **2011 American Psychological Association (APA) Annual Meeting in Washington, D.C., August 4-7.** A number of NIDA staff were involved in the planning of sessions on a wide range of topics related to addiction research. NIDA also co-sponsored an Early Career Investigator Poster Session with APA's Divisions 28 and 50 and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as part of the two Divisions' Social Hour. A special performance of NIDA's, *Reducing the Stigma of Addiction: The Addiction Performance Project*, with a dramatic reading by actress Debra Winger & Arliss Howard and chaired by NIDA Acting Deputy Director, Dr. David Shurtleff, was also featured at this year's meeting.

On May 23-24, 2011, the Special Populations Office hosted a two-day **Research Development Seminar Series** workshop in Bethesda, Maryland. Chaired by Flair Lindsey, this follow-up meeting convened new investigators and NIDA-funded faculty mentors in an intensive grants development workshop setting, culminating with a mock review of research grant applications submitted by seminar participants. During the workshop, Dr. Lula Beatty moderated the debriefing session, immediately following the mock review.

The Special Populations Office coordinated the 15th annual **Summer Research with NIDA program**, which commenced on May 31, 2011. Seventy high school and undergraduate students engaged in drug abuse research at various NIDA-supported research institutions for 8-10 weeks during the summer. Participants received certificates of participation signed by Dr. Nora Volkow and the site principal investigator.

NIDA hosted the inaugural seminar of the **Addressing Health Disparities through Neuroscience** seminar series, in conjunction with NIAAA, NICHD, NIMH and NINDS on June 10, 2011 in Bethesda, Maryland. The seminar's theme was "Genes and environment: Does one-size fit all." Speakers included Drs. Charles Rotimi (NHGRI) and Cindy Ehlers (Scripps). Ms. Flair Lindsey, Special Populations Office, represented NIDA on the seminar series' planning committee.

The Special Populations Office and the NIDA-supported African American Researchers and Scholars Workgroup convened the 4th annual **Addiction Research Training Institute (ARTI)**, a four-day training for new investigators interested in pursuing careers in drug addiction research, on July 18-21, 2011 at the Morehouse School of Medicine in Atlanta, Georgia. Pamela Goodlow, the assigned Contracting Officer Technical Representative (COTR) of the Workgroup's activities, presented on the Special Populations Office and NIDA/NIH funding opportunities. Additionally, Ms. Goodlow met with and advised the new investigator participants.

Dr. Gayathri J. Dowling, Acting Chief, Science Policy Branch, Office of Science Policy and Communications, gave the keynote address entitled "Advances in Drug Abuse and Addiction Research from NIDA: Implications for Treatment" at the 2011 Chief Resident Immersion Training Program – Addiction Medicine: Improving Clinical and Teaching Skills for Generalists in Cape Cod, Massachusetts on May 12, 2011.

Dr. Gayathri J. Dowling presented "NIDAMED: Resources for Physician Training in Drug Abuse and Addiction" at the Annual Society of Teachers of Family Medicine meeting in New Orleans, Louisiana on April 28, 2011.

On July 18, 2011, Carol Krause, Chief, Public Information Liaison Branch, Office of Science Policy and Communications, presented NIDA's music video contest in partnership with the GRAMMY Foundation at "Crowdsourcing: The Art and Science of Open Innovation," at an NIH-sponsored Expo in Bethesda, MD.

On June 27, 2011, Carol Krause presented NIDA's teen outreach efforts "From Blogs to Music Videos," at the NIH Executive Leadership Program in Bethesda, MD.

Carol Krause presented at a seminar series for NIH Management Trainees, "Communicating at NIH with New Media Technologies," at NIH in Bethesda, MD on June 9, 2011.

Dr. Lula Beatty, Director, Special Populations Office, served as a poster presentation judge for the Howard University Health Sciences Research Meeting on April 15, 2011 in Washington, DC.

Dr. Lula Beatty presented a session titled "Finding Your Way: Pathways to Career Success in Drug Abuse Research," at a conference sponsored by Florida International University on April 26, 2011 in Miami, Florida.

Dr. Lula Beatty participated in the Robert Woods Johnson New Connections program held at NIH, May 5, 2011.

Dr. Lula Beatty participated in a panel discussion for the Meyerhoff scholars at the University of Maryland, Baltimore Campus on July 8, 2011 in Baltimore, Maryland.

Dr. Lula Beatty presented sessions on the science of drug abuse for Native American middle school students participating in a Native Youth Academy. The meeting, coordinated by the NIH Office of Equal Opportunity and Diversity Management and the NIAID's Rocky Mountain Laboratories, was held on July 21, 2011 in Hamilton, Montana.

Dr. Lula Beatty presented an overview of the Special Populations Office at the NIDA Mentored K meeting on July 25, 2011, Rockville, Maryland.

Dr. Lula Beatty served as a panelist during the Jegna (mentor) session at the convention of the Association of Black Psychologists on July 30, 2011 in Crystal City, Virginia.

Dr. Lula Beatty, a member of the Executive Committee of the Leadership Institute for Women in Psychology, served as a faculty member at the 4th annual Leadership Institute for Women, American Psychological Association, on August 1 – 3, 2011 in Washington, DC.

Dr. Lula Beatty participated as a panelist on a Funding and Research Opportunities session, American Psychological Association convention on August 6, 2011 in Washington, DC.

Dr. Lula Beatty chaired a symposium titled "Developing Leadership in Health Disparities through Professional Associations" at the American Psychological Association convention on August 6, 2011, Washington, DC.

Dr. Lula Beatty chaired a symposium titled "Trauma in Men of Color: Implications for Prevention and Treatment," at the American Psychological Association on August 4, 2011 in Washington, DC.

Dr. Lula Beatty was a discussant for a symposium titled "Addressing Health Disparities through Clinical Interventions in Substance Abuse and Mental Health," at the American Psychological Association convention on August 5, 2011 in Washington, DC.

Dr. Lula Beatty participated in the mentoring meeting for new trainees of the NIDA American Indian/Alaska Native Work Group, convened by Dr. R. Dale Walker, as a preconvention meeting of the annual meeting of the Association of American Indian Physicians on August 10, 2011, Portland, Oregon.

Ana Anders, M.S.W., Public Health Analyst, Special Populations Office, participated in the Asian American/Pacific Islander Researchers and Scholars meeting on June 2-3, 2011 in Bethesda, Maryland.

Ana Anders participated in a planning meeting to develop a conference in Latin America and the Caribbean on drug abuse and HIV/AIDS on June 14, 2011 in Washington, DC.

Pamela Goodlow, Public Health Analyst, Special Populations Office, met with scholars and presented an overview of research funding opportunities available through NIDA at the NIMHD-sponsored "2nd Translational Health Disparities Course: Integrating Principles of Science, Practice and Policy in Health Disparities Research" on June 22, 2011 in Bethesda, Maryland. New investigators interested in health disparities research were selected to attend the two-week course, held on the NIH campus from June 20-July 1, 2011.

Dr. Teri Levitin and Dr. Mark Swieter, OEA, co-organized and co-presented a workshop on "What's New at NIH and NIDA" at the annual meeting of the College on Problems of Drug Dependence, in Hollywood, FL, June 13, 2011.

At the 119th Annual Convention of the American Psychological Association held in Washington D.C. in August, Dr. Levitin co-organized and co-taught a four hour seminar entitled "Unlock the Mysteries of NIH Research Funding: Improve Your Grant Application and Improve Your Chance at Success."

Dr. Scott Chen, OEA, was on a panel the provided potential applicants with Q&A opportunities at the 13th Annual NIH SBIR/STTR Conference, in the Natcher Building, NIH Campus, in Bethesda, MD, June 22-23, 2011.

Dr. Scott Chen and Dr. Gerald McLaughlin, OEA, co-organized the "Career Development Workshop" (Panelists: Mary Jeanne Kreek, Antonello Bonci, Charles Gorodetzky, Martin Iguchi, and Jennifer Tidey) at the annual meeting of the College on Problems of Drug Dependence, in Hollywood, FL, June 13, 2011.

Dr. Eliane Lazar-Wesley, OEA, made a presentation "The Review Process: It is not a Black Box" as part of a workshop organized with Drs. Nancy Pilotte, Albert Avila and Roger Sorensen, for the NIDA Intramural Research Program, entitled , Early Career Investigators: Navigating Your Future, in Baltimore, MD, May 16, 2011.

Dr. Eliane Lazar-Wesley made a presentation entitled " Peer Review Process, Changes, and How to Interpret Summary Statements" and also was a member of the Panel on Grants Management and Review, at the NIDA Mentored K Awardee meeting, in Rockville, MD, July 25-26, 2011.

Dr. Meena Hiremath, OEA, was on the panel for "What is new at NIH and NIDA," presented at the College of Problems of Drug Dependence, Hollywood, FL, June 18-23, 2011.
Dr. Meena Hiremath organized the mock review of applications and served as SRO of the mock review exercise, presented as part of the National Institute on Drug Abuse (NIDA) Special Populations Research Development Seminar Series, in Bethesda, MD May 23, 2011.

Dr. Laurence Stanford, DCNBR, attended a symposium entitled The Science of Stress: Focus on the Brain, Bad Habits and Chronic Disease at Yale University on June 7th, 2011 and participated in a site visit of the Yale University NIH Roadmap Interdisciplinary Research Center on June 8th, 2011 in New Haven, CT.

Dr. Joseph Frascella, Director, DCNBR, participated in the Interdisciplinary Research Training Institute on Hispanic Drug Abuse that promotes the career development of graduate, postdoctoral, and early career scientists. He gave a presentation NIH Grant-writing Process: Do's, Don'ts, Tips, Tricks, & Strategies, at the University of Houston on June 1, 2011 in Houston, TX.

Dr. Joseph Frascella participated in and presented at a meeting on Food and Addiction sponsored by the Robert Wood Johnson Foundation and the Rudd Center for Food Policy and Obesity at Yale University, June 1-2, 2011 in Princeton, NJ.

Dr. Cheryl Anne Boyce, DCNBR, served as invited lecturer on a panel along with Dr. Lula Beatty, SPO, NIDA, for the summer course on health disparities entitled Race, Science, & Society led by Dr. Shawn Bediako at the University of Maryland Baltimore County (UMBC) on July 8, 2011. The audience included students participating in the UMBC Meyerhoff Scholars Program and National Science Foundation sponsored Maryland's Alliance for Graduate Education and the Professoriate (AGEP) PROMISE Program.

On July 18, 2011, Dr. Cheryl Anne Boyce presented "How to Give a Dynamic Presentation" to advanced doctoral and early career psychologists participating in the American Psychological Association (APA) Minority Fellowship Program's Psychology Summer Institute (PSI). The workshop was held in Washington, DC and taught professional development skills for synthesizing and presenting scientific research ideas to a variety of audiences.

Dr. Cheryl Anne Boyce participated in a workshop panel "Federal Funding in Family Research" along with NIH colleagues Dr. LeShawndra Price, NIMH and Dr. Anna L. Riley, CSR at the: Family Research Consortium V Summer Institute 2011: Mental Health and Substance Use: Risks, Prevention, Treatment and Policies on July 22, 2011 in San Juan, Puerto Rico.

As part of the special convention program targeted for graduate students sponsored by American Psychological Association of Graduate Students (APAGS), Dr. Cheryl Anne Boyce presented on " Federal Funding Opportunities for Your Education" in the session entitled "Obtaining Funding for Your Education---Opportunities for Racial/Ethnic Minority Students" at the American Psychological Association Annual Convention on August 4, 2011.

Dr. Cheryl Anne Boyce served as chair for the symposium, "Addressing Health Disparities through Clinical Interventions in Substance Abuse and Mental Health" at the American Psychological Association Annual Convention on August 5, 2011. Presentations by early career researchers focused on drug abuse prevention for Latino communities, HIV prevention and medical mistrust among African American men, and evidence based treatments for racial/ethnic minorities. Dr. Lula Beatty, SPO, NIDA served as discussant for the session.

Along with Dr. Frederick Leong of Michigan State University, Dr. Cheryl Anne Boyce co-chaired an invited plenary address "Cultural Adaptations of Psychotherapy: Why, How, and Do They Work? " by Dr. Guillermo Bernal of University of Puerto Rico, Río Piedras, at the American Psychological Association Annual Convention on August 5, 2011.

Dr. Cheryl Anne Boyce presented "Culture Counts: Training and Research Opportunities to Increase the Pipeline" at the symposium entitled, "Unequal Treatment for Ethnic/Racial Minority Human Resources: Where are the Researchers and Practitioners?" at the American Psychological Association Annual Convention in Washington, DC on August 5, 2011. The session was sponsored by APA's Commission on Ethnic Minority Recruitment and Retention II Task Force (CEMRRAT2 TF) which is charged with ensuring diversity in psychology's educational and professional pipelines.

Dr, Karen Sirocco, DCNBR, and Dr. Cheryl Anne Boyce co-chaired a plenary session entitled, "Training Executive Function: Using Brain Data to Sell the Evidence that Interventions Work" at the American Psychological Association Annual Convention on August 6, 2011. Drs. Jacqueline Bruce, Yi-Yuan Tang, Brad Sheese and Fiona McNab served as presenters for this session. The presentation is part of the dissemination efforts of NIDA's OSPC sponsored meeting "Developmental Neural Mechanisms of Cognitive Control: Implications for Drug Abuse Interventions' which was held May 3-4, 2010 in Rockville, MD.

