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

Research Findings - Basic Neuroscience Research

Cocaine Dynamically Regulates Heterochromatin and Repetitive Element Unsilencing In Nucleus Accumbens

Repeated cocaine exposure induces persistent alterations in genome-wide transcriptional regulatory networks, chromatin remodeling activity and, ultimately, gene expression profiles in the brain's reward circuitry. Virtually all previous investigations have centered on drug-mediated effects occurring throughout active euchromatic regions of the genome, with very little known concerning the impact of cocaine exposure on the regulation and maintenance of heterochromatin in adult brain. Here, the authors report that cocaine dramatically and dynamically alters heterochromatic histone H3 lysine 9 trimethylation (H3K9me3) in the nucleus accumbens (NAc), a key brain reward region. Furthermore, they demonstrate that repeated cocaine exposure causes persistent decreases in heterochromatinization in this brain region, suggesting a potential role for heterochromatic regulation in the long-term actions of cocaine. To identify precise genomic loci affected by these alterations, chromatin immunoprecipitation followed by massively parallel DNA sequencing (ChIP-Seq) was performed on NAc. ChIP-Seq analyses confirmed the existence of the H3K9me3 mark mainly within intergenic regions of the genome and identified specific patterns of cocaine-induced H3K9me3 regulation at repetitive genomic sequences. Cocaine-mediated decreases in H3K9me3 enrichment at specific genomic repeats [e.g., long interspersed nuclear element (LINE)-1 repeats] were further confirmed by the increased expression of LINE-1 retrotransposon-associated repetitive elements in NAc. Such increases likely reflect global patterns of genomic destabilization in this brain region after repeated cocaine administration and open the door for future investigations into the epigenetic and genetic basis of drug addiction. Maze I, Feng J, Wilkinson MB, Sun H, Shen L, Nestler EJ. Cocaine dynamically regulates heterochromatin and repetitive element unsilencing in nucleus accumbens. *Proc Natl Acad Sci U S A*. 2011 Feb 15; 108(7): 3035-3040.

HDAC3 is a Critical Negative Regulator of Long-Term Memory Formation

Gene expression is dynamically regulated by chromatin modifications on histone tails, such as acetylation. In general, histone acetylation promotes transcription, whereas histone deacetylation negatively regulates transcription. The interplay between histone acetyltransferases and histone deacetylases (HDACs) is pivotal for the regulation of gene expression required for long-term memory processes. Currently, very little is known about the role of individual HDACs in learning and memory. The authors examined the role of HDAC3 in long-term memory using a combined genetic and pharmacologic approach. They used HDAC3-FLOX genetically modified mice in combination with adeno-

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associated virus-expressing Cre recombinase to generate focal homozygous deletions of Hdac3 in area CA1 of the dorsal hippocampus. To complement this approach, we also used a selective inhibitor of HDAC3, RGFP136 [N-(6-(2-amino-4-fluorophenylamino)-6-oxohexyl)-4-methylbenzamide].

Immunohistochemistry showed that focal deletion or intrahippocampal delivery of RGFP136 resulted in increased histone acetylation. Both the focal deletion of HDAC3 as well as HDAC3 inhibition via RGFP136 significantly enhanced long-term memory in a persistent manner. Next they examined expression of genes implicated in long-term memory from dorsal hippocampal punches using quantitative reverse transcription-PCR. Expression of nuclear receptor subfamily 4 group A, member 2 (Nr4a2) and c-fos was significantly increased in the hippocampus of HDAC3-FLOX mice compared with wild-type controls. Memory enhancements observed in HDAC3-FLOX mice were abolished by intrahippocampal delivery of Nr4a2 small interfering RNA, suggesting a mechanism by which HDAC3 negatively regulates memory formation. Together, these findings demonstrate a critical role for HDAC3 in the molecular mechanisms underlying long-term memory formation. McQuown SC, Barrett RM, Matheos DP, Post RJ, Rogge GA, Alenghat T, Mullican SE, Jones S, Rusche JR, Lazar MA, Wood MA. HDAC3 is a critical negative regulator of long-term memory formation. *J Neurosci*. 2011 Jan 12; 31(2): 764-774.

Adolescent Opioid Exposure In Female Rats: Transgenerational Effects On Morphine Analgesia and Anxiety-Like Behavior In Adult Offspring

The use of narcotics by adolescent females is a growing problem, yet very little is known about the long-term consequences for either the user or her future offspring. In the current study, the authors utilized an animal model to examine the transgenerational consequences of opiate exposure occurring during this sensitive period. Female rats were exposed to increasing doses of morphine or its saline vehicle twice daily during adolescent development (postnatal days 30-40), after which they remained drug free. At 60 days of age, all females were mated and their adult offspring were tested for anxiety-like behavior and sensitivity to morphine. Specifically, offspring of adolescent morphine (MOR-F1)- or saline (SAL-F1)-exposed mothers were tested for acute locomotor responses in an open field, followed by testing of acute or chronic morphine analgesia on the hot plate. Open field testing indicated alterations in anxiety-like behavior in MOR-F1 female offspring, with effects dependent upon the stage of the estrus cycle. Hot plate testing revealed sex differences in baseline pain threshold and morphine sensitivity in all offspring, regardless of maternal exposure. However, when compared to their SAL-F1 counterparts, MOR-F1 male offspring demonstrated significantly increased sensitivity to the analgesic effects of acute morphine, and developed analgesic tolerance more rapidly following chronic morphine treatment. The findings indicate that prior opiate exposure during early adolescence in females produces sex-specific alterations of both emotionality and morphine sensitivity in their progeny. Byrnes JJ, Babb JA, Scanlan VF, Byrnes EM. Adolescent opioid exposure in female rats: transgenerational effects on morphine analgesia and anxiety-like behavior in adult offspring. *Behav Brain Res*. 2011 Mar 17; 218(1): 200-205.

Structure of the Human Dopamine D3 Receptor In Complex With A D2/D3 Selective Antagonist

Dopamine modulates movement, cognition, and emotion through activation of dopamine G protein-coupled receptors in the brain. The crystal structure of the human dopamine D3 receptor (D3R) in complex with the small molecule D2R/D3R-specific antagonist eticlopride reveals important features of the ligand binding pocket and extracellular loops. On the intracellular side of the receptor, a locked conformation of the ionic lock and two distinctly different conformations of intracellular loop 2 are observed. Docking of R-22, a D3R-

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selective antagonist, reveals an extracellular extension of the eticlopride binding site that comprises a second binding pocket for the aryl amide of R-22, which differs between the highly homologous D2R and D3R. This difference provides direction to the design of D3R-selective agents for treating drug abuse and other neuropsychiatric indications. Chien EY, Liu W, Zhao Q, Katritch V, Han GW, Hanson MA, Shi L, Newman AH, Javitch JA, Cherezov V, Stevens RC. Structure of the human dopamine D3 receptor in complex with a D2/D3 selective antagonist. *Science*. 2010 Nov 19; 330(6007): 1091-1095.

