# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Index



**Report Index**

- Report for May, 2011
- Report for February, 2011
- Report for September, 2010
- Report for May, 2010
- Report for February, 2010
- Older Reports - go to the Archives

NACDA

Legislation

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page



# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Research Findings - Basic Neuroscience 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

**Publications**

**Staff Highlights**

**Grantee Honors**

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.

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# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Research Findings - 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 22Ð31). 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.

**Publications**

**Staff Highlights**

**Grantee Honors**

### Chronic Administration of THC Prevents Behavioral Effects of Adolescent MDMA in Rats

Most recreational users of 3, 4-methylenedioxymethamphetamine (MDMA or ÒecstasyÓ) 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 x 10 mg/kg x 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 (Òsign-trackersÓ; STs) come to find the cue itself an attractive and desirable incentive stimulus. For other rats (Ògoal-trackersÓ; GTs) the cue is an effective conditional stimulus Ð it evokes a conditional response Ð 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 Ð a 2-choice serial reaction time task and a differential reinforcement of low rates of responding task, and one test of impulsive choice Ð 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 authorsÕ 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.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Research Findings - 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 x 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.

**Publications**

**Staff Highlights**

**Grantee Honors**

### 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 ÒDefault ModeÓ 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 Òdefault modeÓ 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, OÕGrady 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 ÒeasyÓ and ÒdifficultÓ 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 ToddlerÕs 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.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Research Findings - 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 authorsÕ 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 Òmentalizing.Ó 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.

**Publications**

**Staff Highlights**

**Grantee Honors**

### 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 brainÕs 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 authorsÕ 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, ÒEcstasyÓ) 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, ÒecstasyÓ) 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 24Ð55) 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 Òoccult insomniaÓ 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 authorsÕ 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 452Ð508 ms time window. During the 212Ð316 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 (136Ð144 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 Na•ve 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 diffeomorphic 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 ("na•ve," 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 na•ve 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 na•ve 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 ÒraveÓ 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 authorsÕ-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 WomenÕs 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. DopamineÕs 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 estradiolÕs 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 individualÕs 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 womenÕs health. Jacobs E, DÕEsposito M. Estrogen shapes dopamine-dependent cognitive processes: implications for womenÕs 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 authorsÕ 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 peopleÕs 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, [18F]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 [18F]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.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Research Findings - 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

**Publications**

**Staff Highlights**

**Grantee Honors**

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 10Ð12 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 x 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

attendeeÕs). 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 studyÕs 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, TouzŽ 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 oneÕs own and oneÕs 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, Col—n-L—pez 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 x 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.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Research Findings - 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,

**Publications**

**Staff Highlights**

**Grantee Honors**

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 Òheavenly 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 clientsÕ 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).

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Research Findings - Behavioral and 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.

**Publications**

**Staff Highlights**

**Grantee Honors**

### 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 ($R^2$self-report = .15, $R^2$self-report + neural activity = .35, $R^2$change = .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 ($CO^{2}4$ppm). 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 $^{2}4$ppm, 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 (BDI³12) 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-Na•ve 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-na•ve 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) x 2 (neutral vs. trauma script) x 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 x 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 x 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 x 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.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Research Findings - 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

## Index

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 methamphet-amine (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

**Publications**

**Staff Highlights**

**Grantee Honors**

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, ³80% 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. Methamphet-amine 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, 90Ð94]. 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,"$_{x}(2) = 3.67$, $p = 0.056$), went significantly longer before having two consecutive urine samples positive for cocaine ("relapse,"$_{x}(2) = 4.03$, $p = 0.04$) 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 abusedÑby 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 approachÑcombined, for example, with counseling, treatment of additional nonopioid substance use disorders, and treatment of comorbid psychiatric illnessÑ 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 α4B2 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 x 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 x Sex x 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 x 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 Fagerstršm 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 $\Delta^9$-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 $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC), and high efficacy agonists CP 55940 and WIN 55212-2, was determined before and after chronic $\Delta^9$-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 $\Delta^9$-THC (0.1 mgákg$^{-1}$, i.v.). $\Delta^9$-THC decreased responding for both food presentation and stimulus-shock termination; these effects were antagonized by the $CB_1$ antagonist rimonabant. Chronic $\Delta^9$-THC (1 mgákg$^{-1}$ per 12 h, s.c.) resulted in tolerance to the rate-decreasing effects of $\Delta^9$-THC and cross-tolerance to CP 55940 and WIN 55212-2; however, cross-tolerance was less than tolerance. Chronic $\Delta^9$-THC increased sensitivity to rimonabant without changing sensitivity to the non-cannabinoids midazolam and ketamine. In monkeys discriminating $\Delta^9$-THC (0.1 mgákg$^{-1}$, i.v.), both CP 55940 and WIN 55212-2 produced high levels of drug-lever responding. Chronic $\Delta^9$-THC (1 mgákg$^{-1}$ per day, s.c.) decreased sensitivity to $\Delta^9$-THC without producing cross-tolerance to CP 55940 or WIN 55212-2. In $\Delta^9$-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 [$^3$H]DTBZ binding site did not correlate with inhibitory potency in the [$^3$H]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 [$^3$H]DTBZ binding site. These results suggest that the analogs interact at an alternate site to DTBZ on VMAT2. Kinetic analyses of [$^3$H]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 [$^3$H]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 authorsÕ 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 Acetylcholin-esterase: 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 $D_z$ 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($_z$-like) dopamine receptors. These compounds also share structural elements with the classical D($_z$-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 $D_z$ receptor subtype with high affinity (K(i) values < 0.3 nM), (b) exhibit >50-fold $D_z$ versus $D_3$ receptor binding selectivity and (c) be partial agonists at both the $D_z$ 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 $F(ab')_z$, 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 $F(ab')_z$-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, t%frac12;~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 authorÕs 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. Immunopharma-cotherapy 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 authorsÕ 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.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Research Findings - Research on Medical Consequences of Drug Abuse and Co-Occurring Infections (HIV/AIDS, HCV)

### 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 B3-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

**Publications**

**Staff Highlights**

**Grantee Honors**

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 authorÕs 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 (B=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 α6B2-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 α6B2-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.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Research Findings - Services Research

### Moving beyond Parity Ñ 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 lawÕs passage constituted a critical first step toward bringing care for people with mental health and addiction disorders Ñ including depression, anxiety, psychoses, and substance abuse and dependence Ñ 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 Òbehavioral health,Ó 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 Ñ 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 x 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 ÔConnor 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 ÔBrien L, Bride B, Roman P. HIV/AIDS Services In Private Substance Abuse Treatment Programs. Drug Alcohol Depend. 2011; 115 (1-2): 16-22.

**Publications**

**Staff Highlights**

**Grantee Honors**

### 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.

### DepressionÕs 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 ICMÕs 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 depressionÕs 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. DepressionÕs Moderation of the Effectiveness of Intensive. J Stud Alcohol Drugs. 2011; 72: 297-307.

### The ÔCheck EffectÕ Reconsidered

The Ôcheck effectÕ 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 ÔCheck Effect Ô Reconsidered. Addiction. 2011; 106 (6): 1071-1077.

### Gender Differences in ProviderÕs 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 physicianÕs gender may influence differences in screening practices. The purpose of this study is to examine male and female Ob/Gyn physicianÕs 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 physicianÕs 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 Ôs were more likely to Òbelieve inÓ 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 ProviderÕs 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 2007Ð2008. 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, OÕBrien 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. CounselorsÕ substance use disorderÐimpacted 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 counselorsÕ 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 Òenhanced profiles,Ó 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 Òbasic profiles,Ó 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 providerÕs 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 AndersenÕs 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 usersÕ 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 womenÕs disorders were significantly related to increased family member burden. WomenÕs behavioral problems predicted greater family member Worry, Displeasure, and Impact. Extent of womenÕs 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.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Research Findings - 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; $_{x}(2)(1) = 8.22$, $p < .01$. 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

**Publications**

**Staff Highlights**

**Grantee Honors**

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, methamphet-amine), the authors examined the prevalence of amphetamine use among treatment-seeking, opioid-dependent adults, explored whether amphetamine users were as likely as nonampheta-mine 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.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Research Findings - 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[a] 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[a] 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

**Publications**

**Staff Highlights**

**Grantee Honors**

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 (2001Ð2003; n = 1208) and Mexico (2001Ð2002; 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.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Research Findings - 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 authorsÕobservations 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 (³10 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

**Publications**

**Staff Highlights**

**Grantee Honors**

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 ³5 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 ³5 p.p.m. rather than the ³10 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 α4B2*-selective, competitive antagonist dihydro-beta-erythrodine (DHBE) antagonized the

discriminative stimulus effects of both doses, but was less effective against the larger training dose of nicotine. Schild analyses of DHBE 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 α4B2 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 authorsÕ 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, OÕCallaghan 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: 775Ð784.

## 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. Justinov‡ 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, FerrŽ 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.**

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## 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 Òavant-gardeÓ 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

## Index

proposed must be in an area described in the Trans Đ 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 Òavant-gardeÓ 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 Đ 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 SubstanceĐUse 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 Đ including office-based practice settings, family practice, pediatric and adolescent medicine, obstetrics, general practice, and emergency departments. Letter of Intent

**Publications**

**Staff Highlights**

**Grantee Honors**

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 ÒtimestampÓ 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.

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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 WomenÕs 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

### Clinical Trials Network (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 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 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 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 ÒCheeseÓ 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 clinical phase of the study is completed; it is in the data analysis phase.
- **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 qualitative data collected from interviews and focus groups with 281 participants (202 patients, 68 staff, 11 Executive/Program Directors) are currently being coded and analyzed using ATLAS.ti. The first draft of the final report has begun.
- **Protocol CTN 0030A1**, Collection of Economic Data for the Prescription Opioid Addiction Treatment Study. This ancillary study was conducted in collaboration with NIDA DESPR; it is in the data analysis phase. Protocol CTN 0031, Stimulant Abuser Groups to Engage in 12-Step (STAGE-12): Evaluation of a Combined Individual-Group Intervention to Reduce Stimulant and Other Drug Use by Increasing 12-Step Involvement. Recruitment was completed on September 30, 2009, yielding a total of 471 randomized participants across 10 sites. This total represents 21 more participants than proposed and was reached one week earlier than planned. Data lock was June 14, 2010; the study is now in the data analysis phase.