Dr. Karen Sirocco participated in a workshop panel "National Institutes of Health Grant Discussion" along with NIH colleagues Dr. Courtney Ferrell Aklin, NINDS, Dr. LeShawndra Price, NIMH, and Dr. Regina James, NICHD at the 8th Annual Quantitative Training for Underrepresented Groups (QTUG) Conference on August 2, 2011 in Washington, DC.

Dr. Nicolette Borek, DCNBR, organized a seminar on "Developmental Effects of Prenatal Cocaine Exposure" with speakers Dr. Michael Lewis, Dr. Dennis Carmody, and Dr. David Bennett on June 20, 2011 in Rockville, MD.

Dr. Nicolette Borek served as discussant for the symposium "Culturally Based Prevention and Systems of Care Considerations for American Indian Youths and Families" at the American Psychological Association Annual Convention on August 5, 2011.

Dr. Cheryl Anne Boyce presented "NIDA Report and Updates for Early Investigators" for the AACAP-NIDA K12 Program Annual Retreat held in Hollywood, Florida on June 17, 2011. The meeting included current K12 early career investigators and their faculty mentors who meet annually for career development activities designed to facilitate the transition to research independence.

Drs. Cecelia Spitznas of DCNBR and Samia Noursi of NIDA's Women and Gender Office organized a symposium held July 20, 2011 at NIDA called NIDA Science Becomes Reality (TV): The science behind the substance abuse therapy featured on the Oprah Network Television series, "Breaking Down the Bars." Researchers Nena Messina, Ph.D. of UCLA and Stephanie Covington, Ph.D., LCSW, of the Center for Gender and Justice in La Jolla CA, described the process of developing and pilot testing a treatment for women offenders with trauma histories. Dr. Covington later treated patients using these methods on a television series.

Drs. Cecelia Spitznas and Lisa Onken, DCNBR, participated in the American Psychological Association Annual Meeting Symposium Innovation and Opportunities in Mobile Interventions for Addictions on August 6, 2011 in Washington DC. The symposium featured the research of six NIDA grantees. Dr. Onken co-chaired the session and Dr. Spitznas was the discussant.

Dr. Will Aklin, DCNBR, co-chaired a symposium at the College on Problems of Drug Dependence (CPDD) annual meeting symposium on Neurocognitive Dysfunction in Addiction: Mechanisms and Interventions on June 23, 2011 in Fort Lauderdale, FL. This translational symposium focused on recent advances in the study of neurocognitive dysfunction in addiction, the underlying mechanisms, and novel therapeutic approaches to improving cognitive dysfunction.

Drs. Will Aklin and Lisa Onken co-chaired a symposium at the American Psychological Association annual meeting symposium on Neurobehavioral and Technological Mechanisms to Improve the Efficacy and Effectiveness of Substance Abuse Treatment on August 7, 2011 in Washington, DC. The symposium highlighted studies by noted experts that examined mechanisms of action (biological and/or neurobehavioral) associated with treatments, research using innovative technology, and studies using medication to improve the efficacy/effectiveness of substance abuse treatments.

Dr. Lisa Onken facilitated a session, "Emotional self-regulation," at the June 20th -21st 2011 trans-NIH "Science of Behavior Change" Investigator's Meeting. At the session, Dr. B.J. Casey provided introductory remarks on recent research on emotional self-regulation. Drs. Julie Lumeng & Alison Miller discussed "Self-Regulation as a Biological Mechanism for Excess Weight Gain in Toddlers." Dr. Kevin Ochsner spoke about "The Development of Emotion Regulation Mechanisms Impacting Health." Finally, Elizabeth Phelps discussed "Emotions and Choice: Mechanisms of Behavior Change."

Dr. Lisa Onken facilitated a discussion on "Iterative intervention research" at the NIH meeting, "Tailoring and targeting behavioral and social interventions: Weaving a strategy for effective and efficient intervention research," organized by Dr. Melissa Riddle of NIDCR. The meeting took place on August 2nd – 3rd 2011 in Bethesda, Maryland.

Dr. Cecelia Spitznas, DCNBR, participated as a faculty member in the Summer Interdisciplinary Research Training Institute on Hispanic Drug Abuse held in Houston, Texas June 7, 2011.

Dr. James Bjork, DCNBR, gave a presentation on behalf of the NIH Neuroscience Blueprint Workgroup on Neuroimage Data Sharing entitled: "Sharing of NIH-funded Neuroimage Data: Potential Policy and Implementation." This talk was presented at a meeting entitled, Neuroimaging Datasharing and Data Access, which was organized by the International Neuroinformatics Coordinating Facility and held on June 25th, 2011, in Quebec City, Canada.

Dr. Steven Grant, DCNBR, chaired a workshop entitled "Does the Brain Ever Recover From Drug Addiction?" and co-chaired two symposia at the American Psychiatric Association annual meeting entitled: "Brain Mechanisms and Neuropsychiatry in Smoking Cessation" (with Dr. Geetha Subramaniam of DCNBR), and "Cannabis and Psychosis: Epidemiology, Neuroscience and Clinical Perspectives" (with Dr. Wilson Compton of DESPR). The meeting was held on May 14-18, 2011 in Honolulu, Hawaii.

Dr. Yu (Woody) Lin, DCNBR, and Dr. Steve Grant co-chaired a symposium entitled Human Brain Imaging of Opioid Receptors at the annual International Narcotics Research Conference, held in Hollywood, FL on June 22, 2011.

Dr. Yu (Woody) Lin chaired a CCTN/DCNBR/NIDA and NCCAM joint-sponsored symposium on Healthier life Choices and Wellness entitled Cognitive Neuroscience of Mind-Body Exercise. The conference was held in Bethesda, MD on June 27, 2011.

Dr. Roger Sorensen, DBNBR, gave a presentation; Grant Writing for Success: your funded NIH application; at the NICHD Vulvodynia Pre-application Technical Assistance Webinar held on July 22, 2011.

Dr. Nancy Pilotte, DBNBR, participated in an Early Career Grants Workshop at the IRP on May 16, 2011.

Dr. Nancy Pilotte, DBNBR, conducted a grants workshop at University of Pittsburgh on May 18, 2011.

Dr. Hari H. Singh, DBNBR, organized and chaired a workshop on NIDA Research Resources – An Update of The NIDA Drug Supply & Analytical Services Program on Wednesday, June 22, 2011 during the CPDD 73rd Annual Scientific Meeting from June 18 to 23, 2011 in Hollywood, Florida. The presenters were Dr. Hari H. Singh, Dr. F. Ivy Carroll, Mr. Kenneth H. Davis, Dr. David E. Moody, and Dr. Jeffrey R. Deschamps.

Dr. Vishnu Purohit and Dr. Rao Rapaka, DBNBR, organized a symposium on Cannabinoids and HIV Pathogenicity at the International Cannabinoid Research Society meeting that was held in St. Charles, Illinois, USA, July 5-10, 2011. The speakers of the symposium were: Dr. Patricia Molina (Louisiana State University), Dr. Guy Cabral (Virginia Commonwealth University), Dr. Hava Avraham (Harvard Medical School), and Dr. Mauro Maccarrone (University of Teramo, Italy).

On behalf of the Neuroscience consortium, Dr. Rao Rapaka organized a cutting edge research workshop on "Nutrition and Addiction" at the Neuroscience center, on June 2, 2011.
Dr. Rao Rapaka organized a work shop on "Nutrition & Addiction: An Update" at the joint CPDD/INRC Annual Meeting, 2011, Hollywood, Florida.

Dr. Rao Rapaka organized at Workshop at the 21st Annual Symposium of the International Cannabinoid Research Society, held at, Phesant Run, St. Charles, Illinois USA. The NIDA Satellite Symposium/Workshop was entitled *"*Endocannabinoid Metabolic Enzymes and Drug Development *(*FAAH-MAGL-NAAA). Seventeen speakers made presentations and this was followed by an extensive discussion, It is expected that the proceedings of the symposium will be published.

Dr. Cora Lee Wetherington, DBNBR, gave an invited discussant presentation in the symposium, "Milestones in the Development of Sex Differences in the Biological Actions of Drugs of Abuse," at the annual meeting of the Organization for the Study of Sex Differences, Oklahoma City, June 2-4, 2011. Other symposium speakers were Edward J. Wagner (College of Osteopathic Medicine of the Pacific Western University of Health Sciences), Rebecca M. Craft (Washington State University), Jill B. Becker (University of Michigan), and Suzette Evans (Columbia University).

Drs. Cora Lee Wetherington and Samia Noursi, DBNBR, organized and co-chaired the symposium, Prenatal Cocaine Exposure in Animals and Humans: Sex Differences across the Lifespan," at the annual meeting of the College on Problems of Drug Dependence in Hollywood, FL, June 18-23, 2011. Speakers were Diana Dow-Edwards (State University of New York, Downstate Medical Center), Michael A. Nader (Wake Forest University School of Medicine), Emmalee S. Bandstra (University of Miami Miller School of Medicine), and Linda C. Mayes (Yale University School of Medicine).

Drs. Vishnudutt Purohit and Cora Lee Wetherington organized and co-chaired the symposium, "Sex Differences in Pain and Opioid Analgesia,"at the joint meeting of the College on Problems of Drug Dependence and the International Narcotics Research Conference in Hollywood, FL, June 21-23, 2011. Speakers were Linda LeResche (University of Washington), EliseY. Sarton (Leiden University Medical Center), Anne Z. Murphy (Georgia State University) and Alan Gintzler (State University of New York Downstate Medical Center).

Dr. Cora Lee Wetherington made a presentation on NIDA's Women & Sex/Gender Differences Research Program at NIDA's 2011 Mentored K Awardee Meeting: Nuts and Bolts of Developing Independence in a Research Career, Rockville, MD, July 25-26, 2011.

NIDA's Women & Sex/Gender Differences Research Program awarded 28 Women & Gender Junior Investigator Travel Awards for the annual meeting of the College on Problems of Drug Dependence (CPDD), June 18-23, 2011 in Hollywood, Florida. These $750 awards provide travel support to first author junior investigators who make presentations on the topic of women and/or sex/gender differences. These travel awards have been made annually beginning in 1999, and are designed to promote entry of junior investigators into drug abuse research on women and sex/gender differences. A brochure listing all the awardees since 1999 was made available at CPDD. To further promote research in this field, NIDA published a mini-program book, Focus on Women & Sex/Gender Differences, for the CPDD meeting. Excerpted from the CPPD program book, it contains only those program listings related to women and sex/gender differences. These efforts were led by Dr. Samia Noursi who was assisted by Drs. Cora Lee Wetherington, Lynda Erinoff and Joe Frascella.

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Dr. Susan Volman, DBNBR, organized and hosted a Cutting Edge Seminar sponsored by the Neuroscience Consortium and the Comorbidity Interest Group on "Dopaminergic Mechanisms for Individual Differences in Risk for Disinhibitory Psychopathology" (Dr. Joshua W. Buckholtz) and "Neuroimaging of Substance Abuse and Psychopathy: Unraveling the Co-morbidity in Incarcerated Youth and Adult" (Dr. Kent A. Kiehl) on June 1, 2011.
Dr. Cora Lee Wetherington made a presentation, "Sex/Gender Differences in Drug Abuse: The Importance of Conducting a Sex/Gender Analysis of Data," to NIDA's Prevention Research Branch on July 27, 2011.

Drs. Minda Lynch and Joni Rutter, DBNBR, organized and chaired a one-day pre-conference satellite meeting at CPDD entitled "Fundamental Genetics in Drug Abuse and Addiction", June, 2011, in Hollywood, FL. Content targeted the CPDD community of drug abuse and addiction researchers, who might be: "Curious about new genetics findings in drug abuse? Want to better understand and appreciate this emerging literature? Perhaps incorporate genetics techniques in your own research? Maybe you are thinking of multidisciplinary training that includes population or molecular genetics. How might you go about establishing collaborations with genetics experts? Do you want to know about accessing informational resources, e.g., are there polymorphisms for this gene? And, what genes have been associated with this behavior? Is a knock-out mouse available?" The satellite featured an introductory lecture by Dr. Rutter, who is DBNBR Acting Director. This didactic content laid the foundation for subsequent scientific presentations on the "Genetic Basis of Smoking and Nicotine Addiction" delivered by Dr. Laura Bierut, Dr. Jerry Stitzel and Dr. Paul Kenny. In response to requests from participants of last year's satellite, the session also covered fundamentals of epigenetics and a presentation by Dr. Chris Pierce on cocaine-induced epigenetic changes in rodent models of addiction.

Dr. John Satterlee, DBNBR, attended a Gordon Conference entitled "Excitatory Synapses" June 26-July 1, 2011 in Easton MA.

Dr. John Satterlee attended the Steering Committee Meeting for the NIH Roadmap Reference Epigenome Centers, the NHGRI sponsored ENCODE-modENCODE Consortia Meeting, and an ENCODE/Roadmap Epigenomics Program Joint Session May 23-26 in Crystal City, VA.