Molecular Annotation of Integrative Feeding Neural Circuits

The identity of higher-order neurons and circuits playing an associative role to control feeding is unknown. The authors injected pseudorabies virus, a retrograde tracer, into masseter muscle, salivary gland, and tongue of BAC-transgenic mice expressing GFP in specific neural populations and identified several CNS regions that project multisynaptically to the periphery. MCH and orexin neurons were identified in the lateral hypothalamus, and Nurr1 and Cnr1 in the amygdala and insular/rhinal cortices. Cholera toxin B tracing showed that insular Nurr1(+) and Cnr1(+) neurons project to the amygdala or lateral hypothalamus, respectively. Finally, they show that cortical Cnr1(+) neurons show increased Cnr1 mRNA and c-Fos expression after fasting, consistent with a possible role for Cnr1(+) neurons in feeding. Overall, these studies define a general approach for identifying specific molecular markers for neurons in complex neural circuits. These markers now provide a means for functional studies of specific neuronal populations in feeding or other complex behaviors. Perez CA, Stanley SA, Wysocki RW, Havranova J, Ahrens-Nicklas R, Onyimba F, Friedman JM. Molecular annotation of integrative feeding neural circuits. *Cell Metab*. 2011 Feb 2; 13(2): 222-232.

Requirement of Cannabinoid CB(1) Receptors In Cortical Pyramidal Neurons for Appropriate Development of Corticothalamic and Thalamocortical Projections

A role for endocannabinoid signaling in neuronal morphogenesis as the brain develops has recently been suggested. Here the authors used the developing somatosensory circuit as a model system to examine the role of endocannabinoid signaling in neural circuit formation. They first show that a deficiency in cannabinoid receptor type 1 (CB(1)R), but not G-protein-coupled receptor 55 (GPR55), leads to aberrant fasciculation and pathfinding in both corticothalamic and thalamocortical axons despite normal target recognition. Next, they localized CB(1)R expression to developing corticothalamic projections and found little if any expression in thalamocortical axons, using a newly established reporter mouse expressing GFP in thalamocortical projections. A similar thalamocortical projection phenotype was observed following removal of CB(1)R from cortical principal neurons, clearly demonstrating that CB(1)R in corticothalamic axons was required to instruct their complimentary connections, thalamocortical axons. When reciprocal thalamic and cortical connections meet, CB(1)R-containing corticothalamic axons are intimately associated with elongating thalamocortical projections containing DGLB, a 2-arachidonoyl glycerol (2-AG) synthesizing enzyme. Thus, 2-AG produced in thalamocortical axons and acting at CB(1)Rs on corticothalamic axons is likely to modulate axonal patterning. The presence of monoglyceride lipase, a 2-AG degrading enzyme, in both thalamocortical and corticothalamic tracts probably serves to restrict 2-AG availability. In summary, this study provides strong evidence that endocannabinoids are a modulator for the proposed 'handshake' interactions between corticothalamic and thalamocortical axons, especially for fasciculation. These findings are important in understanding the long-term consequences of alterations in CB(1)R activity during development, a potential etiology for the mental health disorders linked to prenatal cannabis use. Wu CS, Zhu J, Wager-Miller J, Wang S, O'Leary D,

Monory K, Lutz B, Mackie K, Lu HC. Requirement of cannabinoid CB(1) receptors in cortical pyramidal neurons for appropriate development of corticothalamic and thalamocortical projections. *Eur J Neurosci.* 2010 Sep; 32(5): 693-706.

Timing of Neurogenesis is a Determinant of Olfactory Circuitry

An odorant receptor map in mammals that is constructed by the glomerular coalescence of sensory neuron axons in the olfactory bulb is essential for proper odor information processing. How this map is linked with olfactory cortex is unknown. Using a battery of methods, including various markers of cell division in combination with tracers of neuronal connections and time-lapse live imaging, the authors found that early- and late-generated mouse mitral cells became differentially distributed in the dorsal and ventral subdivisions of the odorant receptor map. In addition, the late-generated mitral cells extended substantially stronger projections to the olfactory tubercle than did the early-generated cells. Together, these data indicate that the odorant receptor map is developmentally linked to the olfactory cortices in part by the birthdate of mitral cells. Thus, different olfactory cortical regions become involved in processing information from distinct regions of the odorant receptor map. Imamura F, Ayoub AE, Rakic P, Greer CA. Timing of neurogenesis is a determinant of olfactory circuitry. *Nat Neurosci.* 2011 Mar; 14(3): 331-337.

Genetic Association of Bipolar Disorder with the B3 Nicotinic Receptor Subunit Gene

Owing to the clinical relationship between bipolar disorder and nicotine dependence, the authors investigated two research questions: (i) are genetic associations with nicotine dependence different in individuals with bipolar disorder as compared with individuals without bipolar disorder, and (ii) do loci earlier associated with nicotine dependence have pleiotropic effects on these two diseases. This study consisted of 916 cases with bipolar disorder and 1028 controls. On the basis of known associations with nicotine dependence, the authors genotyped eight single-nucleotide polymorphisms (SNPs) on chromosome 8 (three bins) in the regions of CHRN3 and CHRNA6, and six SNPs on chromosome 15 (three bins) in the regions of CHRNA5 and CHRNA3. To determine whether the genetic associations with nicotine dependence are different in bipolar disorder than in the general population, the authors compared allele frequencies of candidate SNPs between individuals with nicotine dependence only and individuals with both nicotine dependence and bipolar disorder. There were no statistical differences between these frequencies, indicating that genetic association with nicotine dependence is similar in individuals with bipolar disorder as in the general population. In the investigation of pleiotropic effects of these SNPs on bipolar disorder, two highly correlated synonymous SNPs in CHRN3, rs4952 and rs4953, were significantly associated with bipolar disorder (odds ratio 1.7, 95% confidence interval: 1.2-2.4, $P=0.001$). This association remained significant both after adjusting for a smoking covariate and analyzing the association in nonsmokers only. Results suggest that (i) bipolar disorder does not modify the association between nicotine dependence and nicotinic receptor subunit genes, and (ii) variants in CHRN3/CHRNA6 are independently associated with bipolar disorder. Hartz SM, Lin P, Edenberg HJ, Xuei X, Rochberg N, Saccone S, Berrettini W, Nelson E, Nurnberger J, Bierut LJ, Rice JP. Genetic association of bipolar disorder with the B3 nicotinic receptor subunit gene. *Psychiatr Genet.* 2010 Dec 28. [Epub ahead of print].

Dysregulated Postsynaptic Density and Endocytic Zone in the Amygdala of Human Heroin and Cocaine Abusers

Glutamatergic transmission in the amygdala is hypothesized as an important mediator of stimulus-reward associations contributing to drug-seeking behavior and relapse. Insight is, however, lacking regarding the amygdala glutamatergic system in human drug abusers. The authors examined glutamate receptors and scaffolding proteins associated with the postsynaptic density in the human postmortem amygdala. Messenger RNA or protein levels were studied in a population of multidrug (seven heroin, eight cocaine, seven heroin/cocaine, and seven controls) or predominant heroin (29 heroin and 15 controls) subjects. The amygdala of drug abusers was characterized by a striking positive correlation ($r > .8$) between α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid glutamate receptor subunit 1 (GluA1) and postsynaptic density protein-95 (PSD-95) mRNA levels, which was not evident in control subjects. Structural equation multigroup analysis of protein correlations also identified the relationship between GluA1 and PSD-95 protein levels as the distinguishing feature of abusers. In line with the GluA1-PSD-95 implications of enhanced synaptic plasticity, Homer 1b/c protein expression was increased in both heroin and cocaine users as was its binding partner, dynamin-3. Furthermore, there was a positive relationship between Homer 1b/c and dynamin-3 in drug abusers that reflected an increase in the direct physical coupling between the proteins. A noted age-related decline of Homer 1b/c-dynamin-3 interactions, as well as GluA1 levels, was blunted in abusers. The authors conclude that impairment of key components of the amygdala postsynaptic density and coupling to the endocytic zone, critical for the regulation of glutamate receptor cycling, may underlie heightened synaptic plasticity in human drug abusers. Okvist A, Fagergren P, Whittard J, Garcia-Osta A, Drakenberg K, Horvath MC, Schmidt CJ, Keller E, Bannon MJ, Hurd YL. Dysregulated postsynaptic density and endocytic zone in the amygdala of human heroin and cocaine abusers. *Biol Psychiatry*. 2011 Feb 1; 69(3): 245-252.