- **Protocol CTN 0031**, Stimulant Abuser Groups to Engage in 12-Step (STAGE-12): Evaluation of a Combined Individual-Group Intervention to Reduce Stimulant and Other Drug Use by Increasing 12-Step Involvement. Recruitment was completed on September 30, 2009, yielding a total of 471 randomized participants across 10 sites. The 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. Data lock was June 14, 2010; 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. It 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. Data lock was June 14, 2010; 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. Study staff has already collected the organizational and counselor level data from all ten STAGE-12 sites. 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 clientsÕ 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.
- **Protocol CTN 0037A1, CTN 0044A1, CTN 0046A1, and CTN 0047A1**, 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 December 9, 2010, 51 participants have been enrolled at four sites. Enrollment will begin at five additional sites in early 2011.
- **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 December 8, 2010, 196 randomized participants have been enrolled from 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 December 8, 2010, 180 randomized participants have been enrolled from 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. Training for the two Wave 1 sites took place July 19-21, 2010 in Albuquerque, NM. The first participant was randomized on October 18, 2010 and enrollment stands at 76 as of December 6, 2010. The four Wave 2 sites are: Massachusetts General Hospital (New England Node); Bellevue Hospital Center (Greater New York Node); Jackson Memorial Hospital (Florida Node); and West Virginia University Hospital (Appalachian Tri-State Node). National training was held January 11-14, 2011 in Albuquerque, NM.

***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 lifetime opioid dependence or cocaine dependence and past year opioid abuse. 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 are in progress and/or being prepared by the investigators. Posters are being presented at scientific meetings for several of the trials.

1. Gender Differences in the Prevalence and Predictors of HIV Risk Behaviors, PI: Audrey Brooks (CA/AZ Node) - paper published by Substance Use and Misuse;
2. Pattern of alcohol use and alcohol-related diagnoses among drug abusing/dependent participants, PIs: Dennis Donovan and Bryan Hartzler (Pacific Northwest Node); poster at ICTAB, paper published by Journal of Substance Abuse Treatment, Manuscript submitted to special issue of AJDAA.
3. The relationships between demographic characteristics of patients and therapists, measures of therapeutic process and therapeutic alliance, and outcomes, PIs: Alyssa Forcehimes (Southwest Node) and Kathleen Burlew (Ohio Valley Node); poster at CPDD, Manuscript submitted to special issue of AJDAA.
4. The Efficacy of Motivational Enhancement Therapy for African Americans, PI: Kathleen Burlew (Ohio Valley Node); poster at CPDD, Manuscript submitted to special issue of AJDAA.
5. Substance Abuse Treatment Outcomes in Racial/Ethnic Minority Populations, PI: Carmen Masson (California-Arizona Node).

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.

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### 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. Ð University of Connecticut School of Medicine/DNT IVR Technology to Mobilize Contingency Management for Smoking Cessation**

**Audrain-McGgovern, Janet E. Ð University of Pennsylvania SmokingÕs Role in Positive Affect & Reward Regulation in Depression-Prone Smokers**

**Basbaum, Allan I. Ð University of California San Francisco Multiple Opioid**

**Receptors and the Control of Pain**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**DÕSouza, Deepak Cyril Ð Yale University Imaging Brain Cannabinoid Receptors in Cannabis Dependence, Withdrawal and Abstinence**

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

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

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

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

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

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

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

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

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

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

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

**Gentry, W Brooks Ð 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. Ð Midwest Biomedical Research Foundation Tacrine Effects on Cocaine Self-Administration and Pharmacokinetic Measures**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Mendelson, Tamar Ð Johns Hopkins University School-Based Mindfulness**

**Intervention to Prevent Substance Use Among Urban Youth**

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

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

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

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

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

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

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

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

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

**OÕCleirigh, Conall Michael Ð Massachusetts General Hospital Integrated Treatment for Smoking Cessation & Anxiety in People with HIV**

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

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

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

**Palmer, Abraham A. Ð University of Chicago Systems Genetic Analysis of MethamphetamineÕs Motivational Effects in a Mouse AIL**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Whiteaker, Paul Ð St. JosephÕs Hospital and Medical Center. HTS Assay Development for alpha6/3beta2beta3 Subtype Nicotinic Receptors**

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

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

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

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

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

**Zheng, Guangrong Ð University of Kentucky Development of M5 Selective Muscarinic Antagonists**

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

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

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

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Extramural Policy and Review Activities

### Receipt, Referral, and Review

NIDA received 1,636 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 949 applications.

OEA arranged and managed 17 grant review meetings in which 216 applications were evaluated. OEA's reviews included applications in chartered, standing review committees and Special Emphasis Panels (SEPs). In addition, OEA staff arranged and managed 7 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 16 Special Emphasis Panels to review grant applications for a variety of reasons:

- Center Grants (P50 & P30)
- 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)
- NIH Summer Research Experience Programs (R25)
- Conference Grants (R13)
- Cutting-Edge Basic Research Awards (CEBRA) (R21)
- Multi-site Clinical Trials (R01)
- Loan Repayment Program
- Requests for Applications (RFAs)

OEA managed the following RFA reviews:

- DA11-001 - Seek, Test, Treat, and Retain: Addressing HIV Among Vulnerable Populations (R01)
- DA11-004 - Pharmacological Development of Treatment Agents and Formulations for Tobacco Dependence (STTR [R41])
- DA11-005 - Training in Computational Neuroscience: from Biology to Model and Back Again (T90/R90)
- DA11-006 - Training in Neuroimaging: Integrating First Principles and Applications (T90/R90)

- DA11-007 - Assay Development for High Throughput Screening for Nicotinic Receptor Subunits (R21)

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

**R&D and non-R&D Concept Reviews**

- NO1DA-11-5565 - Data Management Center for MTA
- NO1DA-11-5568 - Family Smoking Prevention and Tobacco Control Act National Longitudinal Study
- NO1DA-11-7781 - National Children's Imaging Study
- NO1DA-11-1147 - Physician Outreach and Education: Development of E-Tools, E-Learning, and CME Course on Prescription Drug Abuse and Treatment
- NO1DA-11-8900 - Pharmacogenetics Support for NICA Clinical Trials
- NO1DA-11-8901 - Technical and Conference Support for DPMCDA

**Phase II SBIR Contract Reviews**

- N44DA-11-2220 - "Multiplexed Sensitive Testing for Drugs of Abuse"

## CTN Review Activities

The CTN Data and Safety Monitoring Board(s) met:

- January 21, 2011 to review protocol CTN 0049, Project HOPE (Hospital Visit as Opportunity for Prevention and Engagement for HIV-Infected Drug Users)
- January 28, 2011 to review protocol CTN 0050, START Follow-Up Study
- February 28, 2011 to review 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
- March 29, 2011 to review protocol CTN 0044, Web-delivery of Evidence-Based, Psychosocial Treatment for Substance Use Disorders.

## Certificates of Confidentiality

Between December 9, 2010 and March 18, 2011 OEA processed 83 Certificate of Confidentiality applications, including 19 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: The Diversity-Promoting Institutions Drug Abuse Research Program (R24)—What Are We Trying to Achieve?, presented by staff from the NIDA Office of Special Populations; and "NIDA Avant Garde Award for AIDS" presented by staff of the NIDA AIDS Program.

**Publications**

**Staff Highlights**

**Grantee Honors**

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Congressional Affairs (Prepared April 18, 2011)

### Appropriations

After lengthy negotiations, Congress passed and the President signed a continuing resolution that will fund Executive Branch programs for the remainder of FY 2011. As of this writing we await absolutely final funding figures for NIH and NIDA. We expect a cut of approximately 1% from the FY 2010 enacted level (for NIDA, that was $1.059 billion).

The President's Fiscal Year 2012 budget request for NIDA is $1.08 billion, a $21 million increase (approximately 2%) over the FY 2010 actual level and, depending on final figures, an expected 3% increase over the estimated final FY 2011 level.

### 112th CONGRESS

As a result of the November 2010 elections, Republicans control the House of Representatives and Democrats control the Senate. The most relevant committee-related information for NIDA is listed below.

**Senate:** In the Senate, primary focus is on the Committee on Appropriations (Subcommittee on Labor, Health and Human Services, and Education [http://appropriations.senate.gov/sc-labor.cfm]; Financial Services [http://appropriations.senate.gov/sc-financial.cfm]; and Commerce, Justice, Science [http://appropriations.senate.gov/sc-commerce.cfm];

- Committee on Health, Education, Labor, and Pensions (HELP) [http://help.senate.gov/];
- Committee on the Judiciary [http://judiciary.senate.gov/]; and the
- Caucus on International Narcotics Control (this is an officially recognized Caucus, established by law in 1985 - http://drugcaucus.senate.gov/index.html).

**House of Representatives:** In the House, primary focus is on the

- Committee on Appropriations [Subcommittee on Labor, Health and Human Services, Education, and Related Agencies http://appropriations.house.gov/Subcommittees/Subcommittee/?IssueID=34777]; Financial Services [http://appropriations.house.gov/Subcommittees/Subcommittee/?IssueID=34780]; and Commerce, Justice, Science and Related Agencies [http://appropriations.house.gov/Subcommittees/Subcommittee/?IssueID=34794];
- Committee on Energy and Commerce (Subcommittee on Health -

http://energycommerce.house.gov/subcomms/subcommittees.shtml); and the

- Committee on Oversight and Government Reform (http://oversight.house.gov/).

**Publications**

**Staff Highlights**

**Grantee Honors**

## CONGRESSIONAL BRIEFINGS OF INTEREST

### Friends of NIDA Host Briefing on Marijuana Research

On March 8, 2011, the Friends of the National Institute on Drug Abuse (NIDA) coalition presented a briefing, "Marijuana Use Disorders: Dependence and Treatment Research." The American Psychological Association organized the event on behalf of the coalition, and sponsors included 25 scientific and professional associations as well as the Congressional Addiction, Treatment and Recovery Caucus. NIDA Director Dr. Nora Volkow presented critical research findings on topics including the likelihood of developing addiction to marijuana, brain abnormalities associated with long-term marijuana use, brain differences in adolescents with heavy marijuana use, and addiction withdrawal symptoms. Dr. Volkow further demonstrated the relevance of this research with statistics on marijuana in the U.S. Briefing attendees learned about prevalence of use, emergency department visits involving marijuana, changes in attitudes toward marijuana, and the more than threefold increase in potency of marijuana in the last two decades.

Dr. Alan Budney of the University of Arkansas for Medical Sciences presented findings from his NIDA-funded research, focusing on behavioral treatments and determinants of their success. Study topics ranged from motivational incentives to genotypic interactions to adolescent impulsivity to the marijuana-tobacco relationship. Dr. Budney emphasized the need for further neuroscience and behavioral science research to gain a better understanding of marijuana dependence, including the development of innovative, population specific incentive programs.