Dr. John Satterlee attended the Genotype-Tissue Expression Project Meeting and Analysis Workshop June 7-8, 2011 in Silver Spring, MD.

Dr. Jonathan D. Pollock, DBNBR, attended the NHGRI meeting Barriers to Adoption of Genomics in Clinical Medicine and Potential Solutions, June 29, 2011 in Chicago, IL

Dr. Jonathan D. Pollock participated in the NIEHS strategic planning meeting, July 12-14, 2011 in Durham, NC.

Dr. Jonathan D. Pollock gave a talk in the Cold Spring Harbor Course, Cellular Biology of Addiction, entitled, Genetics at NIDA, July 10-11, 2011, Banbury Conference Center, Lloyd Harbor, NY.

Dr. Da-Yu Wu co-organized and co-chaired the NCRR, NIDA, NIMH and NIBIB joint symposium "Advanced Medical Imaging for Neuroscience", June 9, 2011 at Lister Hill Auditorium, Bethesda, MD.

Dr. DaYu Wu visited the research labs of rat genetics and rat genomics at Medical College of Wisconsin and the newly established University of Wisconsin Neuroscience Center at Milwaukee. He presented NIDA's program interest at a research symposium, and discussed research projects for NIDA's mission August 10-11, 2011, Milwaukee, WI.

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Dr. Da-Yu Wu attended the Champalimaud Neuroscience Symposium held in mid September at Lisbon Portugal, and presented NIDA's research program interest in brain development and function. September 18-21, 2011.

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 Policy 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 presented a plenary on "Mainstreaming Addictions in Medicine" at the annual meeting of the Association of American Indian Physicians, Portland, Oregon, August 12, 2011.

Dr. Wilson M. Compton presented on "Terminology of Substance Use Disorders for DSM-5" at the annual meeting of the American Psychological Association, Washington, DC, August 5, 2011.

Dr. Wilson M. Compton presented on "FDA-NIH Collaborations: Longitudinal Study of Tobacco Users" at the Interagency Committee on Smoking and Health, Washington, DC, July 28, 2011.

Dr. Wilson M. Compton presented in a plenary on "Improving Substance Abuse Treatment Through Standardization" at the SAAS National Conference/NIATx Summit, Boston, Massachusetts, July 12, 2011.

Dr. Wilson M. Compton participated in the OBSSR Think Tank Meeting, Bethesda, Maryland, June 27, 2011.

Dr. Wilson M. Compton participated in the NICHD Scientific Vision Conference, Leesburg, Virginia, June 23-24, 2011.

Dr. Wilson M. Compton presented a plenary on "Addressing Addiction Using and Integrated Public Health and Public Safety Approach" at the International Conference on Security and Justice in Democracy: Towards a State Policy at the Dawn of the Third Millennium, National Autonomous University, Mexico City, Mexico, June 6, 2011.

Dr. Wilson M. Compton presented on "United States-Mexico Prevention Research Collaborative Initiative" at the annual meeting of the Society for Prevention Research, Washington, District of Columbia, June 3, 2011.

Dr. Wilson M. Compton attended the annual meeting of the American Psychiatric Association where he chaired a panel on "Marijuans and Psychosis: Epidemiology, Neuroscience and Clinical Perspectives", chaired a forum on "Health Reform: Transforming Addiction Services in the United States", and participated in an early research career meeting, Honolulu, Hawaii, May 15-17, 2011.

Dr. Elizabeth Robertson, DESPR, presented a symposium titled: Primer on Principles of Prevention to the Office on National Drug Control Policy, Lunch and Learn Series in Washington, DC, on June 27, 2011.

Dr. Elizabeth Robertson presented a symposium titled: What's New in PRB: Emerging Principles of Prevention, to the Substance Abuse and Mental Health Services Administration (SAMHSA) as part of the CSA-NIDA Innovations in Prevention Symposium Series in Rockville, MD, on June 13, 2011.

Dr. Elizabeth Robertson made a presentation titled: Emerging Principles of Prevention: Part 2 – Program Delivery for the NIDA-CSAP Symposium Series at the SAMHSA headquarters in Gaithersburg, MD on June 7, 2011.

Dr. Elizabeth Robertson participated in the Garrison Institute's Education Leadership Council on May 10 – 12, 2011 in Garrison, NY at which the upcoming meeting: Garrison Institute Initiative on Contemplation and Education: Education Symposium – Advancing the Science and Practice of Contemplative Teaching and Learning to be held on November 4-6, 2011 was planned.

Dr. Eve Reider, PRB, DESPR, chaired the opening plenary session and corresponding roundtable for the 19th Annual Society for Prevention Research Annual Meeting that was held June 1, 2011 in Washington, D.C. The plenary session was entitled ""Making the World a Smaller Place: International Implementation of Large-Scale Practices, Policies and Programs." Ms. Yvonne Thunnel, Chairman, Mentor Foundation International and Mentor Foundation USA, and Dr. Ken Winters, Chair, Mentor Foundation's Scientific Advisory Network, and Professor, Department of Psychiatry, University of Minnesota, presented on "Mentor Foundation's Role in International Prevention." Drs. Terje Ogden, Ph.D., Research Director at the Norwegian Center for Child Behavioral Development, Unirand, and Professor at the Institute of Psychology, University of Oslo, Norway, and Marion S. Forgatch, Senior Scientist Emerita at Oregon Social Learning Center and Founding Executive Director of Implementation Sciences International, Inc., presented on "Implementing the Oregon Model of Parent Management Training Worldwide." Dr. Geoffrey T. Fong, Professor, Department of Psychology, University of Waterloo, and Senior Investigator, Ontario Institute for Cancer Research, presented on "The International Tobacco Control Policy Evaluation Project (the ITC Project):Evaluating the Impact of the WHO Framework Convention on Tobacco Control."

Dr. Eve Reider was invited by Military Operational Medicine Research Program (MOMRP)/Joint Program Committee for Military Operational Medicine (JPC5) to serve as a subject matter expert for its 2nd annual In-Progress Review (IPR) of Defense Health Program funded research. The meeting focused on Psychological Resilience research was held July 19-20, 2011 and the meeting focused on Families was held July 21-22, 2011 in Frederick, Maryland. The meeting was held in Frederick, Maryland and was conducted by Carl A. Castro, Ph.D., Colonel, U.S. Army, Director, MOMRP.

Dr. Eve Reider 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.

Dr. Eve Reider was a member of the program planning committee for the 19th Annual Society for Prevention Research Annual Meeting that was held June 1-3, 2011 in Washington, D.C.

Dr. Eve Reider presented on "Substance Use Disorders in the Military: The NIDA Perspective" to the Institute of Medicine Committee on "Prevention, Diagnosis, Treatment and Management of Substance Use Disorders in the U.S. Armed Forces." The meeting was held May 3, 2011 at the Doubletree Hotel in Washington, D.C.

Drs. Augusto Diana, Jacqueline Lloyd and Elizabeth Robertson, DESPR, participate in monthly meetings of the CSAP Internal Workgroup for Strategic Prevention Framework State Incentives Grants (SPF SIG). NIDA provides funding for the evaluation of the SPF-SIG and will be releasing a public use data file from this project. The targeted release date is September 2011.

Dr. Jacqueline Lloyd attended the Longitudinal Data on Teen Dating Violence Research Meeting in Washington DC on June 7 and 8, 2011. The meeting was organized by the National Institute on Justice.

Dr. Jacqueline Lloyd organized and chaired a roundtable at the Society for Prevention Research 19th Annual Meeting entitled United States-Mexico Prevention Research Collaborative Initiatives: Implementation and Testing of Two Youth and Family Prevention Initiatives in Mexico, on June 3, 2011. Dr. Wilson Compton served as co-chair.

Dr. Jacqueline Lloyd organized and chaired and Dr. Richard Jenkins served as the Discussant for a roundtable at the Society for Prevention Research 19th Annual Meeting entitled Adaptation and Implementation of Evidenced Based HIV/AIDS Prevention Interventions Internationally, on June 2, 2011 in Washington DC.

Drs. Jacqueline Lloyd and Susannah Allison (NIMH) co-organized and co-chaired a roundtable at the Society for Prevention Research 19th Annual Meeting entitled The How Tos of International Collaborations: Lessons Learned from HIV Prevention Research with Youth, on June 1, 2011 in Washington DC.

Dr. Aria Crump, DESPR, presented a talk entitled "Funding Opportunities at the National Institute on Drug Abuse" at the American Psychological Association's Minority Fellowship Program's ninth annual Psychology Summer Institute on July 18, 2011 in Washington, DC.

Dr. Aria Crump moderated a session entitled "Parenting and Family-Based Interventions" at the NICHD Summer Training Institute on Applied Research in Child and Adolescent Development in Potomac, MD on June 22, 2011.

Drs. Belinda Sims, DESPR, and Aria Crump organized a session entitled "Your First and Second NIH Grant" at the Annual Meeting of the Society for Prevention Research 19th Annual Meeting on June 2, 2011 in Washington DC. Dr. Sims moderated the panel, and Dr. Crump presented on the topic.

Drs. Aria Crump and Augusto Diana, DESPR, presented a talk entitled "A Brief Introduction to NIH Grants" to faculty at Gallaudet University in Washington, DC. On March 29, 2011.

Dr. Augusto Diana attended the SBIR/STTR Annual Conference on June 22-23, 2011, in Washington, DC. Dr. Diana provided one of the speakers, SBIR grantee Michael Borenstein, for a panel entitled, "Interactive Multi-Media Forum," at this conference.
Dr. Augusto Diana co-facilitated a pre-conference workshop entitled, "Tricks of the Trade: Using Marketing Techniques to Promote Healthy Behaviors," at the annual meeting of the

Society for Prevention Research on May 31, 2011. The workshop was coordinated with program staff from NCI.

Dr. Naimah Weinberg, DESPR, with Ms. Beth Babecki of DBNBR, organized and chaired a symposium at the annual meeting of the Behavior Genetics Association entitled "New Statistical Methods for Genetic Research on Addiction" showcasing findings by pre- and post-doctoral students funded under NIDA's R25 program on innovation in statistical genetics, Newport, RI, June 2011.

On June 16, 2011, Drs. Phil Skolnick and David McCann, DPMCDA, chaired a symposium at the NCDEU meeting of the American Society of Clinical Psychopharmacology entitled "Non-Substitution Therapies to Treat Substance Use Disorders." Presenters and their corresponding topics were: Dr. Lori Knackstedt (MUSC), "Glutamate-Based Approaches to Substance Use Disorders;" Dr. Kathryn Cunningham (UT), "The Promise of Selective 5-HT2CR Agonists as Abstinence Enhancers;" and Dr. Charles Chavkin (UW), Kappa Opioid Antagonists show Therapeutic Potential in Animal Models of Stress-induced Mood Disorders and Drug Addiction Risk."

On June 20, 2011, NIDA DPMCDA held "NIDA Medications Development Workshop 2011" at the CPDD meeting in Hollywood, Florida. Speakers included Dr. David McCann ("Abstinence: A new look at an old endpoint"), Dr. Phil Skolnick ("Medication non-compliance: What can we do about it?") and Dr. Jane B. Acri ("What's in the pipeline?").

Drs. Jane B. Acri and David McCann, DPMCDA, organized and chaired a symposium at the NCDEU meeting of the American Society of Clinical Psychopharmacology entitled "Magic Bullets and Arrows: Biologics to Treat Substance Abuse Disorders" on June 13, 2011. The speakers were Raafat Fahim (NABI) on development of the NicVax nicotine vaccine, Merav Bassan (TEVA) on engineered butyrylcholinesterase, and Tom Kosten (Baylor) on cocaine vaccines.

On April 15, 2011, Dr. Ivan Montoya, DPMCDA, co-chaired with Charles O'Brien a one-day symposium at the American Society of Addiction Medicine (ASAM), Washington, DC. Titled "Naltrexone: New Formulations and New Indications". The speakers included Richard Hawks ("Pharmacology and development of naltrexone"), Sandra Comer ("Oral naltrexone for opiate dependence"), David Gastfriend ("Depot naltrexone for opiate dependence"), Elliot Ehrich ("Future research directions of opioid receptor modulators"), Andrea King ("Naltrexone as an aid for smoking cessation"), Ziva Cooper ("Naltrexone for the treatment of marijuana dependence"), Paolo Mannelli ("Ultra-low dose of naltrexone for drug addictions"), Charles O'Brien (Depot "Naltrexone for alcohol dependence"), George Woody ("Naltrexone for amphetamine dependence"), Patrick O'Connor ("Transition from opiate agonist treatment to naltrexone"), Reese Jones ("Combination of naltrexone and buprenorphine for cocaine dependence"), Phil Skolnick ("Naltrexone: past and future perspectives"), and Nora Volkow (Discussant).

At the American Psychiatric Association meeting, Ivan Montoya and Gerry Moeller co-chaired the symposium titled "Decision Making and Addictions: Neurobiology and Treatment Implications". Speakers included Catharine Winstanley ("Basic Neurobiology of Decision Making"), Scott Lane ("The Impact of Drugs of Abuse on Decision Making"), Warren Bickel ("Neuro-Cognitive and Behavioral Interventions to Improve Addict Decision Making"), Gerry Moeller ("Pharmacotherapies for Drug Addiction Aiming at Improving Decision Making"), and Anoine Bechara (discussant).