Activity-induced Notch Signaling in Neurons Requires Arc/Arg3.1 and is Essential for Synaptic Plasticity in Hippocampal Networks

Notch signaling in the nervous system has been most studied in the context of cell fate specification. However, numerous studies have suggested that Notch also regulates neuronal morphology, synaptic plasticity, learning, and memory. Here the authors show that Notch1 and its ligand Jagged1 are present at the synapse, and that Notch signaling in neurons occurs in response to synaptic activity. In addition, neuronal Notch signaling is positively regulated by Arc/Arg3.1, an activity-induced gene required for synaptic plasticity. In Arc/Arg3.1 mutant neurons, the proteolytic activation of Notch1 is disrupted both in vivo and in vitro. Conditional deletion of Notch1 in the postnatal hippocampus disrupted both long-term potentiation (LTP) and long-term depression (LTD), and led to deficits in learning and short-term memory. Thus, Notch signaling is dynamically regulated in response to neuronal activity, Arc/Arg3.1 is a context-dependent Notch regulator, and Notch1 is required for the synaptic plasticity that contributes to memory formation. Alberi L, Liu S, Wang Y, Badie R, Smith-Hicks C, Wu J, Pierfelice TJ, Abazyan B, Mattson MP, Kuhl D, Pletnikov M, Worley PF, Gaiano N. Activity-induced Notch signaling in neurons requires Arc/Arg3.1 and is essential for synaptic plasticity in hippocampal networks. *Neuron*. 2011 Feb 10; 69(3): 437-444.

Reversing Cocaine-induced Synaptic Potentiation Provides Enduring Protection from Relapse

Cocaine addiction remains without an effective pharmacotherapy and is characterized by an inability of addicts to inhibit relapse to drug use. Vulnerability to relapse arises from an enduring impairment in cognitive control of motivated behavior, manifested in part by dysregulated synaptic potentiation and extracellular glutamate homeostasis in the projection from the prefrontal cortex to the nucleus accumbens. Here the authors show in rats

trained to self-administer cocaine that the enduring cocaine-induced changes in synaptic potentiation and glutamate homeostasis are mechanistically linked through group II metabotropic glutamate receptor signaling. The enduring cocaine-induced changes in measures of cortico-accumbens synaptic and chronic treatment with the cystine prodrug, N-acetylcysteine. N-acetylcysteine produced these changes by inducing an enduring restoration of nonsynaptic glutamatergic tone onto metabotropic glutamate receptors. The long-lasting pharmacological restoration of cocaine-induced glutamatergic adaptations by chronic N-acetylcysteine also caused enduring inhibition of cocaine-seeking in an animal model of relapse. These data mechanistically link nonsynaptic glutamate to cocaine-induced adaptations in excitatory transmission and demonstrate a mechanism to chronically restore prefrontal to accumbens transmission and thereby inhibit relapse in an animal model. Moussawi K, Zhou W, Shen H, Reichel CM, See RE, Carr DB, Kalivas PW. Reversing cocaine-induced synaptic potentiation provides enduring protection from relapse. *Proc Natl Acad Sci USA*. 2011 Jan 4; 108(1): 385-390.

Role of Dopamine D1 Receptors in the Activation of Nucleus Accumbens Extracellular Signal-regulated Kinase (ERK) by Cocaine-paired Contextual Cues

Exposure to drug-paired cues can trigger addicts to relapse into drug seeking. Although the molecular mechanisms underlying cue-elicited cocaine seeking are incompletely understood, the protein kinase extracellular signal-regulated kinase (ERK) is known to have an important role. Psycho-stimulants and their associated cues can activate ERK in medium spiny neurons of the nucleus accumbens core (AcbC). These medium spiny neurons can be classified according to their projections (to ventral pallidum and/or substantia nigra) and by their mRNA expression. The present experiments were designed to determine which distinct set of AcbC projection neurons expresses phosphorylated ERK (pERK) in response to cocaine-paired contextual cues. Combined use of the retrograde label Fluorogold with immunohistochemical staining of pERK was used to show that the AcbC pERK accompanying preference for cocaine-paired contexts occurs in both the accumbens (Acb)-nigral and Acb-pallidal projections. The gene expression characteristics of the neurons expressing pERK in response to cocaine-paired cues was further investigated using combined in situ hybridization and immunocytochemistry to show that AcbC pERK+ cells correspond to D1, but not preproenkephalin, mRNA+ cells. Furthermore, intra-AcbC infusion of the D1-antagonist SCH23390 attenuated cue-induced AcbC pERK expression. In aggregate, these results indicate that (i) the D1-expressing AcbC neurons evidence long-term plasticity related to drug-cue memories and (ii) local dopamine D1 receptors are necessary for the expression of cocaine-paired cue-induced pERK in these AcbC neurons. Fricks-Gleason AN, Marshall JF. Role of dopamine D1 receptors in the activation of nucleus accumbens extracellular signal-regulated kinase (ERK) by cocaine-paired contextual cues. *Neuropsychopharmacology*. 2011 Jan; 36(2): 434-444.

Transient Neuronal Inhibition Reveals Opposing Roles of Indirect and Direct Pathways in Sensitization

Dorsal striatum is important for the development of drug addiction; however, a precise understanding of the roles of striatopallidal (indirect) and striatonigral (direct) pathway neurons in regulating behaviors remains elusive. Using viral-mediated expression of an engineered G protein-coupled receptor (hM(4)D), the authors found that activation of hM(4)D receptors with clozapine-N-oxide (CNO) potently reduced striatal neuron excitability. When hM(4)D receptors were selectively expressed in either direct or indirect pathway neurons, CNO did not change acute locomotor responses to amphetamine, but did alter behavioral plasticity associated with repeated drug treatment. Specifically,

transiently disrupting striatopallidal neuronal activity facilitated behavioral sensitization, whereas decreasing excitability of striatonigral neurons impaired its persistence. These findings suggest that acute drug effects can be parsed from the behavioral adaptations associated with repeated drug exposure and highlight the utility of this approach for deconstructing neuronal pathway contributions to behavior. Ferguson SM, Eskenazi D, Ishikawa M, Wanat MJ, Phillips PE, Dong Y, Roth BL, Neumaier JF. Transient neuronal inhibition reveals opposing roles of indirect and direct pathways in sensitization. *Nat Neurosci*. 2011 Jan; 14(1): 22-24.