The briefing was particularly timely, coinciding with news (http://researchnews.osu.edu/archive/aboveinfluence.htm) in February that an independent scientific analysis, supported by a NIDA grant, found the Office of National Drug Control Policy's "Above the Influence" National Youth Anti-Drug Media Campaign to be effective in reducing marijuana use.

To see the presentations and an issue brief provided during the briefing, see below:

- Dr. Volkow's presentation: http://www.apa.org/about/gr/science/spin/2011/03/volkow-marijuana-presentation.pdf
- Dr. Budney's presentation: http://www.apa.org/about/gr/science/spin/2011/03/budney-marijuana-presentation.pdf
- NIDA research brief: http://www.nida.nih.gov/ResearchReports/Marijuana/default.html

### Congressional Caucus on Prescription Drug Abuse Briefing on Prescription Drug Abuse

On March 10, 2011, the Congressional Caucus on Prescription Drug Abuse presented a briefing on prescription drug abuse in the U.S. Members attending included Representatives Mary Bono Mack (R-CA), Harold Rogers (R-KY), Stephen Lynch (D-MA), and Vern Buchanan (R-FL). The caucus members began the hearing by discussing how prescription drug abuse has had a serious impact on people in their respective districts and pointing out that the issue affects people in every geographic, racial, ethnic, and economic group. Representative Rogers added that halting prescription drug abuse will take a

three pronged attack involving law enforcement, treatment, and education. He also said that because the prescription drug abuse problem cuts across State lines, the Federal government has to be involved. He then charged that the Federal government was abdicating its duties, specifically referring to an exchange he had with Attorney General Eric Holder regarding the issue during the Department of Justice (DOJ) Budget Hearing on March 1st.

The Representatives were followed by a constituent witness from Representative Rogers' district who outlined a familial struggle with prescription drug abuse before talking about the efforts of the Operation Unite program to stem the problem in Kentucky. Operation Unite was started by Congressman Rogers in 2003 to serve the 29 counties of Kentucky's fifth district in the Southeastern part of the State by undertaking anti-drug efforts including undercover investigations, coordinating treatment for people with substance abuse problems, supporting families effected by substance abuse, and educating the public about drugs. The program is primarily funded through Federal grants from the Bureau of Justice Assistance within the DOJ and from the Substance Abuse and Mental Health Services Administration (SAMHSA).

Office of National Drug Control Policy (ONDCP) Director Gil Kerlikowske also spoke, pointing out that the challenges surrounding prescription drug abuse constituted a bi-partisan issue. After the Director's statement, ONDCP staff, including Deputy Director David Mineta, presented research findings about prescription drug abuse. They explained that a low perception of harm of prescription drugs contributes to the abuse problem, so there should be education programs in place to alert parents, healthcare providers, and children to the dangers of prescription drug abuse. Additionally, they recommended that drug monitoring programs be in place in every State and that "pill mills" be shut down immediately. They also discussed programs that encourage people to safely dispose of leftover prescription drugs that were legitimately prescribed rather than leaving them in their home and said that all of these efforts must be taken together to lower usage rates as no one solution would work on its own.

**National Association of Drug Court Professionals Holds Congressional Briefing on Drug Courts**

March 31st saw a briefing called "Drug Courts: A Proven Budget Solution" sponsored by the National Association of Drug Court Professionals (NADCP) in conjunction with the Congressional Addiction, Treatment, and Recovery Caucus. The briefing featured a diverse set of speakers including members of Congress, actor Martin Sheen, a Tulsa County District Court Judge, and a drug court graduate. Former Congressman Jim Ramstad (R-MN) kicked off the event by stating that he used to be addicted to alcohol and is alive only because of access to treatment. He explained that Drug Courts are a cost effective and proven way to provide treatment and that the programs have significant bipartisan support. Representatives Tim Ryan (D-OH) and John Sullivan (R-OK), the Caucus Co-Chairs, agreed with Ramstad's statement and added that Drug Courts have been proven to reduce crime and increase public safety. Caucus Co-Vice Chair Representative Mary Bono-Mack (R-CA) echoed their comments while also saying that Drug Courts allow for the consideration of addicts as people that need help rather than as criminals that need punishment.

Sheen used his time to praise the Members of Congress who have supported Drug Courts and called for Congress to, at the least, maintain level funding for the programs, because "ÉDrug Courts are the very best deal Congress can make to reduce crime and the social consequences related to drug addiction." Doug Marlowe, the NADCP Chief of Science, Law, and Policy, discussed the scientific basis for supporting Drug Courts, explaining that six meta-analyses have shown that they reduce crime and produce an estimated 200-350 percent return in savings. He added that the most successful Drug Courts were those

that effectively mixed treatment and supervision and that such models have been applied successfully to Family Drug Courts and DWI Courts and are currently being used to plan new Veteran Drug Courts.

Rebecca Nightingale, a Tulsa County, Oklahoma District Court Judge, talked about outcomes in her area, saying that Drug Court graduates in Oklahoma show a 31 percent reduction in recidivism compared to similar justice-involved people who did not participate in such programs. Nightingale then introduced a graduate of the Tulsa Drug Court who told her story and explained that the program had helped her change the way in which she thought about her substance abuse. She also noted that she had recently completed her certification as a recovery support specialist. The briefing was closed by Earl Hightower, an intervention specialist, who said that Drug Courts restore communities, families, and the nation as a whole and that they serve every resident of the country.

To read a detailed press release about the briefing, see http://www.nadcp.org/learn/nadcp-news-events/nadcp-news/Martin-Sheen-on-Capitol%20Hill.

## BILLS OF INTEREST

**H.R. 366** - On January 25, 2011, the House passed H.R. 366, to provide for an additional temporary extension of programs under the Small Business Act and the Small Business Investment Act of 1958. The bill would temporarily extend programs including SBIR/STTR, until May 31, 2011. On January 26, the Senate passed H.R. 366 under unanimous consent. The bill was signed into law by the President on January 31.

**H.R. 447** - On January 27, 2011, Representative Mazie Hirono (D-HI) introduced H.R. 447, a bill to amend the Small Business Act to improve the Small Business Innovation Research program. The bill was jointly referred to the House Committees on Science, Space, and Technology and Small Business.

**H.R. 448** - On January 27, 2011, Representative Mazie Hirono (D-HI) introduced H.R. 448, a bill to amend the Small Business Act to improve the Small Business Innovation Research program and the Small Business Technology Transfer program. The bill was jointly referred to the House Committees on Science, Space, and Technology and Small Business.

**H.R. 449** - On January 27, 2011, Representative Mazie Hirono (D-HI) introduced H.R. 449, a bill to amend the Small Business Act to improve the Small Business Technology Transfer program. The bill was jointly referred to the House Committees on Science, Space, and Technology and Small Business.

**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).

**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.

**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.

**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.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## International Activities

### Research Funding

***New NIDA Grantees Collaborate To Address HIV/AIDS and Drug Use***
Five new NIDA-supported research teams have begun work to address HIV/AIDS and drug use in areas where it is already at epidemic proportions or where it is quickly emerging. The NIDA grant program was designed to stimulate collaborative research among foreign investigators from the same geographic regions to address regional issues on the intersection of HIV/AIDS and drug use in international settings. Two of the five research teams include IP fellowship alumni as Principal Investigators:

- Dr. Sergii Dvoryak, Ukraine, former Hubert H. Humphrey Fellow and recently awarded INVEST-Clinical Trials Network (CTN) Fellow, is working with U.S. investigator Dr. Frederick Lewis Altice, Yale University, to create an innovative collaborative research program in Ukraine called PRIDE (Prison-Related Research, Intervention Development, and Evaluation) to address research and implementation issues associated with HIV, substance abuse, and the criminal justice system in the former Soviet Union region. PRIDE creates an infrastructure for research that involves both researchers and the criminal justice system partners and includes collaborators from Ukraine, Kazakhstan, and Georgia. The three-phase study will include surveillance activities, selection of evidence-based interventions suggested by the surveillance and needs assessments, and pilot testing of the selected interventions. The research team aims to impede the HIV epidemic among injection drug users (IDUs) in Ukraine.
- Sonia Miranda, Guatemala, and Dr. Carmen Fernandez-Casanueva, Mexico, are conducting research to gain a better understanding of the patterns and context of drug use along the Mexico/Guatemala border and how substance use is related to the spread of HIV, hepatitis C virus (HCV), and other sexually transmitted infections (STIs). They aim to describe the contextual factors affecting drug use and patterns of use in high-risk populations along the border; determine the prevalence and correlates of HIV, HCV, and STIs among substance users; and explore the phylo-geography and molecular epidemiology of HIV-1 infection in at-risk groups. This collaborative project will strengthen regional cooperation between researchers in Guatemala, Mexico, and the United States, and help inform the development of HIV interventions and prevention programs that may avert risky substance use behaviors before they become further established. The U.S. principal investigator for this team is Dr. Kimberly C. Brouwer, University of California, San Diego.
- Olga Levina, NGO Stellit, St. Petersburg, Russia; Anneli Uuskula, University of Tartu, Estonia; and Dr. Robert Heimer, Yale University, are investigating the HIV epidemic in Russia and Estonia, which is largely driven by viral

transmission among IDUs. The researchers intend to determine the impacts of ethnicity and stigma on HIV prevalence and on access to care in cities of both countries. They will begin with a rapid policy assessment that offers a better understanding for how systems of prevention and care are organized and how IDUs feel about accessing these services. Further explorations will be conducted to understand the nature of the three facets of stigma as perceived by IDUs from the dominant and nondominant ethnic groups in each city. The researchers also will conduct a quantitative study to test hypotheses about the impacts of ethnicity and stigma on HIV prevalence and access to prevention and care services.

- Dr. Hendree Jones, RTI International, is collaborating with Dr. Irma Kirtadze, a 2010 World Health Organization/NIDA/College on Problems of Drug Dependence International Traveling Fellow, and Dr. David Otiashvili, M.D., former NIDA Hubert H. Humphrey Fellow, the Republic of Georgia, to identify the patterns of drug use and cultural contexts of risks in order to adapt and test a comprehensive treatment model for women IDUs with the intent to avert an HIV epidemic and further increases in HCV within the country. Dr. Evgeny Krupitsky, Bekhterev Research Psychoneurological Institute, St. Petersburg, Russia, and 2010 recipient of the NIDA International Award of Excellence, is a co-investigator in Russia. He will provide guidance on the similarities and differences between Georgia and Russia that contribute to HIV and comorbid diseases, and on factors that influence drug use among women in those nations.
- South African researchers Drs. Jessie Mbwambo and Anne-Gloria Moleko, along with U.S. investigator Dr. William W. Latimer, Johns Hopkins University, are working to address the large-scale HIV pandemic in Sub-Saharan African countries. The researchers plan to test a brief intervention model that can feasibly reach large numbers of drug users at increased risk for HIV. They also aim to test a more intensive couples intervention that may be needed to foster behavior change among high-risk groups disproportionately affected by HIV, including young women who use drugs and trade sex for drugs.