At the American Psychiatric Association meeting, Ivan Montoya and Bruce Cuthbert co-chaired a symposium titled "The Shrinking Psychotherapeutic Pipeline: Why Has the Spigot Been Turned Off?". Speakers included Irwing Lucki ("Increasing Validity of Animal Models of Depression by Genetic-Environment Interactions"), Armin Szegedi ("New Drugs to No Drugs: Antidepressants and Drug Discovery/Development"), Mark Geyer ("Cross-Species Tests for Cognition Enhancement in Schizophrenia"), Lon Schneider ("Alzheimer's Disease Clinical Trial Failures: Ineffective Drugs or Flawed Clinical Trials"), and David Hough (discussant).

Dr. Ivan Montoya participated in the Program Committee of the New Investigator program of the NCDEU Conference in Boca Raton, Florida on June 11th. He made a presentation titled "Grant Submission and Peer Review Process."

On June 18, 2011, Dr. Ivan Montoya chaired a symposium at the NIDA Satellite Conference before CPDD titled: "Advances in the Development of Medications to Treat Substance Use Disorders". The speakers included Hendree Jones ("Treating Opioid Dependent Pregnant Women with Opioid Agonist Medications: What We Know and What We Need to Know"), Adam Bisaga ("Depot Naltrexone to Prevent Opiate Use Relapse"), and Richard de la Garza ("Novel Pharmacotherapies for Stimulant Dependence").

Dr. Amy Newman, IRP, delivered the plenary lecture to the Virginia Blue Ridge Section of the American Chemical Society Annual Meeting at Radford University, Radford, Virginia in April 2011.

On May 17, 2011, Dr. Paul Wakim, CCTN, organized and chaired an invited session entitled "Practical Application of Adaptive Treatment Strategies in Trial Design and Analysis" at the 32nd annual meeting of the Society for Clinical Trials, May 15-18, 2011. The invited speakers were Drs. Susan Murphy, Kevin Lynch and James McKay.

On June 17, 2011, Dr. Petra Jacobs chaired the International Meeting on Deaths During and After Opioid Treatment which was held in Hollywood, FL. Mortality information for patients in and out of treatment was shared among Australia, United Kingdom and US experts.

The College of Problems on Drug Dependence (CPDD) 74th Annual Meeting was held June 18-23, 2011 in Hollywood, FL. NIDA CTN members and CCTN staff presented the following:

1) Dr. Betty Tai presented "Women's Treatment for Trauma and Substance Use Disorders" as the plenary address at the SAMSHA symposium.
2) Carmen Rosa co-chaired a workshop titled "Drug Use Treatment Outcomes: A Systematic Approach to Selection and Measurement in Clinical Trials Research."

The NIATx Annual Summit & SAAS National Conference was held in Boston, MA on July 10-13, 2011. Dr. Harold Perl presented the following:

1) A symposium with Drs. Roger Weiss, Kathleen Carroll, Michael Levy, Steve Martino and Betsy Wells titled "What the National Institute on Drug Abuse's Clinical Trials Network Can Do for You: Major Findings and Resources for Community-Based Settings."
2) A talk entitled "NIDA's Clinical Trials Network: Science, Practice & Reality" as part of this symposium.

The 119th Annual American Psychological Association Convention was held August 4-7, 2011 in Washington, DC. NIDA CTN members and CCTN staff presented the following:

1) Dr. Harold Perl taught a technical assistance workshop (with Dr. Teresa Levitin [OEA]) entitled "Unlock the Mysteries of NIH Research Funding: Improve Your Grant Application and Improve Your Chance at Success."
2) A symposium entitled "Substance Abuse Treatment with Ethnic Minorities- Lessons Learned in the CTN." Speakers included A. Kathleen Burlew, Alyssa Forcehimes, Audrey Brooks, Jerren C. Weekes and Carmen Rosa.
3) Dr. Udi Ghitza chaired a symposium entitled "CTN Electronic Medical Records Project: Implications of Adopting Standardized Core Data Elements in Health IT Systems of Drug-Abuse Treatment Providers." Speakers included Drs. Betty Tai, A. Thomas McLellan, Robert Lindblad, Robert Gore-Langton.
4) Drs. Paul Wakim and Gregory Brigham co-chaired a session titled "Missing Data in Substance Abuse Clinical Trials-Comparative Approaches and Implications." Speakers included Drs. Sterling McPherson, John Roll, Celestina Barbosa-Leiker, and Paul Wakim.

Dr. Harold Perl led an interactive presentation/discussion entitled "Three Strategies to Enhance Implementation of Evidence-Supported Practices" at the first Global Implementation Conference on August 15, 2011, in Washington, DC.

MEDIA AND EDUCATION ACTIVITIES

MEDIA SUPPORT OF EVENTS AND MEETINGS:

Addiction Performance Project
The Addiction Performance Project (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 patients suffering from addiction. Two performances were presented in August – one at NIH and one at the American Psychological Association Conference. Three-time Oscar Winner Debra Winger was the lead actress in these two performances. To date, media coverage of the APP has included articles in *Modern Healthcare, About.com, Bioephemera Blog, Clinical Psychiatry News* and *NewPublicHealth.* In addition, MusiCares and the Hanley Center posted the APP—*What's It All About* YouTube video on their Facebook pages. MusiCares has 3,643 fans, and the Hanley Center has 716 fans. A Media Tip Sheet about the program was developed. Additional information about APP can be found at www.drugabuse.gov/nidamed/APP.

National Drug Facts Week—MusiCares® and Grammy Foundation contest
In early May, NIDA launched the second annual MusiCares® and GRAMMY Foundation® Teen Substance Abuse Awareness through Music contest. The contest asks young musicians, ages 14-18, to compose or create an original song and/or music video that explores, encourages, and celebrates a healthy lifestyle or accurately depicts a story about drug abuse. Winners will be revealed during NIDA's second annual National Drug Facts Week (NDFW), which begins Oct. 31, 2011. To date, media coverage of the announcement includes eight print articles, including one in *The Washington Post*, Facebook posts reaching 7,706+ and 61 Twitter posts, reaching 221,248. In addition, Country Music Television (CMT) tweeted three times -- with two tweets from @CMTshows (12,000+ followers) and a tweet from @FollowCMT (89,000+ followers). In all, it is estimates that these messages reached a total of 127,137 Twitter users. Along with the music contest, NIDA is planning events around the country to be held during NDFW and is pro-actively pitching a National Drug IQ Challenge Quiz for magazine and website placement.

International AIDS Society Conference
In support of the 6th International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention held July 17-20, 2011 in Rome, Italy, Dr. Nora Volkow and Dr. Jacques Normand contributed entries to the IAS blog, which posted on the days they spoke during the conference. NIDA posted tweets on its Twitter account to promote the IAS conference, NIDA presentations, and blogs.

Dr. Normand participated in a media training for approximately 40 journalists attending the conference in which he informed reporters about the multiple links between drug abuse and

HIV/AIDS and strategies to prevent HIV transmission. NIDA's Public Information and Liaison Branch prepared "plain language" talking points and slides for this presentation, which included NIDA's "Learn the Link" public service announcements (PSAs). In addition, Dr. Volkow participated in the official IAS closing press conference, and 100 press packets that included HIV/AIDS materials and a CD ROM of the "Learn the Link" PSAs were prepared for distribution to reporters on-site.

PRESS RELEASES

March 14, 2011
Mind games! NIH teaches kids about the power of the human brain
Brain Awareness Week activities to be held March 16-17

Inquisitive students and their teachers from the Washington, D.C., area will explore the fascinating and multifaceted human brain at the 12th annual Brain Awareness Week celebration at the National Museum of Health and Medicine, Walter Reed Army Medical Center, on March 16 and 17. Students in grades 5 through 8 will engage in interactive activities sponsored by six institutes from the National Institutes of Health that focus on brain health and research. Students and teachers will see an actual human brain and talk with NIH scientists about how the brain works to create the human experience, as well as careers students might explore in the neuroscience field. Brain Awareness Week is an annual international partnership of government agencies, scientific organizations, and university and volunteer groups. It was begun 16 years ago by the Dana Alliance for Brain Initiatives, a nonprofit organization of more than 200 preeminent neuroscientists dedicated to advancing brain education.

April 5, 2011, 4:00 p.m. ET
Analysis of opioid prescription practices finds areas of concern
NIH report could lead to improved strategies for pain management

An analysis of national prescribing patterns shows that more than half of patients who received an opioid prescription in 2009 had filled another opioid prescription within the previous 30 days. This report also suggested potential opportunities for intervention aimed at reducing abuse of prescription opioids.

Researchers from the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health, will publish results of this analysis in this week's Journal of the American Medical Association (JAMA). "More research is needed to see if current practices are working, with a closer look at why so many patients are getting multiple prescriptions within a short period of time," said NIDA Director Nora D. Volkow, M.D. "As a nation, it is important that we all become better informed about effective pain management and the risks of abusing prescription painkillers." This analysis comes on the heels of a nearly 20 year increase in the use of prescription

painkillers. From 1991 to 2009, prescriptions for opioid analgesics increased almost threefold, to over 200 million. According to the Drug Abuse Warning Network system, which monitors drug related emergency department visits and drug-related deaths, emergency room visits related to the nonmedical use of pharmaceutical opioids has doubled between 2005 and 2009. While these medications are crucial for pain management, their wide availability may also result in leftover pills in family medicine cabinets, increasing opportunities for abuse, as well as a host of serious medical consequences, including addiction. Most abusers report getting these medications from friends and relatives who had been prescribed opioids, or they are abusing their own medications. This study used data from SDI's Vector One National database, a privately owned national-level prescription and patient tracking service. The sample included 79.5 million prescriptions dispensed in the United States during 2009, which represent almost 40 percent of all the opioid prescriptions filled nationwide. They broke down the prescriptions by physician specialty, patient's age, duration of prescription, and whether or not the patient had previously filled a prescription for an opioid analgesic within the past 30 days. The researchers looked at prescribing practices for younger patients, who are more at risk than older adults for opioid abuse and later addiction.

The records show that approximately 56 percent of painkiller prescriptions were given to patients who had filled another prescription for pain from the same or different providers within the past month. In addition, nearly 12 percent of opioids prescribed were to young people aged 10-29. Most of these were hydrocodone- and oxycodone-containing products, like Vicodin and Oxycontin. Dentists were the main prescribers for youth aged 10-19 years old. Nearly 46 percent of opioid prescriptions were given to patients between ages 40 and 59, and most of those were from primary care providers.

The current issue of JAMA also includes an accompanying commentary from Dr. Volkow and Dr. Thomas McLellan of the University of Pennsylvania School of Medicine. They point out that according to the Centers for Disease Control and Prevention, prescription opioid overdose is now the second leading cause of accidental death in the United States, killing more people than heroin and cocaine combined. They also state that this is compelling evidence for the need to develop smart strategies to curtail abuse of opioid analgesics, without jeopardizing pain treatment. The analysis can inform policy makers wanting to implement systems to reduce opioid abuse. Already many states are looking at prescription drug monitoring programs that will give physicians access to information on prescriptions previously received by their patients.
The research letter and commentary can be found online beginning April 6 at http://jama.amaassn.org/. For the NIDAMED website, "Resources for Medical and Health Professionals," go to http://www.drugabuse.gov/nidamed/.

April 8, 2011
New warm line helps clinicians tackle patients' substance abuse
NIH and ASAM launch new screening resources

A free, nationwide service was launched today to help primary care providers seeking to identify and advise substance-abusing patients. The service, Physician Clinical Support System for

Primary Care (PCSS-P), offers peer-to-peer mentorship and resources on incorporating screening and follow-up into regular patient care. PCSS-P is a project of the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health, and the American Society of Addiction Medicine (ASAM). NIDA also launched a quick screening tool to help health care providers identify these patients.

The warm line service—"warm" because the response is within 24 hours rather than an immediate response typical of a hotline—is available to physicians and other health care providers at no cost. Providers register with PCSS-P and receive the contact information of a mentor who is a specialist in screening, brief intervention, treatment and referral for patients with substance abuse problems. Mentors can then be contacted, via phone or email, with specific questions about clinical situations involving alcohol, drugs, and tobacco. To take advantage of the service, physicians can call PCSS-P at 877-630-8812, or register online at www.PCSSmentor.org.

The service is an extension of NIDAMED, NIDA's initiative to give health care professionals the tools and resources to screen their adult patients for tobacco, alcohol, and drug use. The initiative stresses the importance of the patient-doctor relationship in identifying unhealthy behaviors before they evolve into life threatening conditions. NIDA's Quick Screen is an online interactive single-question screen that asks, "In the past year, how many times have you used the following: alcohol (more than 4 or 5 drinks in a day for women or men, respectively); tobacco products; prescription drugs for nonmedical reasons; and illegal drugs?" If a patient indicates past year use of illegal drugs, or prescription drugs for nonmedical reasons, the clinician has the option of conducting NIDA's full screening tool for the specific drugs abused.
"Primary care providers can be the first line of defense against substance abuse and addiction but they need the right tools and resources," said NIDA Director Dr. Nora D. Volkow. "Our NIDAMED screening tool is a user-friendly, interactive means to help providers quickly screen their patients for drug abuse. PCSS-P goes a step further, providing peer-to-peer mentorship in the use of these resources." PCSS-P builds on the success of other warm line models offering peer-to-peer advice on using buprenorphine and methadone to treat opioid dependence. This new warm line is targeted to primary care providers and offers help as providers introduce drug abuse screening into their practices. NIDAMED resources include a companion quick reference guide and a comprehensive resource guide for clinicians. The NIDAMED resources, including the Quick Screen, can be found at http://www.nida.nih.gov/nidamed/.