Potency Trends of Δ 9-THC and Other Cannabinoids in Confiscated Cannabis Preparations from 1993 to 2008

The University of Mississippi has a contract with the National Institute on Drug Abuse (NIDA) to carry out a variety of research activities dealing with cannabis, including the Potency Monitoring (PM) program, which provides analytical potency data on cannabis preparations confiscated in the United States. This report provides data on 46,211 samples seized and analyzed by gas chromatography-flame ionization detection (GC-FID) during 1993-2008. The data showed an upward trend in the mean Δ (9)-tetrahydrocannabinol (Δ (9)-THC) content of all confiscated cannabis preparations, which increased from 3.4% in 1993 to 8.8% in 2008. Hashish potencies did not increase consistently during this period; however, the mean yearly potency varied from 2.5-9.2% (1993-2003) to 12.0-29.3% (2004-2008). Hash oil potencies also varied considerably during this period ($16.8 \pm 16.3\%$). The increase in cannabis preparation potency is mainly due to the increase in the potency of nondomestic versus domestic samples. Mehmedic Z, Chandra S, Slade D, Denham H, Foster S, Patel AS, Ross SA, Khan IA, ElSohly MA. Potency trends of Δ 9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. *J. Forensic Sciences*, 2010; 55: 1209-1217.

Simultaneous Assessment of Rodent Behavior and Neurochemistry Using a Miniature Positron Emission Tomograph

Positron emission tomography (PET) neuroimaging and behavioral assays in rodents are widely used in neuroscience. PET gives insights into the molecular processes of neuronal communication, and behavioral methods analyze the actions that are associated with such processes. These methods have not been directly integrated, because PET studies in animals have until now required general anesthesia to immobilize the subject, which precludes behavioral studies. The authors present a method for imaging awake, behaving rats with PET that allows the simultaneous study of behavior. Key components include the 'rat conscious animal PET' or RatCAP, a miniature portable PET scanner that is mounted on the rat's head, a mobility system that allows considerable freedom of movement, radiotracer administration techniques and methods for quantifying behavior and correlating the two data sets. The simultaneity of the PET and behavioral data provides a multidimensional tool for studying the functions of different brain regions and their molecular constituents. Schulz D, Southeikal S, Junnarkar SS, Pratte, JF, Purschke ML, Stoll SP, Ravindranath B, Maramraju SH, Krishnamoorthy S, Henn FA, O'Connor P, Woody CL, Schlyer DJ, Vaska P. Simultaneous assessment of rodent behavior and neurochemistry using a miniature positron emission tomography. *Nature Methods*. [epub ahead of print 13 March 2011].

Inhibitions of Endocannabinoid Catabolic Enzymes Elicits Anxiolytic-like Effects in the Marble Burying Assay

Cannabinoids have long been shown to have a range of potential therapeutic effects, including antiemetic actions, analgesia, and anxiolysis. However,

psychomimetic and memory disruptive side effects, as well as the potential for abuse and dependence, have restricted their clinical development. Endogenous cannabinoids (i.e., endocannabinoids; eCBs), such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG), are produced throughout the limbic system and other brain regions associated with emotionality and are believed to modulate behavioral responses to stress-related conditions. AEA and 2-AG are rapidly metabolized by the respective enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). Accordingly, inhibition of each enzyme increases brain levels of the appropriate eCB. Although FAAH inhibition has been established to decrease anxiety-like behavior, the role of 2-AG has been difficult to ascertain until the recent synthesis of JZL184, a potent and selective MAGL inhibitor. In the present study, the authors investigated the effects of inhibiting FAAH or MAGL on anxiety-like behavior in marble burying, a model of repetitive, compulsive behaviors germane to anxiety disorders such as obsessive-compulsive disorder. The FAAH inhibitor PF-3845, the MAGL inhibitor JZL184, and the benzodiazepine diazepam decreased marble burying at doses that did not affect locomotor activity. In contrast, Δ^9 -tetrahydrocannabinol (THC), the primary psychoactive constituent of marijuana, did not consistently reduce marble burying without also eliciting profound decreases in locomotor behavior. The CB1 cannabinoid receptor antagonist rimonabant blocked the reduction in marble burying caused by FAAH and MAGL inhibitors, but not by diazepam, indicating a CB1 receptor mechanism of action. These data indicate that elevation of AEA or 2-AG reduces marble burying behavior and suggest that their catabolic enzymes represent potential targets for the development of new classes of pharmacotherapeutics to treat anxiety-related disorders. Kinsey SG, O'Neal ST, Long JZ, Cravatt BF, Lichtman AH. Inhibition of endocannabinoid catabolic enzymes elicits anxiolytic-like effects in the marble burying assay. *Pharmacol Biochem Behav.* 2011 Mar; 98(1): 21-27.

Inhibition of Anti-HIV MicroRNA Expression: A Mechanism for Opioid-Mediated Enhancement of HIV Infection of Monocytes

Several micro RNAs (miRNAs) have the ability to inhibit HIV replication in target cells. Thus, the authors investigated the impact of opioids (morphine and heroin), widely abused drugs among people infected with HIV, on the expression of cellular anti-HIV miRNAs in monocytes. They found that morphine-treated monocytes expressed lower levels of cellular anti-HIV miRNAs than untreated cells. In addition, morphine treatment of monocytes compromised type I interferon (IFN)-induced anti-HIV miRNA expression. These findings paralleled the observation that morphine treatment of monocytes enhanced HIV replication. These morphine-mediated actions on the anti-HIV miRNAs and HIV could be antagonized by the opioid receptor antagonists (naltrexone or Cys2, Tyr3, Arg5, Pen7-amide). Furthermore, the in vitro impact of morphine on miRNA expression was confirmed by the in vivo observation that heroin-dependent subjects had significantly lower levels of anti-HIV miRNAs (miRNA-28, 125b, 150, and 382) in peripheral blood mononuclear cells than the healthy subjects. These in vitro and in vivo findings indicate that opioid use impairs intracellular innate anti-HIV mechanism(s) in monocytes, contributing to cell susceptibility to HIV infection. Wang X, Ye L, Zhou Y, Liu MQ, Zhou DJ, Ho WZ. Inhibition of anti-HIV microRNA expression: a mechanism for opioid-mediated enhancement of HIV infection of monocytes. *Am J Pathol.* 2011 Jan; 178(1): 41-47.

Rescue of Adult Hippocampal Neurogenesis in a Mouse Model of HIV Neurologic Disease

The prevalence of central nervous system (CNS) neurologic dysfunction associated with human immunodeficiency virus (HIV) infection continues to increase, despite the use of antiretroviral therapy. Previous work has focused on the deleterious effects of HIV on mature neurons and on development of

neuroprotective strategies, which have consistently failed to show a meaningful clinical benefit. It is now well established that new neurons are continuously generated in discrete regions in the adult mammalian brain, and accumulating evidence supports important roles for these neurons in specific cognitive functions. In a transgenic mouse model of HIV neurologic disease with glial expression of the HIV envelope protein gp120, the authors demonstrate a significant reduction in proliferation of hippocampal neural progenitors in the dentate gyrus of adult animals, resulting in a dramatic decrease in the number of newborn neurons in the adult brain. The authors identify amplifying neural progenitor cells (ANPs) as the first class of progenitors affected by gp120, and they also demonstrate that newly generated neurons exhibit aberrant dendritic development. Furthermore, voluntary exercise and treatment with a selective serotonin reuptake inhibitor increase the ANP population and rescue the observed deficits in gp120 transgenic mice. Thus, during HIV infection, the envelope protein gp120 may potently inhibit adult hippocampal neurogenesis, and neurorestorative approaches may be effective in ameliorating these effects. This study has significant implications for the development of novel therapeutic approaches for HIV-infected individuals with neurologic dysfunction and may be applicable to other neurodegenerative diseases in which hippocampal neurogenesis is impaired. Lee MH, Wang T, Jang MH, Steiner J, Haughey N, Ming GL, Song H, Nath A, Venkatesan A. Rescue of adult hippocampal neurogenesis in a mouse model of HIV neurologic disease. *Neurobiol Dis.* 2011 Mar; 41(3): 678-687.