**Publications**

**Staff Highlights**

**Grantee Honors**

## Research Results

***DISCA Research Team Studies Potential Inhalant Pharmacotherapy***

Distinguished International Scientist Collaboration Award (DISCA) program awardee Dr. Hwei-Hsien Chen, Taiwan, spent the last 5 months working with Dr. Athina Markou at the University of California, San Diego, to develop a novel pharmaceutical treatment for inhalant abusers. Dr. Chen's research aimed to characterize the reward-enhancing effect of toluene, a clear liquid with the smell of paint thinners, using the intracranial self-stimulation procedure in mice. She also investigated whether modulation of glutamatergic transmission by sarcosine or N-acetylcysteine could counteract the threshold lowering effects of toluene. Her study results indicated that toluene, as predicted, remarkably enhances the brain stimulation reward. Conversely, her findings revealed that N-acetylcysteine effectively attenuates the toluene-enhanced brain stimulation reward. Further studies are needed to determine whether N-acetylcysteine, a clinically used expectorant, might prove effective as an inhalant cessation aid. Dr. Chen plans to continue her studies in Taiwan.

## NIH-Supported Meetings

***NIDA Hosts Iraqis***

The National Institute on Drug Abuse (NIDA) International Program hosted a group of four Iraqis taking part in the Iraq-Substance Abuse and Mental Health Services Administration (SAMHSA) Initiative. In 2008, Iraq and SAMHSA launched the initiative, in which multidisciplinary behavioral health teams from Iraq visit SAMHSA and host sites around the United States to learn about

various interventions the teams want to adapt for implementation in Iraq. The substance abuse team visited NIDA on November 1, 2010, which included a tour of the National Library of Medicine, a meeting with NIDA staff - including Dr. Jag Khalsa, DPMCDA, Dr. Cece McNamara-Spitznas, DCNBR, Drs. Eve Reider and Tom Brady, DESPER, Dr. Petra Jacobs, CCTN, and Dale Weiss, IP - and a visit to the Drug Court of Montgomery County, Maryland.

**2011 Society for Research in Child Development (SRCD) Biennial Meeting**, Montreal, Canada, March 31 through April 2, 2011. NIDA's Child and Adolescent Workgroup sponsored a workshop to provide an interactive discussion on career paths and NIH grant opportunities for early stage investigators. Speakers presented on current NIH and NIDA grant mechanisms available for emerging scholars, successful strategies for research grant review, and NIDA research priorities in developmental research for domestic and international researchers. Participants had the opportunity to interact with program staff in small groups for individualized feedback on their grant applications. Cheryl Anne Boyce (DCNBR) chaired the session with NIDA staff participants: Sarah Lynne Landsman (SRCD/AAAS Fellow); Nicolette Borek (DCNBR); Teresa Levitin (OEA); Belinda Sims (DESPR); and Kathy Etz (DESPR). DCNBR sponsored participants in the paper symposium, "Adolescent Perils and Potential: Exploring the Developing Brain and Understanding Pathways of Addiction". Early investigators Kirsten O'Hearn (University of Pittsburgh) and Omar Mahmood (UCSD) represented their respective research labs at the paper session along with senior research investigators Jay Giedd (NIMH Intramural) and Linda Spear (Binghamton University).

## Fellowships

### *NIDA Selects New INVEST Fellows*

Three new INVEST Drug Abuse Research Fellows were selected to spend 12 months of postdoctoral research training in the United States with professional development activities and grant-writing guidance. The new INVEST fellows include:

- Saeed Momtazi, Ph.D., Iran, will work with Richard A. Rawson, Ph.D., Integrated Substance Abuse Programs, University of California, Los Angeles, to attain expertise in questionnaire construction, sampling strategies and analyzing results of data in order to carry out the project objective of determining how sociocultural risk and protective and resiliency factors change in immigrants and how these same factors interact with the host country's factors.
- Gabor Egervari, Hungary, who will work with mentor Yasmin L. Hurd, Ph.D., Mount Sinai School of Medicine, plans to study the expression of mTOR pathway proteins and related mRNAs in the brains of human heroin abusers, exploring brain regions highly implicated in substance dependence. The aim of the study is to provide significant insights about the role of mTOR in drug-induced synaptic plasticity relevant to human heroin abuse and fine-tuning treatment strategies for specific phases of the abuse cycle. Mr. Egervari will receive his medical degree in June 2011.
- Arina Tyurina, Ph.D., Russia, will work with mentor Jeffrey Samet, M.D., M.P.H., Boston University School of Medicine, to investigate the impact of depressive symptoms of alcohol and marijuana use on HIV risk-behaviors among people with HIV. She plans to assess the impact of these factors on HIV-related risk behaviors, including needle/syringe sharing and high-risk sexual behaviors, while also examining the data with regard to gender differences.

### *New INVEST/CTN Fellow Selected*

A NIDA Hubert H. Humphrey Fellow in 2007-2008, Rushit Ismajli, M.D., Labyrinth Multidisciplinary Substance Abuse Treatment Center, Kosovo, has

been selected as an INVEST/CTN Fellow. He will concentrate on learning about screening, brief intervention, and referral to treatment (SBIRT) methods, working with Dennis M. Donovan, Ph.D., University of Washington, and the CTN Pacific Northwest Node. Dr. Ismajli will then test an SBIRT intervention in two Kosovo secondary schools.

***NIDA Welcomes New Fellows***

NIDA staff welcomed 26 fellows from 22 nations as part of an orientation for new fellowship awardees. IP Director Dr. Steven W. Gust and Associate Director Dale Weiss hosted the Hubert H. Humphrey Fellows from Virginia Commonwealth University, Johns Hopkins University, and Emory University, who were joined by NIDA INVEST and INVEST/CTN Fellows, and a DISCA awardee for the 3-day orientation. Fellows learned about the Institute's international research priorities as well as about NIDA and NIH online resources and collaboration and training tools. Drs. Joseph Perpich and Krystyna Isaacs discussed the NIDA International Virtual Collaboratory (NIVC) and the Humphrey Fellowship Professional Affiliation Directory created through NIVC. The representatives from NIDA Divisions who talked with the fellows about their offices' international research priorities and opportunities for collaborative international research included: Drs. Kevin P. Conway, Richard Jenkins, and Peter Hartsock, DESPR; Dr. Lynda Erinoff, ARP; Dr. Shoshana Kahana, DCNBR; and Dr. Petra Jacobs, CCTN. The fellows visited the IRP in Baltimore, touring the chemistry and drug metabolism laboratories with Dr. David Gorelick, and the magnetic resonance imaging suite with Dr. Eliot Stein. They heard presentations from Dr. George Uhl of the Molecular Neurobiology Section regarding genetic addiction research, and Dr. Steve Heishman of the Nicotine Psychopharmacology Section about the Institute's research on nicotine addiction. Fellows also toured the National Library of Medicine and met with staff at the Fogarty International Center.

**CTN INVEST Fellows**

The National Institute on Drug Abuse (NIDA) International Program and the Clinical Trials Network (CTN) joined forces to offer fellowships to non-U.S. scientists. The researcher works with a mentor who is affiliated with one of the 13 CTN Nodes. The 3 current CTN INVEST fellows visited NIH and NIDA the week of February 1, 2011. They received a tour of the NIH and NIDA campuses in Bethesda, as well as the NIDA Intramural Program in Baltimore, Maryland. On February 4, 2011, the group gave an informal talk to CCTN staff and presented their current work:

- **Suzanne Nielsen (Australia)** (Mentor: Dr. Walter Ling, University of California, Los Angeles). Dr. Nielsen discussed her progress with several secondary analyses that she is conducting with the CTN 0003 dataset, as well as other studies at UCLA.
- **Meera Vaswani (India)** (Mentor: Dr. Wade Berrettini, University of Pennsylvania). Dr. Vaswani presented her work regarding genetic analysis with blood samples from the NIDA repository.
- **Felipe Vallejo Reyes (Chile)** (Mentor: Dr. Eugene Somoza, University of Cincinnati). Dr. Reyes gave a brief description of his plan to test a cognitive assessment with cocaine addicted patients.

On March 16, 2011, the CTN conducted a CTN INVEST/International Forum where current fellows presented their work. They were joined by Dr. Adhi Wibowo Nurhidayat (Indonesia) who is a current recipient of an International AIDS Society (IAS)-NIDA Postdoctoral Research Fellowship and Co-investigator of a NIDA funded study assessing the impact of Behavioral Drug and Risk Counseling in five methadone clinics in Jakarta [Mentor: Dr. David Metzger, University of Pennsylvania]. During this meeting, Dr. Viviana Horigian (Florida Node) presented an update on the ongoing work on establishing a research

network in Mexico. Other presenters included Dr. Nathalie H. Gendron from the Canadian Institutes of Health Research and Drs. Francesco Bricolo & Roberto Mollica from the Department for Anti-Drug Policies, Presidency of the Council of Minister, Rome, Italy.

### International Visitors

A group from Russia sponsored by The American International Health Alliance visited NIDA on February 10, 2011. The group was on a study tour to learn about policy and coordination for AIDS response including internationally accepted practices of HIV prevention for youth and most-at-risk populations. Meeting with the group from NIDA were, Dr. Lynda Erinoff, ARP, Dr. Shoshana Kahana, DCNBR, Dr. Ivan Montoya, DPMCDA and Dr. Steve Gust, IP.

NIDA staff Dr. Rich Jenkins, DESPR, Dr. Shoshana Kahana, DCNBR and Ms. Dale Weiss, IP met with a group of visitors from Turkmenistan. The group was sponsored by the U.S. Department of State's International Visitor Leadership Program. The objectives of the visit were to illustrate the role of the federal, state, and local government agencies in developing and implementing prevention, treatment and rehabilitation programs, to examine education and rehabilitation programs offered by non-governmental organizations, to observe the provision of medical and psychological treatment to drug abusers during site visits to hospitals and drug rehabilitation centers, to explore social problems that compound drug abuse and to understand how U.S. and international organizations collaborate on these matters.

Shoshana Kahana was invited to meet and discuss NIDA priorities, particularly in the context of prevention and treatment interventions related to substance abuse and HIV, with over 20 Hubert H. Humphrey International Fellows at a joint February 4, 2011 meeting.

### Other International Activities

Dr. Wilson M. Compton, Director, DESPR, chaired a panel and presented a paper on "Unemployment and Illicit Drug Use in the United States: Changes During an Economic Recession" (prepared with Joe Gfroerer and Dr. Kevin Conway) at the International Federation of Psychiatric Epidemiogy, Kaoshiung, Taiwan, March 31, 2011.