April 18, 2011
NIDA raises the curtain on addiction
"Addiction Performance Project" premiers for clinicians

The National Institute on Drug Abuse (NIDA) announced today the launch of its Addiction Performance Project, an innovative continued medical education program designed to help primary care providers break down the stigma associated with addiction. The program includes dramatic interpretation of a family's struggle with addiction, followed by a dialogue among participants aimed to foster compassion, cooperation, and understanding for patients living with this disease.

Of the 23.5 million patients who needed specialized treatment for a drug or alcohol problem in 2009, nearly 90 percent had not received it. Research suggests that primary care providers could significantly help reduce drug use, before it escalates to abuse or addiction. However, many express concern that they do not have the experience or tools to identify drug use in their patients. "Primary care providers can play such a vital role in screening for drug abuse, said NIDA Director Dr. Nora D. Volkow. "Yet, for many providers, discussing drug abuse with their patients is beyond their comfort zone. NIDA's Addiction Performance Project is a creative way for doctors to earn CME credit while breaking down the stigma associated with drug addiction." Each performance begins with a dramatic reading of Act III of Eugene O'Neill's Long Day's Journey into Night. The Washington, D.C., launch performance took place this past Saturday, featuring Blythe Danner rea ding the part of Mary Tyrone, the morphine-addicted matriarch of a family devastated by addiction, and Harris Yulin as James Tyrone, Mary's husband. Readings are followed by an expert panel reaction and facilitated audience discussion that fosters compassion, cooperation, and understanding for addicted patients and their families. Expert panelists for the D.C. performance included NIDA Director Nora D. Volkow, M.D., Jeffrey Baxter, M.D., of the University of Massachusetts Medical School and Dr. Robert Taylor, M.D., the dean of Howard University Medical School, Washington, D.C.

Addiction Performance Project is part of NIDAMED, NIDA's outreach to practicing physicians, physicians in training, and other health professionals. It has a limited run during 2011 and 2012, with the next scheduled performance in Phoenix, AZ. on May 6, 2011. Performances are free, but seating is limited, and registration is recommended. Attendees do not have to be registrants at the conferences where some performances take place. For more information on the Addiction Performance Project, or to register for a performance, visit: http://www.drugabuse.gov/nidamed/APP.

May 2, 2011
Moderate levels of secondhand smoke deliver nicotine to the brain
NIH-funded study shows how secondhand smoke may increase vulnerability to nicotine addiction

Exposure to secondhand smoke, such as a person can get by riding in an enclosed car while someone else smokes, has a direct, measurable impact on the brain—and the effect is similar to what happens in the brain of the person doing the smoking. In fact, exposure to this secondhand smoke evokes cravings among smokers, according to a study funded by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health.

The study, published today in Archives of General Psychiatry, used positron emission tomography (PET) to demonstrate that one hour of secondhand smoke in an enclosed space results in enough nicotine reaching the brain to bind receptors that are normally targeted by direct exposure to tobacco smoke. This happens in the brain of both smokers and non-smokers.

Previous research has shown that exposure to secondhand smoke increases the likelihood that children will become teenage smokers and makes it more difficult for adult smokers to quit. Such associations suggest that secondhand smoke acts on the brain to promote smoking behavior.

"These results show that even limited secondhand smoke exposure delivers enough nicotine to the brain to alter its function," said NIDA Director Nora D. Volkow, M.D. "Chronic or severe exposure could result in even higher brain nicotine levels, which may explain why secondhand smoke exposure increases vulnerability to nicotine addiction."
"This study gives concrete evidence to support policies that ban smoking in public places, particularly enclosed spaces and around children," said Arthur Brody, M.D., of the UCLA Department of Psychiatry & Biobehavioral Sciences and corresponding author for the article.

The Surgeon General's Report concluded in 2006 that secondhand smoke causes heart disease and lung cancer in nonsmoking adults and many serious health conditions in children, including sudden infant death syndrome, respiratory infections, and more severe asthma. According to the CDC, almost 50,000 deaths per year can be attributed to secondhand smoke. For more information or for resources to help quit smoking, go to http://www.nida.nih.gov/DrugPages/Nicotine.html. The study can be found online at: http://archpsyc.ama-assn.org/.

May 9, 2011
NIH, MusiCares®, GRAMMY Foundation® announce 2011 Teen contest
Original music and music video competition part of National Drug Facts Week

Today marks the launch of the second annual MusiCares® and GRAMMY Foundation® Teen Substance Abuse Awareness through Music Contest. Announced by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health, along with MusiCares and the GRAMMY Foundation—the two nonprofit organizations of The Recording Academy®—the contest asks young musicians, ages 14-18, to compose or create an original song and/or music video that explores, encourages, and celebrates a healthy lifestyle or accurately depicts a story about drug abuse. Winners will be revealed during NIDA's second annual National Drug Facts Week, which begins Oct. 31, 2011.

"The quality of last year's entries was so impressive that the contest is launching earlier this year to give more students a chance to participate," said NIDA Director Dr. Nora D. Volkow. "This competition gives teens a unique opportunity to express and share their feelings and experiences about how living a drug-free life helps them navigate their way safely into adulthood."

"When we launched this contest last year, we thought it would be an ideal way to showcase aspects of our nonprofit missions—music education for young people for the GRAMMY Foundation and health and human services and addiction recovery for MusiCares," said Neil Portnow, president/CEO of the GRAMMY Foundation, MusiCares, and The Recording Academy®**.** "The submissions from teens were so powerful and moving that we are eager to see the results of this year's campaign, and continue to spread the word to young people about the toll of addiction and the benefits of a healthy lifestyle."

The first place winner will be invited to Los Angeles to attend the 54th annual GRAMMY Awards® Backstage Experience, a special backstage tour that takes place while artists rehearse for the live GRAMMY® Awards. In addition, the first, second and third place winners will have

their musical entries posted on the GRAMMY365® website and the MTV Act blog, as well as on the Above the Influence campaign site sponsored by the National Youth Anti-Drug Media Campaign—a program of the White House Office of National Drug Control Policy. All winners will receive a small cash award from the Visions Adolescent Treatment Center in Malibu, Calif., and a certificate from NIDA acknowledging their role in the dissemination of health information about substance abuse. NIDA will provide technical expertise in the judging process, with points given for an accurate depiction of the subject matter. Original music compositions or compositions with accompanying videos must be sent to MusiCares postmarked no later than Monday, Oct.10, 2011. Entries must be no more than three minutes long. More information can be found on the National Drug Facts Week website: http://drugfactsweek.drugabuse.gov.

May 13, 2011
Altruistic decision making focus of NIDA's Addiction Science Award
New York high school senior looks at the behavioral economics of intergenerational preferences

A study of what influences decision making on issues whose consequences will only be felt by future generations won first prize in the annual Addiction Science Awards at this year's Intel International Science and Engineering Fair (ISEF) -- the world's largest science competition for high school students. The Intel ISEF Addiction Science Awards were presented at an awards ceremony Thursday night in Los Angeles. The awards were presented by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health, and Friends of NIDA, a coalition that supports NIDA's mission.

First place distinction went to Sarah Susie Pak, a 17-year-old senior at Roslyn High School in Roslyn Heights, N.Y., for her project *Would You Do It for the Kids?* Factors Involved in the Prediction of Intergenerational Preferences. The project was based on well-known phenomenon, called delayed discounting, in which people tend to discount the value of a reward that will be received at a later time vs. an immediate, but smaller, reward. Delayed discounting is abnormally high in people who are addicted to drugs and contributes to their impulsive risk taking behaviors, especially drug use. Pak's project identified generosity and patience as two key interacting factors that increase the likelihood that a person will make altruistic decisions that will primarily help future generations. The senior plans to attend Princeton in the fall. "Our first place winner took a fresh look at delayed discounting at the social and generational level," said NIDA Director Dr. Nora D. Volkow. "Her studies illuminate aspects of neuroeconomics that are relevant not only to drug abuse and addiction, but that could have far reaching social, ethical, and public health policy implications."

Second place distinction in the Addiction Science Awards went to Darby Kathryn Schumacher, a 15-year-old freshman at the Girls Preparatory School in Chattanooga, Tenn. Her project, *Making Heartbeats Go LOKO*, investigated the effects of the alcoholic caffeinated beverage branded as Four Loko on the heart rate of the water flea (Daphnia). She chose to use this invertebrate model to test the effects of Four Loko not only because Daphnias show clear signs of intoxication when exposed to alcohol, but also because their heart rate can be easily monitored through their translucent bodies. She was able to demonstrate that alcohol, a depressant, and caffeine, a stimulant, can lower and boost Daphnia's heart rate, respectively. The caffeine content in Four

Loko appears to have partially mitigated the depressant effect of the alcohol present in this beverage, supporting the notion that the caffeine in alcoholic energy drinks could mask some of alcohol's behavioral effects, making the user less aware of the true extent of their impairment. "Ms. Schumacher took a simple model of a nervous system that recreates some of the most basic features of human physiology to show how the combination of a stimulant and a depressant can affect heart function," said Dr. Susan Weiss, NIDA's head judge and acting director of the Office of Science Policy and Communications. "She took a systematic and elegant approach to demonstrate why these drinks can be dangerous." The U.S. Food and Drug Administration issued warning notices to manufacturers of caffeinated alcoholic beverages in November 2010.

Third place went to 16-year-old Yamini T. Naidu, a student at Valley Catholic High School in Beaverton, Ore., for her entry, *From Models to Medications: Identification of Medication Leads for Treating Methamphetamine Addiction*. Using molecular modeling software that incorporated eye-catching 3D structural illustrations and vivid computer animations, Naidu discovered two potential sites in the methamphetamine binding TAA receptor. Her work predicted that these sites could have the ability to modulate the binding affinity of methamphetamine for this receptor. This work has resulted in the development of several lead compounds that are the subject of pending patents for possible novel medications for methamphetamine addiction. There are currently no medications approved for the treatment of methamphetamine addiction; thus, these lead compounds represent a potentially exciting new development in the addiction treatment field. The sophomore says she became interested in neuroscience after her uncle died of a stroke.

The non-profit organization, Friends of NIDA, partnered with NIDA to sponsor the awards as part of its ongoing support of NIDA research into the causes, consequences, and treatment of drug abuse and addiction. "We are delighted to see three young women win this year, and we hope these awards encourage them to continue their interest in addiction science," said Dr. William Dewey, Louis S. and Ruth S. Harris Professor and Chair, Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, and president and chair of the Executive Committee, Friends of NIDA. The awards were judged by Dr. Weiss, NIDA's Dr. Ruben Baler, and Dr. Walter Ling, a NIDA grantee at the University of California at Los Angeles, which hosted the fair. This year, about 1,500 students from 63 countries participated in the Intel ISEF competition, coordinated by the Society for Science and the Public, at the Los Angeles Convention Center. The nonprofit organization Society for Science and the Public partners with Intel - along with dozens of other corporate, academic, government and science-focused sponsors - to provide support and awards each year. Winners received cash awards provided by Friends of NIDA in a ceremony, with a $2,500 scholarship for the first-place honoree. NIDA has developed a special section on its website, which includes other resources on addiction science, to showcase the winning projects and to help science fair entrants understand the criteria for the awards: http://www.nida.nih.gov/sciencefair.

June 9, 2011
Potential new target for smoking cessation without weight gain
NIH-fund ed study identifies brain pathway in rodents that could be target of new treatments for smoking and weight control

A new study uncovers a brain mechanism that could be targeted for new medications designed to help people quit smoking without gaining weight. This research, funded by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health, shows that a specific subclass of brain nicotinic receptor is involved in nicotine's ability to reduce food intake in rodents. Prior research shows that the average weight gain after smoking is less than 10 pounds, but fear of weight gain can discourage some people who would like to quit.

In the study, to be published in the June 10 issue of Science, researchers found that a nicotinelike drug, cytisine, specifically activated nicotinic receptors in the hypothalamus - a brain center that controls feeding. This resulted in the activation of a circuit that reduced food intake and body fat in a mouse model. This effect was very specific, since a drug that prevented cytosine from binding to its hypothalamic receptors blocked the reduction in food intake.
Through the use of tobacco, nicotine is one of the most heavily used addictive drugs and the leading preventable cause of disease, disability, and death in the United States. According to the Centers for Disease Control and Prevention, cigarette smoking results in more than 440,000 preventable deaths each year – about 1 in 5 U.S. deaths overall. Despite the well-documented health costs of smoking, many smokers report great difficulty quitting.
"These mouse models allow us to explore the mechanisms through which nicotine acts in the brain to reduce food intake," said Dr. Marina Picciotto, of Yale University, New Haven, Conn. and senior author for the article. "We found that nicotine reduced eating and body fat through receptors implicated in nicotine aversion and withdrawal rather than reward and reinforcement."
"These results indicate that medications that specifically target this pathway could alleviate nicotine withdrawal as well as reduce the risk of overeating during smoking cessation," said NIDA Director Dr. Nora D. Volkow. "Although more research is warranted, such a highly selective compound might be more effective than drugs that act on more than one type of nicotinic receptor."