Binding Between a Distal C-Terminus Fragment of Cannabinoid Receptor 1 and Arrestin-2

Internalization of G-protein-coupled receptors is mediated by phosphorylation of the C-terminus, followed by binding with the cytosolic protein arrestin. To explore structural factors that may play a role in internalization of cannabinoid receptor 1 (CB1), the authors utilize a phosphorylated peptide derived from the distal C-terminus of CB1 (CB1(5P)(454-473)). Complexes formed between the peptide and human arrestin-2 (wt-arr2(1-418)) were compared to those formed with a truncated arrestin-2 mutant (tr-arr2(1-382)) using isothermal titration calorimetry and nuclear magnetic resonance spectroscopy. The pentaphosphopeptide CB1(5P)(454-473) adopts a helix-loop conformation, whether binding to full-length arrestin-2 or its truncated mutant. This structure is similar to that of a heptaphosphopeptide, mimicking the distal segment of the rhodopsin C-tail (Rh(7P)(330-348)), binding to visual arrestin, suggesting that this adopted structure bears functional significance. Isothermal titration calorimetry (ITC) experiments show that the CB1(5P)(454-473) peptide binds to tr-arr2(1-382) with higher affinity than to the full-length wt-arr2(1-418). As the observed structure of the bound peptides is similar in either case, the authors attribute the increased affinity to a more exposed binding site on the N-domain of the truncated arrestin construct. The transferred NOE data from the bound phosphopeptides are used to predict a model describing the interaction with arrestin, using the data driven HADDOCK docking program. The truncation of arrestin-2 provides scope for positively charged residues in the polar core of the protein to interact with phosphates present in the loop of the CB1(5P)(454-473) peptide. Singh SN, Bakshi K, Mercier RW, Makriyannis A, Pavlopoulos S. Binding between a distal C-terminus fragment of cannabinoid receptor 1 and arrestin-2. *Biochemistry.* 2011 Mar 29; 50(12): 2223-2234.

A Single Amino Acid in Human APOBEC3F Alters Susceptibility to HIV-1 Vif

Human APOBEC3F (huA3F) potently restricts the infectivity of HIV-1 in the absence of the viral accessory protein virion infectivity factor (Vif). Vif functions to preserve viral infectivity by triggering the degradation of huA3F but not rhesus macaque A3F (rhA3F). Here, the authors use a combination of

deletions, chimeras, and systematic mutagenesis between huA3F and rhA3F to identify Glu(324) as a critical determinant of huA3F susceptibility to HIV-1 Vif-mediated degradation. A structural model of the C-terminal deaminase domain of huA3F indicates that Glu(324) is a surface residue within the α 4 helix adjacent to residues corresponding to other known Vif susceptibility determinants in APOBEC3G and APOBEC3H. This structural clustering suggests that Vif may bind a conserved surface present in multiple APOBEC3 proteins. Albin JS, LaRue Rs, Weaver JA, Brown WL, Shindo K, Harjes E, Matsuo H, Harris RS. A single amino acid in human APOBEC3F alters susceptibility to HIV-1 Vif. J Biol Chem 2010 Dec 24; 285(52): 40785-40792.

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

Research Findings - Basic Behavioral Research

Habenular $\alpha 5$ Nicotinic Receptor Subunit Signalling Controls Nicotine Intake

Genetic variation in *CHRNA5*, the gene encoding the $\alpha 5$ nicotinic acetylcholine receptor subunit, increases vulnerability to tobacco addiction and lung cancer, but the underlying mechanisms are unknown. Here the authors report markedly increased nicotine intake in mice with a null mutation in *CHRNA5*. This effect was 'rescued' in knockout mice by re-expressing $\alpha 5$ subunits in the medial habenula (MHb), and recapitulated in rats through $\alpha 5$ subunit knockdown in MHb. Remarkably, $\alpha 5$ subunit knockdown in MHb did not alter the rewarding effects of nicotine but abolished the inhibitory effects of higher nicotine doses on brain reward systems. The MHb extends projections almost exclusively to the interpeduncular nucleus (IPN). The authors found diminished IPN activation in response to nicotine in $\alpha 5$ knockout mice. Further, disruption of IPN signalling increased nicotine intake in rats. These findings indicate that nicotine activates the habenulo-interpeduncular pathway through $\alpha 5$ -containing nAChRs, triggering an inhibitory motivational signal that acts to limit nicotine intake. Fowler CD, Lu Q, Johnson PM, Marks MJ, Kenny PJ. Habenular $\alpha 5$ nicotinic receptor subunit signalling controls nicotine intake. *Nature*. 2011 30 Jan; [Epub ahead of print].

Behavioral Characterization of Adult Male and Female Rhesus Monkeys Exposed to Cocaine throughout Gestation

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 this 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

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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.

Methylphenidate Treatment In Adolescent Rats With An Attention Deficit/Hyperactivity Disorder Phenotype: Cocaine Addiction Vulnerability and Dopamine Transporter Function

Appropriate animal models of attention deficit/hyperactivity disorder (ADHD) and drug reinforcement allow investigation of possible underlying biological bases of ADHD and its comorbidity with cocaine addiction. Toward this end, spontaneously hypertensive rats (SHRs) exhibiting an ADHD phenotype were compared with Wistar-Kyoto (WKY) and Wistar (WIS) rats. Initially, 1.5 mg/kg oral methylphenidate or vehicle was administered between postnatal days 28 and 55, and acquisition of visual discrimination learning was examined. After discontinuing adolescent treatments, adult rats were evaluated for cocaine self-administration and dopamine transporter (DAT) function in the prefrontal cortex (PFC) and striatum. During adolescence, SHRs showed deficits in visual discrimination relative to WKY and WIS rats when non-medicated.

Methylphenidate improved visual discrimination only in SHRs. Compared with WKY and WIS rats, SHRs with previous methylphenidate treatment acquired cocaine self-administration faster, identified cocaine as a highly efficacious reinforcer by displaying an upward shift in the cocaine dose-response function, and showed the greatest motivation to self-administer cocaine by exhibiting the highest progressive ratio breakpoints. In the PFC, the maximal dopamine uptake (V_{max}) at DAT was decreased in SHRs and increased in WKY and WIS rats by previous methylphenidate treatment. The affinity (K_m) for dopamine at DAT in the PFC was not different between strains, nor was V_{max} or K_m altered in the striatum by previous methylphenidate treatment in any strain.