Dr. Wilson M. Compton chaired a panel at the Society for Research on Nicotine and Tobacco on "Unassisted Quitting vs. Cessation Interventions in the Era of Tobacco Regulation and Health", Toronto, Canada, February 17, 2011.

Dr. Richard A. Jenkins, Prevention Research Branch, DESPR, attended a meeting with academic and government representatives from Turkmenistan regarding drug treatment and prevention services on February 17, 2011.

Dr. Belinda Sims, Prevention Research Branch, DESPR, attended the Society for Research in Child Development, 2011 Biennial Meeting in Montreal, Quebec, Canada, from March 30, through April 1, 2011. During the meeting, she participated in several panel presentations related to NIH and NIDA research priorities: "Millennium Scholars Preconference—Predoctoral Funding Opportunities at NIH;" "Implementation Research: Federal Research Initiatives and Funding Opportunities" (with DHHS Administration for Children and Families, Assistant Secretary for Planning and Evaluation, Centers for Disease Control and Prevention, and the US Department of Education); "NIDA Emerging Scholars Workshop for Early Stage and New Investigators" (with NIDA's DCNBR, DESPR, and OEA); and "NIH Update on Policy Issues, Scientific Review, and Research Priorities" (with the National Institute of Mental Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Center for Scientific Review, and Office of Behavioral and Social

Sciences).

Dr. Peter Hartsock, DESPR, participated in a conference sponsored by the Center for Strategic and International Studies (CSIS) on "Drug Abuse in Russia: Scope, Trends, Implications, and Policy Responses," held February 23, 2011 in Washington, D.C.

Dr. Peter Hartsock participated in the CSIS Global Health Policy Center's launch of the semiannual CSIS Forum on "Advancing U.S. Leadership in Global Health," March 7, 2011, in Washington D.C. Government officials, members of the CSIS Commission on Smart Global Health Policy, and leading health experts met for a discussion on preserving and building on the legacy of U.S. bipartisan support for global health. The first meeting established the cornerstone for an on-going, long-term dialogue and planning process, focusing on achievements from the last decade and strategies for continuing their success.

Dr. Jonathan D. Pollock attended the 17th Annual Meeting of the Society for Research on Nicotine and Tobacco, February 16-19, 2011, in Toronto, CA. Dr. Cora Lee Wetherington gave a keynote presentation, "Sex Differences in Drug Abuse: The Importance of Conducting a Sex/Gender Analysis of Data," at the 4th World Congress on Women's Mental Health, Madrid, Spain, March 16-19, 2011.

Dr. Amy Newman, IRP, gave an invited lecture at the University of Camerino, Camerino, Italy, in March 2011.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Meetings/Conferences

NIDA participated in the annual **Brain Awareness Week** activities at the **National Museum of Health and Medicine** on March 16 and 17, 2011. This annual event brings in children from schools throughout the Washington, D.C. area for a celebration of the brain and nervous system. NIDA played the interactive computer based game "NIDA Brain Derby," where students test their knowledge of how drugs of abuse act in the brain and body. This year, there were approximately 350 students who participated in the two-day event. Other NIH institutes involved were: NIMH, NINDS, NIAAA, NIA and NICHD. Brain Awareness Week is an annual international partnership of government agencies, scientific organizations, and university and volunteer groups. NIDA has participated in this event for each of the 12 years that it has been held.

NIDA participated in **Take Your Child to Work Day**, an annual event for the children of NIH staff, on April 28, 2011. This day-long event brought NIDA scientists together with the children of NIH staff to play the game "NIDA Brain Derby." The children had the opportunity to see how much they know about how drugs act in the brain and body. Winners of the game received a certificate declaring that they are an official "Brain Scientist." NIDA also distributed our many publications that have been developed for children.

On March 28-29, 2011, NIDA, in partnership with the U.S. Surgeon General's Office and other Federal Agencies, held an **Expert Panel on Preventing Prescription Drug Abuse in Youth**. Leading academics, practitioners, advocacy groups, professional associations, and Federal agencies were convened to review the science and engage in a dialogue to guide the development of a product from the Office of the Surgeon General. Topics discussed included the state of prevention science, media and messaging opportunities, prescription drug abuse among military personnel, engaging health care professionals, and working with state prescription drug monitoring programs.

A meeting of the Principal Investigators of the **National Drug Abuse Treatment Clinical Trials Network** was held on January 14, 2011. Investigators from all Nodes attended to address the future planning of CTN activities.

On March 8, 2011, the **Delaware Valley Node Dissemination Conference** was held in Philadelphia, PA. Drs. Geetha Subramaniam and Petra Jacobs, Carmen Rosa, and Ron Dobbins attended the workshop. The workshop was titled, "Integrating Treatment for Substance Use Disorders with Other Health Care Services." The one-day conference was sponsored by the Delaware Valley Node of the NIDA Clinical Trials Network, University of Pennsylvania Department of Psychiatry, Center for Studies of Addictions; Treatment Research Institute; NeATTC and IRETA, and was held in Philadelphia, PA on the University of Pennsylvania Campus.

**Publications**

**Staff Highlights**

**Grantee Honors**

**The National CTN Steering Committee Meetings** were held March 15-17, 2011 in Bethesda, Maryland. The following workshops and meetings convened.

- Treatment Guide
- MEIDAR 2.0 Workshop
- D & A Workshop
- CTP and PI Caucuses
- Executive Committee
- Research Utilization Committee
- Research Development Committee
- Node Coordinator Workgroup
- Invest Fellows Meeting
- Steering Committee
- Pharmacotherapy Special Interest Group
- CTN 0037, STRIDE
- CTN 0044, Web-based TES
- CTN 0046, S-CAST
- CTN 0047, SMART-ED
- CTN 0050, START Follow-up
- Psychopharmacotherapy SIG

On March 15, 2011, the **NIDA/ATTC Blending Product Team** gave a demonstration and led a focus group discussion of a new web Portal featuring a suite of products on Motivational incentives (revised PAMI awareness training; newly developed on-line training system addressing practical aspects of implementing Incentives in treatment programs [MI-PRESTO: Motivational Incentives - Patient Reinforcement to Enhance Successful Treatment Outcomes]; and MIIS (Motivational Incentives Implementation Software) - software system developed by NIDA IRP to establish and track incentive programs).

On March 15, 2011, a workshop titled **Handling Missing Data in the Analysis of CTN Trials: Pitfalls and Possible Solutions** addressed the problem of missing data from CTN trials. The focus was mostly on primary outcomes data, which may be missing for a variety of reasons, including discontinuation of the study, outcomes undefined for some participants (such as quality of life measures after death), or attrition. A variety of approaches for dealing with missing data were discussed, including ways to design trials to help minimize the likelihood of missing data. Ways to analyze missing data were also provided, including repeated-measure designs, linear and quadratic time trend or spline models, and the importance of sensitivity analysis.

The **4th Annual NIH Conference on the Science of Dissemination and Implementation: Policy and Practice** was held March 21-22, 2011 in Bethesda, Maryland. NIDA CTN members and CCTN staff presented the following:

1. Dr. Udi Ghitza chaired a workshop entitled "Use of Innovative E-Technology to Disseminate and Implement Treatments."
2. Dr. Barbara Moquin, CCTN, and Dr. Dennis McCarty, CTN Western States Node, co-chaired a Think Tank entitled "NIH Networks: Platforms for Dissemination Research."

Dr. Lisa Onken, DCNBR, in collaboration with Drs. Susan Czajkowski of the National Heart, Lung, & Blood Institute and Patty Mabry, of the Office of Behavioral & Social Sciences Research, co-chaired a Society for Behavioral

Medicine- and NIH-sponsored Preconference Workshop, **From Discovery to Public Health Impact: New Approaches to Developing, Testing & Optimizing Behavioral Interventions**, on April 26, 2011. In this workshop, leading scientists and methodologists with expertise in fields such as qualitative and clinical trials research, adaptive treatment strategies, engineering and systems science approaches highlighted study designs, methods and analytic techniques that can facilitate research on the development, testing and optimization of behavioral interventions.

Jerry Frankenheim, Ph.D., DBNBR, organized and chaired a session, **Stress and Drug Abuse Converge on Serotonergic Function**, which took place on January 23, 2011, at the 44th Winter Conference on Brain Research, in Keystone, Colorado. Presenters were Lynn G. Kirby, Ph.D., Abbie G. Schindler, B.S. (graduate student in Charles Chavkin, Ph.D., lab), Kathryn G. Commons, Ph.D., and Samir Haj-Dahmane, Ph.D.

On February 17, 2011, Dr. Betty Tai, Director, CCTN, presented a talk titled "Clinical Trials Network - Model for Interfacing Basic Neuroscience, Clinical Research and Practice" at the Lost in Translation Symposium in Vancouver, British Columbia. Dr. Walter Ling, PI of the Pacific Node of the CTN presented "New treatment for stimulant users - agenda for the next years." This program was sponsored by the Canadian Centre of Substance Abuse (CCSA), the Mental Health Commission of Canada (MHCC), the Canadian Institute of Health Research, and the University of British Columbia (UBC).

On February 23, 2011, Dr. Betty Tai presented "National Drug Abuse Treatment Clinical Trials Network - A Forum for Community Engagement and CER in Substance Use Disorders" at the CTSA Community Engagement Key Function Committee meeting in Bethesda, MD.

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 on "Terminology of Substance Use Disorders for DSM-5" at the annual meeting of the American Society of Addiction Medicine, Washington, DC, April 16, 2011.

Dr. Wilson M. Compton chaired a panel on "Marijuana and Schizophrenia" at the International Congress on Schizophrenia Research, Colorado Springs, Colorado, April 6, 2011.

Dr. Wilson M. Compton presented to the NIH/Association of American Geographers Geospatial Infrastructure Workshop, Rockville, Maryland, February 22 and 23, 2011.

Dr. Wilson M. Compton chaired a panel at the Society for Research on Nicotine and Tobacco on "Unassisted Quitting vs. Cessation Interventions in the Era of Tobacco Regulation and Health", Toronto, Canada, February 17, 2011.

Drs. Wilson Compton and Aria Crump, DESPR, held a workshop entitled, "The Epidemiology and Prevention of Prescription Drug Abuse: A NIDA Update," for the Community Anti-Drug Coalitions of America's 21st Annual National Leadership Forum, held on February 8, 2011 at the Gaylord National Conference Center in Maryland.