For information on tips to maintain a healthy weight while quitting smoking go to Forever Free: Smoking and Weight, a publication of the National Cancer Institute. For additional information on resources to help quit smoking, go to www.nida.nih.gov/DrugPages/Nicotine.html and smokefree.gov. The study can be found online at: www.sciencemag.org/.

NIDA issued Notes to Reporters on the following topics:

June 16, 2011 — A NIDA-funded study published in *Nature Medicine* used a rat model of intractable pain — severe, chronic pain that common prescription painkillers cannot treat — to identify a new compound that reduced pain symptoms with little to no adverse effects. View study here www.nature.com/nm/journal/vaop/ncurrent/full/nm.2345.html.

June 21, 2011 —The entire publication series describing the 2010 Monitoring the Future Survey results are now available for immediate online access. View the publications here http://monitoringthefuture.org/pubs.html.
June 29, 2011 — A NIDA-funded study published in *Nature* used a cutting-edge optical technique to temporarily turn on and off specific brain circuits in mice, allowing scientists to see how these pathways contribute to reward-seeking behavior. View study at www.nature.com/.

July 1, 2011 — A new review, published today in The Journal of the American Dental Association, outlines steps dentists can take to help reduce potential sources for prescription painkiller abuse and to identify substance abusing patients and link them to treatment. A 2009 analysis showed areas of concern with respect to painkiller prescribing practices for specific types of health care providers, including dentists.

July 1, 2011 — "Drugged Driving: The Hidden Dangers," a free video now available online, brings together leading experts to discuss which drugs are most involved, challenges in roadside testing for drugged driving, and public safety programs to raise awareness of this issue. Available for free download at https://mctft.icfwebservices.com/webcasts/w.aspx?ID=619

July 12, 2011 — Titan Pharmaceuticals released the highlights of the results of a Phase III clinical trial demonstrating the safety and efficacy of Probuphine™ in reducing opioid abuse. View Titan press release here www.titanpharm.com/press/110711-Probuphine-phase3-data.htm.

July 14, 2011 — A NIDA-funded study published in *Science Magazine* using a rat model in which NIDA researchers have found a brain pathway, beginning in the brain's memory center and ending in its reward center, which could help explain how environmental cues become strong motivators in drug taking. View study at www.sciencemag.org/.

July 25, 2011-- A NIDA-funded study published in *Nature Neuroscience* which found that activating brain CB2 cannabinoid receptors in mice reduced cocaine self administration, as well as cocaine's ability to increase dopamine and stimulate motor activity. This finding suggests that brain CB2 receptors may play a much more prominent role in a variety of brain functions than previously recognized. View study at http://www.nature.com/neuro/index.html.

HIGHLIGHTS OF INTERVIEWS: March 2011 – July 2011

Time online — Dr. Nora Volkow was interviewed about substance abuse in gastric bypass surgery patients

NBC Today Show — Dr. Volkow was interviewed about prescription drug abuse among college students

JAMA podcast — Dr. Volkow was interviewed about JAMA research letter/commentary

LA Times – Dr. Volkow was interviewed about addiction vaccines

CNN – Dr. Volkow was interviewed about wiring of brain/technology

New York Times — Dr. Volkow was interviewed for profile piece in Science section and about buprenorphine treatment of pregnant women

Wall Street Journal — Dr. Phil Skolnick was interviewed on background about vaccines for cocaine and nicotine/tobacco addiction

NPR Diane Rehm Show – Dr. Volkow was interviewed about prescription drug abuse

New York Times — Dr. Lisa Onken was interviewed about DBT treatment

USA Today – Dr. Volkow was interviewed about cell phone research

Yahoo Sports – Dr. Ruben Baler was interviewed about steroid abuse

Reuters – Dr. Volkow was interviewed about prescription drug abuse and cell phone research

60 Minutes — Dr. Volkow was interviewed on background about vaccines and prescription pain medicine abuse.

American Medical News — Dr. Gaya Dowling was interviewed about NIDAMED

ABC News – online — Dr. David Shurtleff was interviewed about health consequences and prevalence of hallucinogens

Univision — Dr. Ruben Baler was interviewed about NicVax.

Australian TV – Dr. Kenzie Preston, Mr. Ian Craig, and Dr. David Epstein were interviewed about personal tracking devices for drug abusers/general addiction

San Diego Union-Tribune – Dr. Nicolette Borek was interviewed about prenatal drug exposure

Fort Worth Weekly — Dr. Marilyn Huestis was interviewed about K2/Spice

Other Educational Activities

NIH K-12 LAB Challenge

The NIH Office of Science Education has recently issued K-12 **L**essons **A**bout **B**ioscience Challenge 2011-12. Students, teachers, parents, scientists and science enthusiasts are encouraged to submit engaging, inexpensive experiments for use in the K-12 classroom by December 1, 2011. NIH will review the experiments submitted and winners will be announced on March 2, 2012. Winners will receive an electronic badge and their name and experiment will appear in the free online collection of experiments. This initiative is part of NIH's efforts to bring engaging science to the classroom. NIDA, represented by Dr. Cathrine Sasek, is one of the key institutes involved in organizing this science education effort. More information is at: http://LAB.challenge.gov.

ARTICLES OF INTEREST

May, 2011. *Monitor on Psychology,*42 (5), p. 36. "New Research, new insights—Change your thinking, change your brain." Interview with Dr. Karen Sirocco and Dr. Cheryl Anne Boyce. In anticipation of the NIDA-sponsored plenary session on executive control at the American

Psychological Association 2011 annual convention, Drs. Sirocco and Boyce were interviewed on the importance of executive control and the promise of interventions based on developmental neuroscience and behavior. (http://www.apa.org/monitor/2011/05/plenary-speakers.aspx)

TN's 10th Anniversary Booklet, titled "Bridging the Gap between Research and Practice: National Drug Abuse Treatment Clinical Trials Network – The First Decade", won a Gold Level Award for Plain Language and Clear Communication (PL/CC) in NIH Publications. This booklet commemorates the CTN's 10th Anniversary and aims to inform diverse audiences about key CTN scientific accomplishments and their impact to improve drug abuse treatment practice. Authors Harold Perl, Gaya Dowling, Jennifer Elcano, Mary Ellen Michel, Cindy Miner, Joan Nolan, Betty Tai, and Susan Weiss were recognized at the May 17, 2011 awards ceremony on the NIH Campus in Bethesda, MD.

Research currently being conducted in the Treatment Section of the NIDA IRP was highlighted on the Radio New Zealand science show "This Way Up: Slices of Life for Curious Minds," in a segment called "Tracking drug users with GPS," on Saturday July 16, 2011. The work described is part of a project funded by a U01 in the NIH Genes and Environment Initiative in which we are developing field tools to measure environmental exposure to psychosocial stress and illicit drugs. Heroin/cocaine users in outpatient opioid agonist therapy carry GPS units and make self-reports of their mood, activities, drug use, and stress on electronic diaries as they go about their daily lives for about 20 weeks. We are combining the participants' real-time self-report and location data with information characterizing the city and surrounding counties on socioeconomic variables, physical disorder, crime, and presence of illicit drugs. We will use these data to conduct a more fine-grained analysis of the effects of environment and stress on drug use and relapse. The show can be heard on the web: http://www.radionz.co.nz/thiswayup.

RECENT AND UPCOMING CONFERENCES/EXHIBITS

American Psychological Association Annual Convention--August 4-7, 2011--Washington, DC

National HIV Prevention Conference -- August 14-17, 2011 – Atlanta, GA

National Conference on Addiction Disorders, NAADAC: The Association for Addiction Professionals -- September 17-22, 2011 -- San Diego, CA

Latino Behavioral Health Institute Conference --September 14-16, 2011 – Universal City, CA

American Academy of Child & Adolescent Psychiatry and Canadian Academy of Child & Adolescent Psychiatry Joint Annual Meeting -- October 18-23, 2011 -- Toronto, Canada

139th American Public Health Association Annual Meeting and Exposition
October 29-November 2, 2011 -- Washington, DC

Society for Neuroscience 2011 -- November 12-16, 2011 -- Washington, DC

American Academy of Addiction Psychiatry Meeting --December 8-11, 2011--Scottsdale, AZ

PLANNED MEETINGS

Dr. Yu (Woody) Lin of DCNBR is organizing a symposium entitled **Toward Evidence-based and Personalized Analgesic Medication**. The meeting is sponsored by the NIDA Prescription Opioid and Pain Workgroup and NIDA's DCNBR, and will be held in Bethesda, MD on September 14, 2011.

The next **National CTN Steering Committee Meetings** will be held September 26-28, 2011 in Bethesda, Maryland.

Dr. Paul Wakim and biostatisticians from CTN's Data and Statistics Center have organized a workshop entitled **Determining Stimulant Drug Use by Combining Results from Timeline Follow-Back and Urine Drug Screening**. This workshop will compare several algorithms to determine drug use, which is the primary outcome in most CTN trials. The workshop will be held on September 26, 2011, in conjunction with the CTN Steering Committee meetings.

Dr. Cheryl Anne Boyce and Dr. Sarah Lynne-Landsman (NIDA SRCD/AAAS Fellow) will co-chair a DCNBR workshop entitled **Integrating Neuroscience and Adolescent Substance Abuse Treatment** on September 27, 2011 in Rockville, MD. The meeting will highlight presentations from research grants funded by the NIDA RFA-DA-10-003: "Integrating Translational Neuroscience and Adolescent Drug Abuse Treatment." The meeting will convene multidisciplinary researchers to facilitate translational research that integrates findings from research on brain development, cognition and neuroscience into the development of innovative and effective, developmentally sensitive drug abuse treatments for adolescents.

NIDA will once again conduct the **Frontiers in Addiction Research NIDA Mini-convention** just prior to the Society for Neuroscience Meeting, November 11, 2011. This year's meeting will include thematic sessions on: Autism, Addiction, and MeCP2; Using Optogenetic Tools to Shed Light on the Neural Mechanisms of Addiction; Synapse Organization and Plasticity in Drug Addiction; and Neurobiology of Behavioral and Emotional Regulation/Dysregulation. In addition, the Early Career Investigators Poster Session and Lunch and the announcement of, and presentation by, the 2011 Jacob P. Waletzky Memorial Award Recipient will take place during the meeting. Registration and additional information is available at https://www.seiservices.com/nida/2011sfn/.

NIDA will conduct an **NIH Grant Workshop for Early Career Investigators** on November 14, 2011 at the annual meeting of the Society for Neuroscience. The goal is to provide information to those seeking predoctoral or postdoctoral NRSAs or early career mentored awards, including the F31, F32, K99/R00, K01, K08, K23, and independent research grants (R01, R21, R03, DP1 / Early Investigator Award). NIDA staff will also present material on writing an application and the review process for these types of awards. NIDA staff involved include Albert Avila, Harold Gordon, Eliane Lazar-Wesley, Roger Sorensen, and Nancy Pilotte.

PUBLICATIONS

NIDA PUBLICATIONS

CTN-RELATED PUBLICATIONS

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

Ghitza UE, Sparenborg S, Tai B. Improving drug abuse treatment delivery through adoption of harmonized electronic health record systems. Subst Abuse Rehabilitation. 2011 Jul; (2): 125-131.

Tai B, Sparenborg S, Liu D, Straus M. The National Drug Abuse Treatment Clinical Trials Network: Forging a Partnership between Research Knowledge and Community Practice. Subst Abuse Rehabilitation 2011 Mar; (2): 21-28.

INTERNATIONAL PROGRAM-RELATED PUBLICATIONS

Journal Supplement Examines the Global Impact of Volatile Substance Misuse
In response to the global demands for increased research to support the development of evidence-based policies and interventions on inhalant abuse, NIDA IP sponsored the publication of a special issue of the journal *Substance Use & Misuse.* The supplement, *Volatile Substance Misuse: A Global Perspective*, contains 20 peer-reviewed articles by authors from 12 nations, presenting data from countries where inhalant abuse was previously underdocumented, as well as from countries reporting inhalant use among school populations; discussing medical complications of inhalant abuse and the potential for central nervous system recovery with abstinence; and describing successful interventions that address inhalant abuse based on cultural understandings.

International Program-Related Publications

2010 Annual Report
The NIDA IP 2010 annual report describes the interconnected initiatives that the IP supports to promote research, build international research capacity, and exchange scientific information with countries, organizations, and individual researchers around the world. It lists collaborative research partnerships that stimulate new approaches to addiction research and treatment by blending the partners' unique perspectives into shared solutions, and reports on former NIDA IP fellows who play influential roles in the drug abuse research community by directing university programs, leading policy initiatives, and winning recognition for their research.