Methylphenidate-induced decreases in dopamine clearance by DAT in the PFC may underlie increased cocaine self-administration in SHRs. These preclinical findings suggest that caution should be exercised when methylphenidate is prescribed for first-time treatment of ADHD in adolescent patients, as cocaine addiction vulnerability may be augmented. Harvey RC, Sen S, Deaciuc A, Dwoskin LP, Kantak KM. Methylphenidate treatment in adolescent rats with an attention deficit/hyperactivity disorder phenotype: cocaine addiction vulnerability and dopamine transporter function. *Neuropsychopharmacology*. 2011 Mar; 36(4): 837-847.

Synaptic Adaptations in the Nucleus Accumbens Caused by Experiences Linked to Relapse

Excitatory synaptic transmission in the nucleus accumbens (NAc) regulates the reinstatement of drug seeking, an animal model of relapse in human drug addicts. However, the functional adaptations at NAc synapses that mediate reinstatement are not clearly understood. The authors assessed the behavioral responses of mice to cocaine administration by measuring locomotor stimulation and the acquisition, extinction, and reinstatement of conditioned place preference. Synaptic function was then examined by preparing acute brain slices and performing whole cell voltage-clamp recordings from individual medium spiny neurons in the NAc shell. They found that reduced excitatory synaptic strength in the NAc shell is a common functional adaptation induced by multiple experiences known to cause reinstatement, including stress and drug re-exposure. The same synaptic adaptation is observed shortly after reinstatement of conditioned place preference by a cocaine priming injection. The authors conclude that this common synaptic modification associated with stress, drug re-exposure, and reinstatement defines a potential synaptic gateway to relapse. Rothwell PE, Kourrich S, Thomas MJ. Synaptic adaptations in the nucleus accumbens caused by experiences linked to relapse. *Biol Psychiatry*. 2011 In Press, Corrected Proof, Available online 16 February 2011.

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Induction of Hyperphagia and Carbohydrate Intake by μ -Opioid Receptor Stimulation in Circumscribed Regions of Frontal Cortex

Frontal cortical regions are activated by food-associated stimuli, and this activation appears to be dysregulated in individuals with eating disorders. Nevertheless, frontal control of basic unconditioned feeding responses remains poorly understood. Here the authors show that hyperphagia can be driven by μ -opioid receptor stimulation in restricted regions of ventral medial prefrontal cortex (vmPFC) and orbitofrontal cortex. In both ad libitum-fed and food-restricted male Sprague Dawley rats, bilateral infusions of the μ -opioid agonist [d-Ala², N-Me-Phe⁴, Gly⁵-ol]-enkephalin (DAMGO) markedly increased intake of standard rat chow. When given a choice between palatable fat-enriched versus carbohydrate-enriched test diets, intra-vmPFC DAMGO infusions selectively increased carbohydrate intake, even in rats with a baseline fat preference. Rats also exhibited motor hyperactivity characterized by rapid switching between brief bouts of investigatory and ingestive behaviors. Intra-vmPFC DAMGO affected neither water intake nor nonspecific oral behavior. Similar DAMGO infusions into neighboring areas of lateral orbital or anterior motor cortex had minimal effects on feeding. Neither stimulation of vmPFC-localized δ -opioid, κ -opioid, dopaminergic, serotonergic, or noradrenergic receptors, nor antagonism of D1, 5HT1A, or α - or β -adrenoceptors, reproduced the profile of DAMGO effects. Muscimol-mediated inactivation of the vmPFC, and intra-vmPFC stimulation of κ -opioid receptors or blockade of 5-HT_{2A} (5-hydroxytryptamine receptor 2A) receptors, suppressed motor activity and increased feeding bout duration—a profile opposite to that seen with DAMGO. Hence, μ -opioid-induced hyperphagia and carbohydrate intake can be elicited with remarkable pharmacological and behavioral specificity from discrete subterritories of the frontal cortex. These findings may have implications for understanding affect-driven feeding and loss of restraint in eating disorders. Mena JD, Sadeghian K, Baldo BA. Induction of hyperphagia and carbohydrate intake by μ -opioid receptor stimulation in circumscribed regions of frontal cortex. *J Neurosci*. 2011 Mar 2; 31(9): 3249-3260.

Postsynaptic TRPV1 Triggers Cell Type-specific Long-term Depression in the Nucleus Accumbens

Synaptic modifications in the nucleus accumbens (NAc) are important for adaptive and pathological reward-dependent learning. Medium spiny neurons (MSNs), the major cell type in the NAc, participate in two parallel circuits that subservise distinct behavioral functions, yet little is known about differences in their electrophysiological and synaptic properties. Using bacterial artificial chromosome transgenic mice, the authors found that synaptic activation of group I metabotropic glutamate receptors in NAc MSNs in the indirect, but not direct, pathway led to the production of endocannabinoids, which activated presynaptic CB1 receptors to trigger endocannabinoid-mediated long-term depression (eCB-LTD) as well as postsynaptic transient receptor potential vanilloid 1 (TRPV1) channels to trigger a form of LTD resulting from endocytosis of AMPA receptors. These results reveal a previously unknown action of TRPV1 channels and indicate that the postsynaptic generation of endocannabinoids can modulate synaptic strength in a cell type-specific fashion by activating distinct pre- and postsynaptic targets. Grueter BA, Brasnjo G, Malenka RC. Postsynaptic TRPV1 triggers cell type-specific long-term depression in the nucleus accumbens. *Nat Neurosci*. 2010 Dec; 13(12): 1519-1525.

Selective Enhancement of Fentanyl-induced Antinociception by the Delta Agonist SNC162 but not by Ketamine in Rhesus

Monkeys: Further Evidence Supportive of Delta Agonists as Candidate Adjuncts to Mu Opioid Analgesics

Mu-opioid receptor agonists such as fentanyl are effective analgesics, but their clinical use is limited by untoward effects. Adjunct medications may improve the effectiveness and/or safety of opioid analgesics. This study compared interactions between fentanyl and either the noncompetitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist ketamine or the delta-opioid receptor agonist SNC162 [(+)-4-[(alphaR)-alpha-[(2S,5R)-2,5-dimethyl-4-(2-propenyl)-1-piperazinyl]-(3-phenyl)methyl]-N,N-diethylbenzamide] in two behavioral assays in rhesus monkeys. An assay of thermal nociception evaluated tail-withdrawal latencies from water heated to 50 and 54 C. An assay of schedule-controlled responding evaluated response rates maintained under a fixed-ratio 30 schedule of food presentation. Effects of each drug alone and of three mixtures of ketamine + fentanyl (22:1, 65:1, 195:1 ketamine/fentanyl) or SNC162 + fentanyl (59:1, 176:1, 528:1 SNC162/fentanyl) were evaluated in each assay. All drugs and mixtures dose-dependently decreased rates of food-maintained responding, and drug proportions in the mixtures were based on relative potencies in this assay. Ketamine and SNC162 were inactive in the assay of thermal antinociception, but fentanyl and all mixtures produced dose-dependent antinociception. Drug interactions were evaluated using dose-addition and dose-ratio analysis. Dose-addition analysis revealed that interactions for all ketamine/fentanyl mixtures were additive in both assays. SNC162/fentanyl interactions were usually additive, but one mixture (176:1) produced synergistic antinociception at 50 C. Dose-ratio analysis indicated that ketamine failed to improve the relative potency of fentanyl to produce antinociception vs. rate suppression, whereas two SNC162/fentanyl mixtures (59:1 and 176:1) increased the relative potency of fentanyl to produce antinociception. These results suggest that delta agonists may produce more selective enhancement than ketamine of mu agonist-induced antinociception. Banks ML, Folk JE, Rice KC, Negus SS. Selective enhancement of fentanyl-induced antinociception by the delta agonist SNC162 but not by ketamine in rhesus monkeys: Further evidence supportive of delta agonists as candidate adjuncts to mu opioid analgesics, *Pharmacology, Biochemistry and Behavior*. 2010 Dec 97(2): 205-212.