Drs. Elizabeth Robertson and Augusto Diana, Prevention Research Branch, DESPR, organized and moderated a workshop entitled, "NIDA's Research and Practice Emphasis: Implications for Evidence-Based Designation," for the Community Anti-Drug Coalitions of America's 21st Annual National Leadership Forum, held on February 10, 2011 at the Gaylord National Conference Center in Maryland.

Dr. Belinda Sims, Prevention Research Branch, DESPR, attended the "Tribal, Maternal, Infant, and Early Childhood Home Visiting Program Grantee Kickoff Meeting and Tribal Early Learning Communities Consortium," January 18-19, 2011. This initiative is supported through a partnership between the Administration for Children and Families (ACF) and the Health Resources and Services Administration (HRSA).

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 in Spring 2011.

Dr. Richard A. Jenkins, Prevention Research Branch, DESPR, attended the mid-Winter meeting of the Executive Committee of the Society for Community Research and Action in Washington, DC on February 10, 2011.

Dr. Dionne Jones, DESPR, participated on the planning committee and was moderator and Workgroup leader for a conference sponsored by NCI and OBSSR on The Science of Research on Discrimination and Health, held at Natcher Conference Center, February 2-4, 2011.

Dr. Ivan Montoya, DPMCDA, attended and presented at the conference titled "Lost in Translation: Seeking Answers in Addiction and Concurrent Disorders" in Vancouver (BC), March 15-17, 2011.

Dr. Kristopher Bough, DPMCDA, volunteered at the Brain Awareness Week at the National Museum of Medicine where he worked alongside several other NIDA colleagues to present information on addiction and general neuroscience to school kids from DC and Maryland, Walter Reed Medical Center, Washington DC, March 16-17, 2011.

Dr. Kristopher Bough presented at a NIH-neuroscience outreach program to a group of middle-school students from Darnell-Cookman School of Medical Arts at the Lipsett Amphitheater on February 11, 2011.

Drs. Kristopher Bough and Jamie Biswas, DPMCDA, served as volunteer reviewers of applications for the NIDA Summer Internship Program, March 8 - 17, 2011.

Dr. Da-Yu Wu, DBNBR, was invited as staff faculty panelist for the NIH ESA CORE 4 Training - STAFF INTERACTIONS Class at Natcher on March 17, 2011. He led group discussions as well as the faculty panel Q&A session on NIH program initiative development.

Dr. John Satterlee, DBNBR, played a key role in organizing a trans-NIH Translational Epigenomics meeting entitled " From Epigenomic Discovery to Improvements in Human Health", March 8-9, 2011 Rockville, MD where he presented an overview of the accomplishments of the NIH Roadmap Epigenomics Program.

Dr. John Satterlee attended the NICHD Scientific Vision Workshop: Developmental Origins of Health and Disease, Bethesda, MD, February 14-15, 2011.

Dr. John Satterlee attended "A Decade with the Human Genome Sequence: Charting a Course for Genomic Medicine." Bethesda, MD, February 11, 2011.

Dr. John Satterlee attended "Data and Tools from the Allen Institute for Brain Science", Rockville, MD, February 3, 2011.

Dr. Jonathan D. Pollock, DBNBR, attended the 17th Annual Meeting of the Society for Research on Nicotine and Tobacco, February 16-19, 2011, in Toronto, CA.

The American Psychological Association (APA) Cyber Mentors Program featured Dr. Cheryl Anne Boyce, DCNBR, Ms. Ericka Wells, GMB, and Dr. Alfiee Breland-Noble, Duke University, for the webinar, "Constructing Successful Budgets for NIH Research Applications" on Wednesday, March 23, 2011.

Dr. Karen Sirocco, DCNBR, took part in a session presented by the NIH Office of Research on Women's Health which was held at the Women's Health 2011: The 19th Annual Congress in Washington, D.C. on March 31, 2011. The session was entitled "Towards a Better Understanding of the NIH Grant Process" and Dr. Sirocco spoke on "The Role of NIH Program Officials".

Dr. Nicolette Borek, DCNBR, represented NIDA and participated in developing the scientific research agenda at the Spring Network Meeting of the Pediatric HIV/AIDS Cohort Study (PHACS) March 14-15, 2011 in New Orleans.

Dr. Nicolette Borek organized and co-chaired the annual Steering Committee meeting of the Maternal Lifestyle Study (MLS) in Bethesda, MD on April 26-27, 2011. The MLS cooperative agreement is the largest longitudinal study of prenatal exposure to cocaine and other substances of abuse. It is co-funded by NIDA, NICHD, and NIMH.

Dr. Yu (Woody) Lin, DCNBR, was invited by the American Academy of Pain Medicine to organize and moderate a workshop session entitled NIH Pain Research: Optimizing Funding through Grant Writing. The conference was held at the society's 27th annual conference on March 2-7, 2011 in National Harbor, Maryland.

Dr. Yu (Woody) Lin was invited by the Society for NeuroImmune Pharmacology to introduce to its members at a NIH workshop on NIDA DCNBR's HIV/AIDS program including preparation of the grant applications for translational studies. The conference was at the society's 17th annual conference, April 06-10, 2011 in Clearwater, Florida.

Dr. Harold Gordon, DCNBR, participated in the annual meeting of the National Sleep Awareness Roundtable (NSART) an organization whose members are medical and advocacy groups associated with sleep and sleep disorders; representatives from several government agencies (CDC, DOT, NSF, NIH) who have interest in sleep research and consequences of sleep disturbances. The meeting was held on March 16, 2011 in Washington, D.C.

Dr. Steven Grant, DCNBR, chaired two symposia at the International Congress on Schizophrenia Research entitled: Nicotine Receptors: Crossroads of Substance Abuse and Schizophrenia and Cannabis and Psychosis: Epidemiology and Neuroscience Perspectives (co-chaired with Dr. Wilson Compton of DESPR). The meeting was held on April 2-6, 2011 in Colorado Springs, Colorado.

Drs. Cecelia Spitznas, Shoshana Kahana, and Lisa Onken, all of DCNBR, were invited to participate in the Treatment Improvement Protocol (TIP)

Stakeholders Meeting on Using Telephone and Web-Based Technologies in Behavioral Health Settings on March 23rd 2011. The meeting was sponsored by SAMHSA and involved key representatives of Federal agencies and national organizations with a vested interest in the TIP who provided feedback on the prospectuses for this planned SAMHSA publication.

Dr. Lisa Onken participated in the Stakeholder's Meeting on the Treatment Improvement Protocol (TIP) on Reintegration-Related Behavioral Health Issues in Veterans and Military Families on February 16, 2011. The meeting was sponsored by SAMHSA and involved key representatives of Federal agencies and national organizations with an interest and expertise in the TIP.

Dr. Lisa Onken represented NIDA by providing opening remarks at a February 23-24, 2011, meeting at the University of Maryland on Incentives and Health, organized by Captain Neal Naito, M.D., U.S. Navy, and Stephen Higgins, Ph.D. The conference was sponsored by the U.S. Navy and grew directly out of activities that began at the January 6th and 7th, 2009 Bethesda NIDA/DOD/VA/NIMH/NIAAA/NCI/NHLBI conference, "Addressing Substance Abuse and Comorbidities Among Military Personnel, Veterans and their Families: A Research Agenda." The Behavioral & Integrative Treatment Branch, including Drs. Cecelia Spitznas, Will Aklin, Shoshana Kahana, and Debra Grossman participated in the meeting.

Dr. Lisa Onken gave a presentation on NIDA funding opportunities and priorities at the March 24 and 25, 2011, Behavioral Economics and Health meeting of the Penn CMU Roybal Center in Philadelphia, Pennsylvania. Dr. James Bjork, DCNBR, gave a talk entitled "The Relationship of Drugs, Alcohol and Violence" to the Southern Maryland Hospital Center (Clinton, MD) for the NIH LifeWorks Speakers Bureau, on March 9, 2011.

Dr. Lula Beatty attended the National Multicultural Summit and Conference on January 27-28, 2011 in Seattle, Washington and participated in the executive committee meeting of the Society for the Psychology of Women, American Psychological Association.

Dr. Lula Beatty attended the Science of Research on Discrimination and Health conference sponsored by the NCI, February 2-4, 2011 in Bethesda, Maryland.

Dr. Lula Beatty is participating on the planning committee of the AIDS Family Day program sponsored by the NIMH and convened by the American Psychological Association as a preconvention event to be held August 3, 2011 in Washington, DC.

Dr. Lula Beatty met with Dr. Maria Cecilia Zea and the Latino Mental Health Center staff and students at George Washington University on March 9, 2011 in Washington, D.C. to discuss research development opportunities.

Dr. Lula Beatty and Flair Lindsey, Program Analyst, Special Populations Office, presented an overview of the Diversity-promoting Institutions Drug Abuse Research Development Program (DIDARP) at the NIDA OEA Symposium on March 15, 2011 in Bethesda, Maryland.

Dr. Lula Beatty participated as a faculty member in the Leadership Institute for Women in Psychology program for midcareer women psychologists in academic/medicine careers on March 24, 2011 in Washington, DC.

Dr. Lula Beatty attended the meeting of the Committee of Women in Psychology on March 25, 2011 in Washington, DC.

Dr. Lula Beatty is participating with Dr. Dionne Jones, Chair, as a research advisor for the Climbing Up Reaching Back (CURB) scientific mentoring program for 10th grade high school students at the University of Maryland, College Park. The group is developing a project on HIV/AIDS among young

people.

Dr. Lula Beatty presented a talk titled "Drug Use in Racial/Ethnic Minority Populations: Avoiding Risks and Seeking Care" for the NIH Focus on You Wellness Seminar Series on April 5, 2011 in Bethesda, Maryland.

Ana Anders, M.S.W., Public Health Analyst, Special Populations Office, participated in the National Hispanic Science Network bi-annual planning meeting, February 28-March 1, 2011 in New Orleans, Louisiana.

Dr. Teri Levitin, Director, OEA, was on the panel that presented "NIDA Emerging Scholars Workshop for Early Stage and New Investigators" at the Society for Research in Child Development biennial meeting in Montreal, March 31 - April 2, 2011.

Dr. Teri Levitin was on the panel for the workshop "Grants 201 for Mid-Career and Senior Level Scientists: Supporting Thyself and Mentoring the Next Generation of Researchers." at the Society for Research in Child Development biennial meeting in Montreal, March 31-April 2, 2011.

Dr. Gerald McLaughlin, OEA, was a member of the trans-NIH training faculty expert panel for the Core 4 training session "Staff Interactions; How the Extramural Team Functions." March 17th, 2011.

Dr. Scott Chen, OEA, provided guidance in "feedback sessions" for SBIR companies to practice the delivery of their business opportunity to industry experts, CAP alumni/past SBIR awardees, and NIH staff at the 7th Annual NIH Commercialization Assistance Program (CAP), Washington DC, January 31, 2011.