NIDA International Program E-News
- *June 2011* – This issue introduces the new IP Web site, announces the IP journal supplement on inhalant abuse, reports on NIDA-supported events at the Society for Prevention Research and American Society of Addiction Medicine annual meetings, and describes international

collaborative research projects funded in fiscal year 2010 under the NIDA International Program Announcements.

- *August 2011* – This issue announces new cooperative agreements with Mexico Spain, and Italy, including the new U.S. – Mexico Prevention Research Fellowship and a new U.S. – Spain research exchange program. Other stories detail new research awards for projects funded in fiscal year 2011 by the U.S.- Netherlands Binational Agreement or the NIDA International Program Announcements.

IP Introduces New Web Site

NIDA IP unveiled its redesigned Web site in June 2011 with new features for more direct access to information essential to the international drug abuse research community. The redesigned site features navigation that makes it easier to find information on NIDA IP funding opportunities, fellowships, tools, and information, with news and announcements now featured prominently on the site's home page. A new keyword feature allows for faster access to information by topic area. Web site visitors are encouraged to use the new "share" button to share information found on the site with their social media networks including Facebook, Twitter, LinkedIn, and StumbleUpon.

Other Publications

Baladi MG, Newman AH, France CP. Influence of body weight and type of chow on the sensitivity of rats to the behavioral effects of the direct-acting dopamine receptor agonist quinpirole. Psychopharmacology, 2011, e-pub May 5, 2011.

Banala AK, Levy BA, Khatri SS, MishraY, Griffin SA, Luedtke RR, Newman AH. N-(3-Fluoro-4-(4-(2-methoxy or 2,3-dichlorophenyl) piperazine-1-yl)-butyl)-aryl carboxamides as Selective Dopamine D3 Receptor Ligands: Critical Role of the Carboxamide Linker for D3 Receptor Selectivity. J. Med. Chem. 2011; 54: 3581-3694.

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. Epub 2010 Jul 2.

Collins GT, Cunningham AR, Chen J, Wang S, Newman AH, Woods JH. Effects of Pramipexole on the reinforcing effectiveness of stimuli that were previously paired with cocaine reinforcement in rats. Psychopharmacology, 2011, e-pub June 24, 2011.

Czobor P, Skolnick P. The secrets of a successful clinical trial: compliance, compliance, and compliance. Mol Interv. 2011 Apr; 11(2): 107-110. PubMed PMID: 21540470; PubMed Central PMCID: PMC3109858.

Drgon T, Johnson CA, Nino M, Drgonova J, Walther DM, Uhl GR. ."Replicated" genome wide association for dependence on illegal substances: genomic regions identified by overlapping clusters of nominally positive SNPs. Am J Med Genet B Neuropsychiatr Genet. 2011 Mar; 156(2): 125-388.

Garcés-Ramírez L, Green JL, Hiranita T, Kopajtic TA, Mereu M, Thomas A, Mesangeau C, Narayanan S, McCurdy CR, Katz JL, Tanda G. Sigma receptor agonists: Receptor binding and effects on mesolimbic dopamine neurotransmission assessed by microdialysis in rats. Biological Psychiatry 2011; 69: 208–217.

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). 2011 Jul 1.

Hall FS, Schwarzbaum JM, Perona MT, Templin JS, Caron MG, Lesch KP, Murphy DL, Uhl GR. A greater role for the norepinephrine transporter than the serotonin transporter in murine nociception. Neuroscience. 2011 Feb 23; 175: 315-327.

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Ide S, Minami M, Uhl GR, Satoh M, Sora I, Ikeda K. (-)-Pentazocine induces visceral chemical antinociception, but not thermal, mechanical, or somatic chemical antinociception, in μ-opioid receptor knockout mice. Mol Pain. 2011 Apr 10; 7: 23.

Kitanaka J, Kitanaka N, Hall FS, Uhl GR, Tatsuta T, Morita Y, et al., Histamine H(3) Receptor Agonists Decrease Hypothalamic Histamine Levels and Increase Stereotypical Biting in Mice Challenged with Methamphetamine. Neurochem Res. 2011 May 15.

Koffarnus MN, Katz JL. Response requirement and increases in accuracy produced by stimulant drugs in a 5-choice serial reaction-time task in rats. Psychopharm 2011; 213: 723–733.

Koffarnus, MN, Newman, AH, Grundt P, Rice KC, Woods, JH. Effects of selective dopaminergic compounds on a delay discounting task. Behav. Pharm. 2011, e-pub June 20, 2011.

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 Pharm Biochem Behav. 2011 Jun 15.

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 Apr 25; 6(4): e19179.

Li S-M, Kopajtic TA, O'Callaghan MJ, Agoston GE, Cao J, Newman AH, Katz JL. N-Substituted benztropine analogs: Selective dopamine transporter ligands with a fast onset of action and minimal cocaine-like behavioral effects. JPET 2011; 336: 575-585.

Luo AH, Tahsili-Fahadan P, Wise RA, Lupica CR, Aston-Jones G. Linking context with reward: a functional circuit from hippocampal CA3 to ventral tegmental area. Science, 2011 Jul 15; 333(6040): 353-357.

Munafò MR, Johnstone EC, Walther D, Uhl GR, Murphy MF, Aveyard P. CHRNA3 rs1051730 Genotype and Short-term Smoking Cessation. Nicotine Tob Res. 2011 Jun 20.

Perles-Barbacaru TA, Procissi D, Demyanenko AV, Hall FS, Uhl GR, Jacobs RE. Quantitative pharmacologic MRI: mapping the cerebral blood volume response to cocaine in dopamine transporter knockout mice. Neuroimage. 2011 Mar 15; 55(2): 622-628.

Purohit V, Rapaka RS, Schnur P, Shurtleff D. Potential impact of drugs of abuse on mother-to-child transmission (MTCT) of HIV in the era of highly active antiretroviral therapy (HAART). Life Sci. 2011 23; 88: 909-916.

Purohit V, Rapaka R, Shurtleff D. Drugs of Abuse, Dopamine, and HIV-Associated Neurocognitive Disorders/HIV-Associated Dementia. Mol Neurobiol. 2011; 44(1): 102-110.
Ramachandra V, Kang F, Kim C, Nova AS, Bajaj A, Hall FS, Uhl GR, Gonzales RA. The mu opioid receptor is not involved in ethanol-stimulated dopamine release in the ventral striatum of C57BL/6J mice Alcohol Clin Exp Res. 2011 May; 35(5): 929-938.

Robertson EB, Ginexi EM. Translating Research on Inhibitory Control for Prevention of Drug Abuse, in Inhibitory Control and Drug Abuse Prevention edited by Michael T. Bardo, Diana H. Fishbein and Richard Milich 3-9, Springer Science Business Media, 2011.

Soto PL, Grandy DK, Hursh SR, Katz JL. Behavioral economics of food reinforcement and the effects of prefeeding, extinction, and eticlopride in dopamine D2 receptor mutant mice. Psychopharmacology 2011; 215: 775–784.

Suto N, Wise RA, Vezina P. Dorsal as well as ventral striatal lesions affect levels of intravenous cocaine and morphine self-administration in rats. Neurosci Lett. 2011 Apr 8; 493(1-2): 29-32.

Uhl GR, Walther D, Behm FM, Rose JE. Menthol Preference Among Smokers: Association With TRPA1 Variants. Nicotine Tob Res. 2011 Jun 30.

Wise RA, Kiyatkin EA. Differentiating the rapid actions of cocaine. Nat Rev Neurosci 2011 Jun 2; 12(8): 479-484.

The proceedings of the symposium entitled “Mother-to-Child Transmission of HIV and Drugs of Abuse in the Era of HAART”, organized by Vishnudutt Purohit, CPSRB/DBNBR, Rockville, Maryland, October 26-27, 2009, have been published in the journal of Life Sciences. Volume 88: 909-999, 2011. The editors of this publication are Vishnudutt Purohit, Rao S. Rapaka, Paul Schnur, and David Shurtleff.

Proceedings from the Workshop “Peptidome/Proteome to Genome/Phenome Bottleneck: Fishing for the hidden proteome in health and disease (drug abuse)” organized by Rao S. Rapaka, has appeared as Special Volume in AAPS Jouranl, and the Porceedings Volume is entitled “Fishing for the hidden preteome in helath and disease: Focus on drug abuse”. The volume is edited by Rapaka, Fricker and Sweedler

STAFF HIGHLIGHTS

Staff Honors and Awards

2011 NIDA DIRECTOR'S INNOVATOR AWARD

Redonna Chandler

In recognition of her outstanding contributions to increasing comparability of methods across disparate studies in order to enhance the value of HIV Seek, Test, and Treat grants

2011 NIDA DIRECTOR'S AWARDS

CENTER FOR THE CLINICAL TRIALS NETWORK

The CTN Treatment Effect and Assessment Measures (TEAM) Taskforce

Paul Wakim	Michelle Straus
Carmen Rosa	David Liu

In recognition of their leadership in bringing consensus among investigators and implementing common outcome measures/assessments to be used in CTN trials

DIVISION OF BASIC NEUROSCIENCE AND BEHAVIORAL RESEARCH

David Thomas

In recognition of your contributions to the NIDA Centers of Excellence for Pain Education, and your dedication and support to meet the mission of NIDA

John Satterlee

In recognition of your leadership in developing NIDA's Epigentics and Systems Biology Program

DIVISION OF CLINICAL NEUROSCIENCE & BEHAVIORAL RESEARCH

James Bjork

In recognition of your dedication, contributions, and support to meet the mission of NIDA in the advancing the understanding of human brain connectivity

NIDA American Psychological Association Committee

Meyer Glantz	Udi Ghitza	Harold Perl
Jane Acri	Sarah Landsman	Paul Schnur
Beth Babecki	Teresa Levitin	David Shurtleff
Lula Beatty	Minda Lynch	Belinda Sims
Cheryl Boyce	Carol Myers	Jane Smither
Aria Crump	Lisa Onken	Cecelia Spitznas
		Cora Lee Wetherington

In recognition of their contributions to the Dissemination of Drug Abuse Research to meet the mission of NIDADivision of Epidemiology, Services and Prevention Research

Kevin Conway

In recognition of your dedication, positive work ethic and extraordinary contributions to the mission of the National Institute on Drug Abuse

Data Harmonization Teams

Will Aklin	Bethany Deeds	David Liu	Joni Rutter
James Bjork	Kathy Etz	Marsha Lopez	Steven Sparenborg
Mark Caulder	Bennett Fletcher	Mary Ellen Michel	Larry Stanford
Redonna Chandler	Petra Jacobs	Ivan Montoya	Genevieve Vullo
Christine Colvis	Dionne Jones	Harold Perl	Paul Wakim
Kevin Conway	Shoshana Kahana	Kenzie Preston	

In recognition of their Seek, Test and Treat in Criminal Justice, NIDA Harmonization Project, and Secondary Data Analysis Project

DIV. OF PHARMACOTHERAPIES & MEDICAL CONSEQUENCES OF DRUG ABUSE

The DPMCDA Immunotherapy Program Team

Jamie Biswas
Nora Chang

In recognition of their dedication and contributions to the development of novel immunotherapies for the treatment of addictive disorders

The DPMCDA Informatics Program Restructuring Team

Robert Walsh
Richard Kline
David White

In recognition of their leadership in restructuring the DPMCDA Informatics Program

INTRAMURAL RESEARCH PROGRAM

Jennifer Bossert

In recognition of your outstanding contribution to the elucidation of the cortical mechanisms involved in context-induced drug relapse

NIDA Intramural and Extramural Collaboration

Massound Vahabzadeh	Kenzie Preston
Denise Pintello	Betty Tai

In recognition of their partnership to accelerate the translation of NIDA's research into substance abuse practice

NIDA IRP Mentoring Plan Task Force

Stephen Heishman	Alice Devolve
Mary Pfeiffer	Michelle Jobes
Annabelle Belcher	Vani Pariyadath
Sheine Schanuel	

In recognition of their exceptional leadership and vision in establishing a Mentoring Plan that will enhance the mentoring and training of postdoctoral fellows at NIDA IRP

NIDA OFFICE OF THE DIRECTOR

NIDA OD Team

Linda Thomas Susan Schlossberg Joan Deckow

In recognition of their outstanding team performance to support the Office of the Director and NIDA's mission

OFFICE OF EXTRAMURAL AFFAIRS

Scott Chen

In recognition of his dedication and innovations related to NIDA's involvement with smoking cessation initiatives and related activities.