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

Research Findings - Behavioral and Brain Development Research

Memory Maintenance and Inhibitory Control Differentiate from Early Childhood to Adolescence

Existing evidence suggests that the organization of cognitive functions may differentiate during development. The authors investigated two key components of executive functions, memory maintenance and inhibitory control, by applying latent factor models appropriate for examining developmental differences in functional associations among aspects of cognition. Two-hundred and sixty-three children (aged 4 to 14 years) were administered tasks that required maintaining rules in mind or inhibiting a prepotent tendency to respond on the same side as the stimulus. Memory maintenance and inhibitory control were not separable in children of 4-7 or 7-9.5 years, but were differentiated in an older group (9.5-14.5 years). Shing YL, Lindenberger U, Diamond A, Li SC, Davidson MC. Memory maintenance and inhibitory control differentiate from early childhood to adolescence. *Dev Neuropsychol*. 2010 Nov; 35(6): 679-697.

Prenatal Methamphetamine Exposure and Motor and Cognitive Outcomes through Age Three

Methamphetamine (MA) use among pregnant women is an increasing problem in the United States. The impact of prenatal MA exposure on development in childhood is unknown. The objective of this study was to examine the effects of prenatal MA exposure on motor and cognitive development in children at 1, 2, and 3 years of age. IDEAL enrolled 412 mother-infant pairs at four sites (Tulsa OK, Des Moines IA, Los Angeles CA, and Honolulu HI). MA subjects (n=204) were identified by self report or GC/MS confirmation of amphetamine and metabolites in infant meconium. Comparison subjects (n=208) were matched (race, birth weight, maternal education, and type of insurance), denied amphetamine use, and had a negative meconium screen. Both groups included prenatal alcohol, tobacco and marijuana use, but excluded use of opiates, lysergic acid diethylamide, phencyclidine or cocaine only. The Peabody Developmental Motor Scales (PDMS-2) were administered to the infants at the 1 and 3 year visits. This analysis includes a subsample (n=350) of the IDEAL study with completed 1 and/or 3 year visits (n=330 and 281, respectively). At each annual visit we also conducted the Bayley Scales of Infant Development (BSID-II) as a general evaluation of mental and motor development. The BSID-II analysis includes a subsample (n=356) of the IDEAL study with completed 1, 2, and/or 3 year visits (n=331, 288, and 278 respectively). GLM analysis conducted on the PDMS-2 and BSID-II examined the effects of MA exposure and heavy MA exposure (3 days of use/week), with and without covariates. Longitudinal analyses were used to examine the effects of MA

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exposure on changes in motor and cognitive performance over time. Heavy MA exposure was associated with significantly lower grasping scores than some and no use at 1 year ($P=0.018$). In longitudinal analysis, lower grasping scores associated with any MA exposure and heavy exposure persisted to 3 years. There were no effects of MA exposure, including heavy exposure, on the Bayley Mental Development Index (MDI) or Psychomotor Development Index (PDI) at any or across age. There were no differences in cognition as assessed by the BSID-II between the groups. There was a subtle MA exposure effect on fine motor performance at 1 year with the poorest performance observed in the most heavily exposed children. By 3 years, no differences in fine motor performance were observed. These findings suggest MA exposure has modest motor effects at 1 year that are mostly resolved by 3 years. Smith LM, LaGasse LL, Derauf C, Newman E, Shah R, Haning W, Arria A, Huestis M, Strauss A, Della Grotta S, Dansereau LM, Lin H, Lester BM. Motor and cognitive outcomes through three years of age in children exposed to prenatal methamphetamine. *Neurotoxicol Teratol*. 2011 Jan-Feb; 33(1): 176-184.

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Prenatal Tobacco Exposure and Neonatal Development

Smoking during pregnancy is a persistent public health problem that has been linked to later adverse outcomes. The neonatal period--the first month of life--carries substantial developmental change in regulatory skills and is the period when tobacco metabolites are cleared physiologically. Studies to date mostly have used cross-sectional designs that limit characterizing potential impacts of prenatal tobacco exposure on the development of key self-regulatory processes and cannot disentangle short-term withdrawal effects from residual exposure-related impacts. In this study, pregnant participants ($N = 304$) were recruited prospectively during pregnancy, and smoking was measured at multiple time points, with both self-report and biochemical measures. Neonatal attention, irritable reactivity, and stress dysregulation were examined longitudinally at three time points during the first month of life, and physical growth indices were measured at birth. Tobacco-exposed infants showed significantly poorer attention skills after birth, and the magnitude of the difference between exposed and nonexposed groups attenuated across the neonatal period. In contrast, exposure-related differences in irritable reactivity largely were not evident across the 1st month of life, differing marginally at 4 weeks of age only. Third-trimester smoking was associated with pervasive, deleterious, dose-response impacts on physical growth measured at birth, whereas nearly all smoking indicators throughout pregnancy predicted level and growth rates of early attention. The observed neonatal pattern is consistent with the neurobiology of tobacco on the developing nervous system and fits with developmental vulnerabilities observed later in life. Espy KA, Fang H, Johnson C, Stopp C, Wiebe SA. Prenatal tobacco exposure: Developmental outcomes in the neonatal period. *Dev Psychol*. 2011 Jan; 47(1): 153-156.

Prenatal Cigarette Smoke Exposure and Behavior in 10-year Old Children of Adolescent Mothers

In this prospective study, adolescent mothers (mean age=16; range=12-18; 70% African-American) were interviewed about their tobacco use during pregnancy. When their children were ten, mothers reported on their child's behavior and the children completed a neuropsychological battery. The authors examined the association between prenatal cigarette smoke exposure (PCSE) and offspring neurobehavioral outcomes on data from the 10-year phase ($n=330$). Multivariate regression analyses were conducted to test if PCSE predicted neurobehavioral outcomes, adjusting for demographic characteristics, maternal psychological characteristics, prenatal exposure to other substances, and exposure to environmental tobacco smoke. Independent effects of PCSE were found. Exposed offspring had more delinquent, aggressive, and externalizing behaviors (CBCL). They were more active (Routh, EAS, and

SNAP) and impulsive (SNAP) and had more problems with peers (SNAP). On the Stroop test, deficits were observed on the more complex interference task that requires both selective attention and response inhibition. The significant effects of PCSE on neurobehavioral outcomes were found for exposure to as few as 10 cigarettes per day. Most effects were found from first trimester PCSE exposure. These results are consistent with results from an earlier assessment when the children were age 6, demonstrating that the effects of prenatal tobacco exposure can be identified early and are consistent through middle childhood. Cornelius MD, DeGenna NM, Leech SL, Willford JA, Goldschmidt L, Day NL. Effects of prenatal cigarette smoke exposure on neurobehavioral outcomes in 10-year-old children of adolescent mothers. *Neurotoxicol Teratol.* 2011 Jan-Feb; 33(1): 137-144.