Dr. Scott Chen was a NIDA Co-Representative, with Dr. Ericka Boone, OSPC, at the 2011 National Tobacco Cessation Collaborative Annual Meeting, in Washington D.C., March 24, 2011.

Dr. Amy Newman, IRP, gave an invited lecture at the Wake Forest University School of Medicine, Department of Pharmacology and Physiology, Winston-Salem, NC in February 2011.

Dr. Eliot L. Gardner, IRP gave a lecture entitled Endocannabinoids: basic physiology and function at the New York Society of Addiction Medicine, New York NY, February 2011.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Media Support of Events and Meetings

A teleconference was held on February 22, 2011 as a result of the over 100 calls and emails received by NIDA regarding research by Dr. Nora Volkow on the effects of cell phone radiofrequency signal exposure on brain glucose metabolism that was published in the *Journal of the American Medical Association*. Eighteen media outlets participated in the teleconference, including the San Francisco Chronicle, Newsweek, Bloomberg News, New York Times, Newsday, National Journal, Associated Press, ABC News, among others. Dr. Volkow conducted interviews about the study with nearly 40 major media outlets, including USA Today, CBS News, NBC Nightly News, ABC News, Reuters, National Public Radio, Voice of America, PBS NewsHour, Washington Post, Los Angeles Times, and others.

Planning and media outreach was conducted for the launch of the Addiction Performance Project (APP), a continuing medical education (CME) program that offers healthcare providers the opportunity to help break down the stigma associated with addiction and promote a healthy dialogue that fosters compassion, cooperation, and understanding for patients living with this disease. This project is part of NIDAMED, NIDA's outreach program targeted to practicing physicians, physicians in training, and other health professionals. Each performance begins with a dramatic reading of Act III of Eugene O'Neill's "Long Day's Journey into Night" by award-winning, professional actors. The reading is followed by a brief expert panel presentation and facilitated audience discussion on caring for drug-addicted patients. Performances were scheduled in Boston, MA (March 28); Washington, D.C. (April 16); and Phoenix, AZ (May 6). Additional information about APP can be found at www.drugabuse.gov/nidamed/APP. Activities supporting this project included planning and executing each performance; marketing the program to promote registration among physicians, residents, and medical school faculty; and conducting outreach to national, local, trade, and social media to raise awareness about the project among targeted audiences.

Dr. Susan Weiss, Acting Director, Office of Science Policy and Communications, participated in the PRISM Nomination Review Committee (for the 2011 PRISM Awards) in Los Angeles, CA on January 29-30, 2011.

On April 28, 2011, the Community Anti-Drug Coalitions of America (CADCA) aired a pre-recorded TV program entitled: Dispelling Drug Myths, featuring Dr. Ruben Baler. During this hour-long program Dr. Baler helped the audience dispel myths about drugs using scientific facts. He also used the forum to explain how NIDA is working to answer teens' questions.

## Press Releases & Notes to Reporters

**December 9, 2010**—"Buprenorphine treatment in pregnancy: less distress to

babies"

**December 14, 2010**—"Teen marijuana use increases, especially among eighth-graders"

**January 18, 2011**—NIH-funded study uses new technology to peek deep into the brain

**March 2, 2011**—NIH-funded study shows early brain effects of HIV in mouse model

**Publications**

**Staff Highlights**

**Grantee Honors**

### NIDA issued the following Notes to Reporters

**December 1, 2010**—World AIDS Day message from NIDA Director, and the posting on NIDA's website of a series of video interviews with Drs. Volkow, Normand, and several NIDA grantees about current research related to HIV/AIDS. The message can be found at http://www.nida.nih.gov/about/welcome/MessageHIV1210.html.

**December 10, 2010**—2010 Drug Facts Chat Day Transcript available on NIDA's website, www.drugabuse.gov/chat/2010.

**January 4, 2011**—Study about a new vaccine which produces a long lasting immunity to cocaine's effects in mice in *Molecular Therapy*, www.nature.com/mt/journal/vaop/ncurrent/full/mt2010280a.html.

**January 14, 2011**—Research on a potential new strategy to relieve chronic pain without the risks associated with opioid medications in *Nature*, http://www.nature.com/neuro/journal/v13/n10/abs/nn.2632.html.

**January 19, 2011**—Study about what happens inside a smoker's brain while watching a movie actor light up on the screen in *The Journal of Neuroscience*, http://www.jneurosci.org/content/31/3/894.full?sid=f7fcbcf7-c8c3-4d91-b8db-3552c9892275.

**January 20, 2011**—New teaching resources on substance abuse and addiction for medical students as part of NIDA's CoE curriculum, http://www.drugabuse.gov/coe/cr-overview.htm.

**January 31, 2011**—Study of why some may find it difficult to limit their smoking in *Nature*, http://dx.doi.org/10.1038/nature09797.

**February 20, 2011**—Innovative technique to determine if drug-associated environmental cues will trigger heroin seeking in an animal model of relapse in *Nature Neuroscience*, http://www.nature.com/neuro/journal/vaop/ncurrent/full/nn.2758.html.

**February 22, 2011**—Study on efficacy of two popular anti-marijuana media campaigns in *Prevention Science*, http://www.springerlink.com/content/ljl437nx38745452/fulltext.pdf.

**February 23, 2011**—Special edition of *Neuron*, devoted entirely to advances in addiction research. Includes commentary by NIDA Director Dr. Nora Volkow entitled "Addiction: Pulling at the Neural Threads of Social Behavior," http://www.cell.com/neuron/abstract/S0896-6273%2811%2900075-4.

### Highlights of Interviews: December 2010 - September, 2011

*Discovery Magazine* — Dr. Nora Volkow was interviewed about nicotine and cocaine vaccine research.

*Multiple Print/Broadcast Outlets*—Dr. Nora Volkow was interviewed by national

and local newspapers, news services, television and radio stations about the results of the Monitoring the Future 2010 Survey.

*Associated Press*—Dr. Volkow was interviewed about behavioral change.

*Reuters Health*—Dr. Wilson Compton was interviewed about accidental poisonings.

*Glamour*—Dr. Volkow was interviewed about food addition.

*Voice of America*—Dr. Volkow was interviewed about the cocaine vaccine.

*ESPN*—Dr. Compton was interviewed about research published in Drug and Alcohol Dependence on opioid abuse in retired NFL players.

*Doctor Radio*—Dr. Steve Grant was interviewed about a NIDA-funded study on nicotine; Dr. Compton was interviewed about NIDAMED initiative.

*Atlantic TV News*—Dr. Susan Weiss was interviewed about marijuana use among teens.

*Los Angeles Times*—Dr. Marilyn Huestis was interviewed about drugged driving.

*National Public Radio*—Dr. Volkow was interviewed about nicotine/tobacco addiction.

*Men's Health*—Dr. Ivan Montoya was interviewed about nicotine/smoking addiction among men.

*Chemical and Engineering News*—Dr. Amy Newman was interviewed about IRP research published in Science.

*National Geographic*—Dr. Elliot Stein was interviewed and appeared on television as part of the documentary: Drugged: High on Cocaine.

## Other Educational Activities

### CCTN Seminar Series

As part of the CCTN seminar series, on February 10, 2011, Dr. George E. Woody, Professor in the Department of Psychiatry, School of Medicine at University of Pennsylvania and Principal Investigator of the Delaware Valley Node of the NIDA Clinical Trials Network (CTN) presented the Classroom Seminar. Dr. Woody reviewed the outcomes of the study, "Extended vs. short-term buprenorphine-naloxone for treatment of opioid addicted youth: A randomized trial", and presented data from a cost-effectiveness analysis of the two treatment arms followed by findings from four secondary analyses.

As part of the CCTN seminar series, on February 22, 2011, Drs. Barbara A. Marin and R. Gregory Lande presented, "Implementing Evidence-Based Practices in a Military Setting." Dr. Barbara A. Marin is Chief, Integrated Department of Addictions Treatment Services for Walter Reed Army Medical Center and National Naval Medical Center. She is also the Clinical Director of the Walter Reed Army Substance Abuse Program. Dr. R. Gregory Lande is Chief, Psychiatry Continuity Service and the Clinical Consultant for the Army Substance Abuse Program. They discussed The Army Substance Abuse Program, Evidenced Based Practices employed, and recent research activities. They also discussed results from the Performance Improvement Project Alcohol Safety and Attitudes Survey.

As part of the CCTN seminar series, on March 8, 2011, Dr. Matthew Burke, a Senior Clinical Consultant at the Health Resources and Services Administration (HRSA), DHHS gave a presentation titled, "Patient Centered Medical Home in the Community Health Centers: A model for quality, patient centric care and its impact on mental health and substance abuse." He discussed HRSA's current

efforts implementing health information technologies in the context of healthcare reform, and patient centered medical home (PCMH) transformation in federally qualified health centers (FQHCs). He also discussed the implications of this work to improved coordination of care and prevention among these healthcare delivery settings, primary care, and community-based specialty substance use disorder treatment settings.

## Upcoming Conferences/Exhibits

**American College of Physicians/American Society of Internal Medicine Internal Medicine 2011 Conference**
April 7-9, 2011—San Diego, CA

**American Psychiatric Association Annual Meeting**
May 14-18, 2011—Honolulu, HI

**American College Health Association Annual Meeting**
May 31-June 4, 2011—Phoenix, AZ

**National Parent and Teacher Association Annual Convention**
June 9-11, 2011—Orlando, FL

**National Association of School Nurses Annual Conference**
June 29-July 3, 2011—Washington, DC

**State Associations of Addiction Services and the Network for the Improvement of Addiction Treatment**
July 10-13, 2011—Boston, MA

**National Association of Drug Court Professionals Annual Training Conference**
July 17-20, 2011—National Harbor, MD

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Planned Meetings

NIDA will once again co-sponsor its Addiction Science Award at the **Intel International Science and Engineering Fair** to be held May 8-13 in Los Angeles, CA. Intel ISEF is the world's largest international pre-college science competition. More than 1,500 high school students from over 50 countries, regions, and territories showcase their independent research at the annual event. Scientists from NIDA's Office of Science Policy and Communications and NIDA grantees serve as judges for the event every year, and will award first, second, and third place honors. The Friends of NIDA provides funding for the awards.