The SRO/ESA Team

Gerald McLaughlin	Lyle Furr
Eliane Lazar-Wesley	Nadine Rogers
Jose Ruiz	Tanya Barnett
Minna Liang	Sonya Freeman
Scott Chen	Jason Hill

In recognition of dedication to grant and contract reviews and other contributions to NIDA in a time of high workload

OFFICE OF MANAGEMENT

Susan Cook

In recognition of her exceptional leadership, advisory and management skills

NIDA Renovation Workgroup

David Daubert	Chanvadey Nhim
Berhane Yitbarek	Renata Baginski
Donna Tolson	

In recognition of their significant administrative support efforts which contributed substantially towards the accomplishment of NIDA's mission

OFFICE OF SCIENCE POLICY AND COMMUNICATIONS

National Drug Facts Week Team

Carol Krause	Stephanie Older	Jane Smither
Susan Weiss	Sharan Jayne	Patricia Anderson
Gaya Dowling	Mark Fleming	Bukeeia Goodson
Jennifer Elcano	Geoffrey Laredo	Redonna Chandler
Elisabeth Davis	Jan Lipkin	Kimberly DiFonzo
Joan Nolan	Ruben Baler	Janet Linton
Brian Marquis	Cathrine Sasek	Aaron Martinek
Shirley Simson		

In recognition of their establishing an annual program of activities that foster multifaceted community involvement in drug abuse education

NIDA Director's Award for EEO, Diversity and Quality of Worklife

The NIDA IRP Diversity and Outreach Committee

Jean Lud Cadet	Susan Harrelson	Leslie Premo
Christie Brannock	Stephen Heishman	Kenzie Preston
David Epstein	Jonathan Katz	Toni Shippenberg
William Freed	Mary Lee	

In recognition of their commitment to creating diversity in science

Dr. Jane Acri, DPMCDA, received a distinguished service award from Division 28 (Psychopharmacology and Substance Abuse) of the American PsychologicAl Association in Washington, DC on August 4, 2011.

Dr. Lula Beatty, SPO, received the "Outstanding Alumnae Award" from Lincoln University on April 29, 2011 in Lincoln University, PA.

Dr. James Bjork, of DCNBR, received an NIH Plain Language Award on May 17, 2011.

IP director **Steven W. Gust, Ph.D.**, received the College on Problems of Drug Dependence (CPDD) J. Michael Morrison Award for outstanding contributions in the area of scientific administration related to drugs of abuse. The award was presented June 19, 2011, at the Plenary Session of the CPDD Annual Scientific Meeting held in Hollywood, Florida. Dr. Gust was cited for his service as NIDA IP director, which he has led since 1999, especially his expansion of research funding opportunities, fellowship and other capacity-building programs, and scientific exchange activities like the NIDA International Forum. The award also noted Dr. Gust's service as acting director of the NIDA Office on AIDS, from 1994 to 1998, where he brought national and international attention to the connections between drug use and AIDS, and the office was responsible for more than a third of the NIDA budget. Dr. Gust first joined NIDA in 1986, and has also served in the Clinical and Behavioral Pharmacology Branch and the Division of Applied Research.

Michelle Jobes, Ph.D., (Treatment Section), IRP, was a winner of a FARE (Fellows Award for Research Excellence) award for the second year in a row. FARE abstract submissions are rated by a study section on scientific merit, originality, experimental design, and overall quality/presentation. Dr. Jobes' submission, entitled "Drinking and Drug Use from a Prospective Perspective," reported on the relationships between alcohol consumption and other drug use and craving during day-to-day experiences as assessed in real time with ecological momentary assessment (EMA) in a prospective, longitudinal cohort study of heroin and cocaine users who did not meet DSM criteria for alcohol abuse or dependence. Analysis of electronic-diary entries showed that compared to entries collected at random time points throughout the day, the frequency of drinking was over two times higher in entries in which craving for cocaine and/or heroin was reported, and almost eight times higher when actual use of cocaine or heroin was reported. This prospective EMA study confirmed the association between alcohol and other drug use previously suggested by retrospective studies and showed that even among participants with low baseline rates of alcohol consumption, drinking was associated with other drug craving and actual use.

Dr. Harold Perl, CCTN, has been selected as one of three 2011 recipients of the American Psychological Association (APA) Meritorious Research Service Commendation. This Commendation was initiated by the APA Board of Scientific Affairs to recognize individuals who have made outstanding contributions to psychological science by enhancing opportunities and resources for the field through their service as employees of the federal government or other organizations. He was honored for his significant leadership contributions at NIDA and NIAAA.

Dr. Massoud Vahabzadeh, IRP, was listed as the first inventor for a PHS Employee Invention entitled "Extensible Platform for Motivational Incentives software system" filed March 3, 2011. Co-inventors include Dr. Kenzie L. Preston, William A. Elgie, Mustapha Mezghanni, and Dr. Jia-Ling Lin.

Staff Changes

Dr. Sarah Lynne –Landsman has successfully completed her Society for Research in Child Development (SRCD)/American Association for the Advancement of Science (AAAS) Executive Branch Fellowship at NIDA. She completed work in support of the integration of biomedical and behavioral research and policy in the NIDA Office of Science Policy and Communications (OSPC), NIDA Blending Initiative, Prevention Research Branch (PRB/DESPR), Behavioral and Brain Development Branch (BBDB/DCNBR) and NIDA Child and Adolescent Workgroup. She also participated in NICHD's Summer Institute in Applied Research in Child and Adolescent Development. In September, 2011 she will begin an appointment as a Research Assistant Professor at the University of Florida-Gainesville.

After many years of distinguished federal service as Chief of the Prevention Research Branch in DESPR, **Dr. Liz Robertson** will leave her position as Chief to become DESPR's Senior Advisor for Prevention beginning in July 2011. Dr. Robertson has moved the field of prevention science forward through applying a developmentally-based, bio- psycho- social approach to intervention theory and testing. Moreover, she has enriched the field through promoting and incorporating a framework for research activities that includes basic prevention, efficacy and effectiveness, implementation and dissemination, and methodology. In her new role, Dr. Robertson will continue to provide scientific advice and leadership to all of NIDA, particularly through her work on special projects that advance NIDA's prevention research mission.

Dr. Kevin Conway, Deputy Director of DESPR will serve as the Acting Chief of the Prevention Research Branch in addition to his role as Division Deputy.

Dr. Amy Newman was named Chief of the Molecular Targets and Medications Discovery Branch.

Dr. Shwe Gyaw joined the Clinical Medical Branch in the Division of Pharmacotherapies and Medical Consequences of Drug Abuse as a Medical Officer in May 2011.

Dr. Aidan Hampson joined the Medications Research Grants Branch in the Division of Pharmacotherapies and Medical Consequences of Drug Abuse as a Health Scientist Administrator.in June 2011.

Anna Staton, Science Policy Branch, Office of Science Policy and Communications, has accepted an advisor position with the Food and Drug Administration's Center for Devices and Radiological Health. Her work there will focus on risk communications related to a portfolio of medical devices.

GRANTEE HONORS

Deborah A. Frank, M.D., Boston University School of Medicine, was honored on May 31, 2011 as the inaugural incumbent of the Professorship in Child Health and Well-Being at Boston University School of Medicine. Dr. Frank graduated from Harvard Medical School in 1976 and completed her residency at Children's Orthopedic Hospital in Seattle, WA from 1976-1979. She served as a Fellow in Child Development under Dr. T. Berry Brazelton at Boston's Children's Hospital from 1979-1981. Dr. Frank has been a professor of Pediatrics at Boston University School of Medicine since 2001. Dr. Frank has dedicated her career to improving the lives of impoverished children particularly in the areas of exposure to drugs in utero, failure to thrive, breastfeeding, and nutrition for low income and homeless families. She received two awards for her outstanding work in 2010: the Physician Merit Award from the IOM and the Massachusetts Health Council Outstanding Leadership Award. Dr. Frank is the Principal Investigator of a NIDA funded prospective longitudinal study on intrauterine exposure to cocaine and other drugs of abuse.

Dr. Steve Higgins, University of Vermont, was awarded the APA Division 28 Brady-Schuster Award, which is given for outstandig research that underscores the fundamental importance of behavioral science to psychopharmacology or substance abuse.

Dr. Victor Hruby of the University of Arizona received the 2011 Goodman award at the 22nd American Peptide Symposium, June 2011, for his work in peptide science and in the training of students.

Dr. Leslie Leve, Oregon Social Learning Center, received the Prevention Science Award from the Society for Prevention Research during the SPR annual meeting, held May 31-June 1, in Washington, DC. This award is given to an individual or team of individuals for a significant body of research that has applied scientific methods to test one or more preventive interventions or policies.

Dr. David MacKinnon, Arizona State University, received the Nan Tobler Award for Review of the Prevention Science Literature during the SPR annual meeting, held May 31-June 1, in Washington, DC. This award is given for contributions to the summarization or articulation of the empirical evidence relevant to prevention science.

Dr. Raphael Mechoulam will be awarded, THE LIFETIME Achievement award to be presented by the "Bioactive Lipids in Cancer, Inflammation and Related Diseases" conference, sponsored by the Eicosanoid Research Foundation, September 18-21, Seattle, Washington.

Dr. Mary Ann Pentz, University of Southern California, received the Presidential Award from the Society for Prevention Research during the SPR annual meeting, held May 31-June 1, in Washington, DC. The award is a "lifetime achievement" award for a significant body of research or theory in any area related to prevention that has had a major impact on the field.

Roseann Peterson, a pre-doctoral trainee under R25 DA 26119 Research Education in Statistical Genetics of Substance Abuse, was awarded the Thompson Award for Outstanding Graduate Student presentation at the annual meeting of the Behavior Genetics Association in Newport, RI, in June, 2011.

Dr. Ty A. Ridenour, University of Pittsburgh, received the Service to SPR Award during the SPR annual meeting, held May 31-June 1, in Washington, DC. This award is given in recognition of outstanding service to the SPR organization.

Dr. Luanne Rohrbach, University of Southern California, received the Translational Science Award during the SPR annual meeting, held May 31-June 1, in Washington, DC. This award is given in recognition of contributions to the field of prevention science in the area of Type 1 or Type 2 translational researh.

Dr. Daniel Shaw, University of Pittsburgh, received the Friend of ECPN (Early Career Preventionist Network) Award from the Society for Prevention Research during the SPR annual meeting, held May 31-June 10, 2011 in Washington, DC. This award is presented to a mid-career or senior preventionist who has supported and encouraged early career persons or issues.

CTN Delaware Valley Node

Dr. George Woody (Principal Investigator of the Delaware Valley Node) was selected by the School of Medicine at the University of Pennsylvania to receive the Scott Mackler Award. This award is given annually at the medical school graduation ceremony to a faculty member for contributions to teaching medical students, residents and fellows about diagnosis and treatment of persons with substance use disorders. Scott Mackler MD, PhD is an internist and basic science addiction researcher who has made major contributions to addiction teaching at Penn and who played a major role in helping Drs. Woody and Charles O'Brien integrate medical and substance abuse treatment services at the Philadelphia Veteran's Affairs Medical Center.

CTN New England Consortium Node

Two New England Consortium Node Community Treatment Programs—**Stanley Street Treatment & Resources, Inc. (SSTAR)** in Fall River, Massachusetts and **Hartford Dispensary** in Connecticut—were among five behavioral health organizations that were recently selected by the Annapolis Coalition on the Behavioral Health Workforce and the Hitachi Foundation as the 2011 National Behavioral Health Pacesetter Award Winners. This award recognizes behavioral healthcare treatment and support organizations throughout the United States that employ best workforce practices, especially for direct-care workers, while also improving outcomes for clients and organizational performance.

CTN Texas Node

Chad Rethorst, Ph.D., Assistant Professor at the University of Texas Southwestern Medical Center at Dallas and National Intervention Director for STRIDE (CTN 0037) was selected as a 2011 NCDEU New Investigator Award recipient this past June. This scientific meeting focuses on the latest developments in psychopharmacologic clinical research and related methodology.

Dr. Rethorst also was selected to participate in the 11th Annual Office of Behavioral and Social Sciences Research (OBSSR)/National Heart, Lung, and Blood Institute (NHLBI) Summer Institute on the Design and Conduct of Randomized Clinical Trials involving Behavioral Interventions. The Summer Institute provides a thorough grounding in the conduct of randomized clinical trials to researchers and health professionals.

The Memorial Hermann Prevention and Recovery Center (PaRC) in Houston, Texas, one of the nine sites participating in STRIDE (CTN 0037), received the James W. West, M.D. Quality Improvement Award by NAATP (National Association of Addiction Treatment Providers) for its "body of work" involving performance improvement and relating to four quality initiatives. This award was presented at the annual NAATP conference on May 16th. An article highlighting the achievement appeared in the April edition of Behavioral Healthcare magazine.

CTN Ohio Valley Node

Kathy Burlew, Ph.D., from The Crossroads Center CTP, received the APA Award for Mentorship of Ethnic Graduate Students. Additionally, she received an internal grant from the University of Cincinnati to fund a project entitled "Safer Sex for African American Substance Abusing Women" which will utilize data from the NIDA CTN.

CTN Western States Node

Dr. Dennis McCarty, Co-PI of the Western States Node, received the National Association of State Alcohol and Drug Abuse Directors, Inc (NASADAD) Bob Anderson Research Award. The award was given at the annual NASADAD meeting in June. NASADAD is a private, not-for-profit educational, scientific, and informational organization. Its basic purpose is to foster and support the development of effective alcohol and other drug abuse prevention and treatment programs throughout every State.

CTN Clinical Coordinating Center PI – SCT Award

Dr. Robert Lindblad, Principal Investigator of the Clinical Coordinating Center at EMMES, was awarded the 2011 Sylvan Green Award from the Society for Clinical Trials (SCT) at its annual meeting in May 2011. His submission on "Suicide Risk in Substance Abuse Treatment Clinical Trials, Is Adverse Event Reporting Alone Sufficient?*"* met the high standards set forth for receipt of this particular recognition.