The National Institute on Drug Abuse (NIDA) is conducting a research track at the **American Psychiatric Association (APA) Annual Meeting** in Honolulu, Hawaii, May 14-18, 2011. NIDA will hold a number of sessions on topics unique to addiction science. Topics include: Decision Making and Addictions: Neurobiology and Treatment Implications; Does the Brain Ever Recover from Drug Addiction?; Brain Mechanisms and Neuropsychiatry in Smoking Cessation; Update on the Treatment of Comorbid Opioid Addiction and Chronic Pain; Marijuana and Psychosis: Neuroscience, Genetics and Clinical Perspectives, and; The Shrinking Psychotherapeutic Pipeline: Why has the Spigot Been Turned Off. NIDA will also lead a Forum titled, Health Reform: Transforming Addiction Services in the United States, and NIDA Director, Dr. Nora Volkow, will give an APA invited Frontiers of Science Lecture.

The National Institute on Drug Abuse (NIDA) is collaborating with the National Center for Research Resources (NCRR), the National Institute of Mental Health (NIMH) and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) to host a meeting entitled **Advanced Medical Imaging Developments and Applications for Neuroscience Research** to be held in Bethesda, MD on June 9, 2011.

The National Institute on Drug Abuse (NIDA) is organizing a program at the **2011 American Psychological Association (APA) Annual Meeting** in Washington, D.C., August 4-7. NIDA staff throughout the Institute are involved in the planning of sessions on a wide range of topics related to addiction research. NIDA will also co-sponsor an Early Career Investigator Poster Session with APA's Divisions 28 and 50 and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as part of the two Divisions' Social Hour.

The next National CTN Steering Committee Meetings will be held September 2011 in Bethesda, Maryland.

**Publications**

**Staff Highlights**

**Grantee Honors**

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Publications

### NIDA Publications

**Drugs: Shatter the Myths**
**NIH Pub. No.: 11-7589**
Booklet that answers teens' most frequently asked questions about drugs and drug abuse. Written and designed specifically for teens, with teen input, this must-have resource provides scientific facts with engaging images and designs to help teens *shatter the myths* about drugs and drug abuse.

**Research Report Series: Prescription Drug Abuse**
**NIH Pub. No.: 11-4881**
Describes the dangers of prescription drug abuse and reviews research in this area. Offers approaches for patients and providers to help them avoid the misuse of prescription and OTC drugs. Reviews most commonly abused prescription drugs.

**Marijuana: Facts for Teens (Revised) (In Press)**
**NIH Pub. No.: 10-4037**
The booklet explains current knowledge about marijuana and the latest scientific information on its effects. It provides teens with answers to questions about marijuana, including what it is, who uses it, and how it affects a person physically and mentally after short- and long-term use.

**Marijuana: What Parents Need to Know (Revised) (In Press) NIH Pub. No.: 10-4036**
The booklet provides valuable information from research on the dangers of marijuana. It gives parents explanations of the latest scientific information about the drug and suggestions on how to talk to teenagers about the drug.

**Principles of Drug Abuse Treatment for Criminal Justice Populations (Revised)**
**NIH Pub. No.: 11-5316**
Designed as a complement to NIDA's Principles of Drug Addiction Treatment: A Research-Based Guide, this booklet provides treatment principles and research findings that are of particular relevance to the criminal justice community and to treatment professional working with drug-abusing offenders.

**Research Report Series: Marijuana Abuse (Spanish) (In Press)**
**NIH Pub. No.: 11-3859S**
This Research Report summarizes what the science tells us about marijuana abuse in the United States and its effects on the brain and body. It includes an extensive review of the latest research literature presented for a general audience interested in learning more about marijuana's consequences for physical, mental, and emotional health.

**Publications**

**Staff Highlights**

**Grantee Honors**



***NIDA Notes*, Vol. 23, No. 4**

This issue features articles on: Communities That Care, a program that implements evidenced-based substance abuse prevention programs which helped students reduce delinquency, decrease initiation of alcohol and tobacco use, and lessen binge drinking; research showing that more than 1,000 proteins in the neurons of the brain's reward system may be altered by chronic cocaine abuse, contributing to the transition from voluntary to compulsive drug taking; a comparison of five smoking cessation programs, showing that a combination of nicotine patch and lozenge offered the best results; and a report showing that assisting HIV-infected prisoners with the paperwork necessary to obtain free antiretroviral therapy after release substantially reduced treatment interruptions. Finally, in the Director's Perspective, Dr. Volkow outlines the Institute's commitment to research that addresses the potential for physical activity to prevent substance abuse.

***NIDA Notes*, Vol. 23, No. 5**

This issue of NIDA Notes reports that: male and female children exposed to prenatal maternal smoking, have different genetic variants associated with a higher risk of developing a conduct disorder; gender-specific, multi-session programs designed to teach safe-sex behaviors are effective in patients receiving drug abuse treatment; and state and federal prison systems underutilize opioid replacement therapy, an evidence-based treatment for opioid addiction. This issue also reports on a neuropeptide blocker that dampens rats' motivation for cocaine and rich food--the finding may introduce a new strategy for treating both drug addiction and obesity. Finally, in this month's Director's Perspective, Dr. Volkow discusses NIDA's effort to develop treatments for groups with the highest smoking rates, including high school dropouts, Native Americans, and people with psychiatric disorders.

## CTN-Related Publications

Five editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN. The Bulletin has wide readership within and outside the CTN and NIDA.

Data from 23 CTN studies are now available on the CTN Data Sharing Web Site http://www.nida.nih.gov/CTN/Data.html. Over 800 data sets have been downloaded by researchers from 13 countries. These data sets are in compliance with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap. The CTN Data Share is also part of the Neuroscience Information Framework (NIF), which is a dynamic inventory of Web-based neuroscience resources: data, materials, and tools accessible via any computer connected to the Internet.

## International Program-Related Publications

### *NIDA International Program E-News*

- *January 2011* - This issue featured the November 2010 NIDA-Fogarty International Center meeting in Hanoi, Vietnam, that initiated an Asian Regional Research Collaboration Network. Other stories reported on an Iraq-Substance Abuse and Mental Health Services Administration (SAMHSA) partnership that brought four Iraqis to meet with NIDA staff on November 1, 2010; a new NIDA Program Announcement that supports research partnerships between the United States and India; and the selection of new INVEST and INVEST/CTN fellows.
- *March 2011* - This issue reported on the NIDA Request for Applications to support implementation research that will inform projects supported by the

President's Emergency Program of AIDS Relief (PEPFAR) and international collaborative research teams investigating HIV/AIDS and drug use. Other stories reported on a potential treatment for inhalant abuse developed by the IP Distinguished International Scientist team of Dr. Hwei-Hsien Chen, Taiwan, and Dr. Athena Markou, University of California, San Diego; the orientation for IP fellows that brought 26 drug abuse professionals from 22 nations to NIDA and NIH in late January; and an innovative writing mentorship program for scientists from developing countries organized by the International Society of Addiction Journal Editors.

### Other Publications

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# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Staff Highlights

### Staff Honors

**Dr. Lula Beatty**, Director, SPO, served as a reviewer for the American Journal of Drug and Alcohol Abuse.

**Dr. Jennifer Bossert**, IRP, received the Intramural Research Program's "Women in Neuroscience Award" in the staff scientist category.

**Dr. Cheryl Anne Boyce**, DCNBR, was selected as a senior scholar with a central role in the field of child development for SRCD's "Lunch with Leaders" forum on April 1, 2011 at the 2011 SRCD Biennial Meeting in Montreal, Canada.

**Dr. Donna Calu**, IRP, a post-doctoral fellow in the Neurobiology of Relapse Section, was one of five finalists chosen by an NIH central committee for the prestigious 'Early Independent Scientist Program'.

**Dr. Meena Hiremath**, OEA, was appointed as the NIDA consultant to the Enhancing Peer Review Survey Group, a workgroup tasked with providing input on the next round of Peer Review Enhancement Surveys.

**Dr. Jag Khalsa**, DPMCDA, received a special Presidential Award for his outstanding contributions to the American Society of Addiction Medicine, in Washington, April 15, 2011, at the Annual Meeting of ASAM.

**Dr. Peng Zhang**, IRP, received a travel award to attend and present a poster at the Behavior, Biology and Chemistry Translational Research in Addiction meeting held March 4-6, 2011, in San Antonio, TX.

### Staff Changes

**Dr. Aidan Hampson**, the Scientific Review Officer for the Emerging Technologies and Training in Neurosciences IRG in the Center for Scientific Review, began a detail in the Medications Research Grants Branch of the Division of Pharmacotherapies and Medical Consequences of Drug Abuse in February 2011.

**Dr. Lorena Rodriguez Bores Ramirez** has joined the Molecular Neuropsychiatry Section, IRP as a Guest Researcher. Dr. Rodriquez Bores Ramirez is currently completing her medical residency in Psychiatry at the Universidad Nacional Autónoma de México, Instituto Nacional de Psiquiatr'a Ramón de la Fuente Muñiz in Mexico City.

**Rodden Reyes** has joined the Neural Protection and Regeneration (NPR) Section, IRP as a Special Volunteer. Rodden is currently a junior attending

## Index

Patterson High School.

**Dr. Kristen Huntley** left NIDA to take a position with National Center for Complementary and Alternative Medicine. She will be hard to replace, both for her contributions to peer review and her significant contributions to NIDA-wide workgroups.

**Publications**

**Staff Highlights**

**Grantee Honors**

# Director's Report to the National Advisory Council on Drug Abuse - September, 2011

## Grantee Honors

**Dr. Margaret Brandeau** of the Stanford University Department of Management Science and Engineering was confirmed as the first holder of the Coleman F. Fung Professorship in the School of Engineering by the Stanford University Board of Trustees in December 2010.

**Dr. Krista L. Medina, Ph.D.** of the University of Cincinnati was given a 2011 DCNBR Outstanding Early Career Investigator Award. Her work on the neurocognitive effects of chronic marijuana use in adolescents was highlighted in the DCNBR seminar series on March 16, 2011.

**CTN New England Consortium Node**
The **CAB Health and Recovery Services** was a recent recipient of the SAMHSA 2010 Science and Service Award. Now in its fourth year, this annual award program recognizes public- and private-sector organizations, as well as community-based coalitions, that have worked to improve their communities and the lives of individuals by providing the best services available. These awards recognize exemplary implementation of evidence-based interventions that have been shown to prevent and/or treat mental illnesses and substance abuse.

Researchers from the **New England Consortium Node** were contributors to the December 2010 issue (Vol. 5, No. 2) of *Addiction Science & Clinical Practice*. Steve Martino, PhD authored an article entitled "Strategies for Training Counselors in Evidence-Based Treatments." Michael Levy, PhD of CAB Health and Recovery Services was a respondent to the article. Samuel Ball, Ph.D. was a co-author of "Cost Evaluation of Evidence-Based Treatments."

## Index

**Publications**

**Staff Highlights**

**Grantee Honors**

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page