Modeling to Minimize Confounding Risks Related to Prenatal Tobacco Exposure

Despite efforts to control for confounding variables using stringent sampling plans, selection bias typically exists in observational studies, resulting in unbalanced comparison groups. Ignoring selection bias can result in unreliable or misleading estimates of the causal effect. Generalized boosted models were used to estimate propensity scores from 42 confounding variables for a sample of 361 neonates. Using emergent neonatal attention and orientation skills as an example developmental outcome, the authors examined the impact of tobacco exposure with and without accounting for selection bias. Weight at birth, an outcome related to tobacco exposure, also was used to examine the functionality of the propensity score approach. Without inclusion of propensity scores, tobacco-exposed neonates did not differ from their nonexposed peers in attention skills over the first month or in weight at birth. When the propensity score was included as a covariate, exposed infants had marginally lower attention and a slower linear change rate at 4 weeks, with greater quadratic deceleration over the first month. Similarly, exposure-related differences in birth weight emerged when propensity scores were included as a covariate. The propensity score method captured the selection bias intrinsic to this observational study of prenatal tobacco exposure. Selection bias obscured the deleterious impact of tobacco exposure on the development of neonatal attention. The illustrated analytic strategy offers an example to better characterize the impact of prenatal tobacco exposure on important developmental outcomes by directly modeling and statistically accounting for the selection bias from the sampling process. Fang H, Johnson C, Chevalier N, Stopp C, Wiebe S, Wakschlag LS, Espy KA. Using propensity score modeling to minimize the influence of confounding risks related to prenatal tobacco exposure. *Nicotine Tob Res.* 2010 Dec; 12(12): 1211-1219.

A New Look at Quantifying Tobacco Exposure During Pregnancy

Prenatal tobacco exposure is a risk factor for the development of externalizing behaviors and is associated with several adverse health outcomes. Because pregnancy smoking is a complex behavior with both daily fluctuations and changes over the course of pregnancy, quantifying tobacco exposure is a significant challenge. To better measure the degree of tobacco exposure, costly biological specimens and repeated self-report measures of smoking typically are collected throughout pregnancy. With such designs, there are multiple, and substantially correlated, indices that can be integrated via new statistical methods to identify patterns of prenatal exposure. A multiple-imputation-based fuzzy clustering technique was designed to characterize topography of prenatal exposure. This method leveraged all repeatedly measured maternal smoking variables in our sample data, including (a) cigarette brand; (b) Fagerstrom nicotine dependence item scores; (c) self-reported smoking; and (d) cotinine level in maternal urine and infant meconium samples. Identified exposure groups then were confirmed using a suite of clustering validation indices based

on multiple imputed datasets. The classifications were validated against irritable reactivity in the first month of life and birth weight of 361 neonates (Male(n)=185; Female(n)=176; Gestational Age (Mean) =39 weeks). This proposed approach identified three exposure groups, non-exposed, lighter-tobacco-exposed, and heavier-tobacco-exposed based on high-dimensional attributes. Unlike cut-off score derived groups, these groupings reflect complex smoking behavior and individual variation of nicotine metabolism across pregnancy. The identified groups predicted differences in birth weight and in the pattern of change in neonatal irritable reactivity, as well as resulted in increased predictive power. Multiple-imputation-based fuzzy clustering appears to be a useful method to categorize patterns of exposure and their impact on outcomes. Fang H, Johnson C, Stopp C, Espy KA. A new look at quantifying tobacco exposure during pregnancy using fuzzy clustering. *Neurotoxicol Teratol.* 2011 Jan-Feb; 33(1): 155-165.

Prenatal Cocaine Exposure and Childhood Obesity

Little is known about the association between prenatal cocaine exposure and obesity. The authors tested whether prenatal cocaine exposure increases the likelihood of obesity in 561 9-year-old term children from the Maternal Lifestyle Study (MLS). Overall, 21.6% of children met criterion for obesity (body mass index [BMI] 95th percentile, age and sex-specific). While there was no overall cocaine effect on obesity, multivariate logistic analysis revealed that children exposed to cocaine but not alcohol were 4 times more likely to be obese (OR 4.11, CI 2.04-9.76) than children not exposed to either drug. No increase in obesity prevalence was found in children exposed to alcohol but not cocaine (OR 1.08, CI .59-1.93) or both (OR 1.21, CI 0.66-2.22). Alcohol exposure may attenuate the effect of cocaine exposure on obesity. Increased obesity associated with cocaine but not alcohol exposure was first observed at 7 years. BMI was also elevated from 3 to 9 years in children exposed to cocaine but not alcohol, due to increasing weight but normal height. Prenatal exposure to cocaine may alter the neuroendocrine system and metabolic processes resulting in increased weight gain and childhood obesity. Lagasse LL, Gaskins RB, Bada HS, Shankaran S, Liu J, Lester BM, Bauer CR, Higgins RD, Das A, Roberts M. Prenatal cocaine exposure and childhood obesity at 9 years. *Neurotoxicol Teratol.* 2010 Nov 23. [Epub ahead of print].

Cessation of Tobacco, Alcohol, and Illicit Drug Use During Pregnancy

Pregnancy is a time of relative urgency and opportunity for the treatment of substance use disorders in women, yet little is known about modifiable factors that contribute to successful abstinence. The authors examined self-worth, depression, anxiety, and novelty seeking in the context of substance use cessation during pregnancy in a sample of women with a high prevalence of substance abuse. Subjects were 448 birth mothers who participated in a prospective adoption study. Discontinuation rates were: tobacco 22.2%, alcohol 64.7%, marijuana 77.2%, and other drugs, 73.7-100%. Depression, anxiety, and novelty seeking were lower among women who discontinued substance use, compared to those who did not. Self-worth was higher in women who discontinued substance use. Among 110 polysubstance users, the number of substances discontinued during pregnancy was correlated with depression, anxiety, and self-worth in the hypothesized direction. Possible clinical implications are discussed. Massey SH, Lieberman DZ, Reiss D, Leve LD, Shaw DS, Neiderhiser JM. Association of clinical characteristics and cessation of tobacco, alcohol, and illicit drug use during pregnancy. *Am J Addict.* 2011 Mar-Apr; 20(2): 143-150.

Development of Inhibitory Control and Prenatal Cocaine

Exposure: Gender, Risk and Aggressive Behavior

The goal of the present investigation was to characterize the development of inhibitory control, an aspect of executive functions, in a sample of prenatally cocaine exposed (CE; $n=165$) children compared to an at risk, but prenatally cocaine unexposed (NCE; $n=119$) sample across time (i.e. 7.5 to 11.5 years of age). Gender and cumulative risk, a combination of postnatal medical (i.e. low birth weight and APGAR scores) and demographic risk, indexed by maternal educational attainment, were examined as predictors of change in inhibitory control across time and aggression was modeled as an outcome when children reached 14 years of age. Multiple group latent growth models indicated that CE children made more errors at 7.5 years of age during a standard Stroop interference task, however, over time CE children had greater age-related improvements, narrowing the initial gap, with NCE children in the ability to inhibit errors. Gender effects at 7.5 years within the NCE group were identified with NCE boys making initially more errors than NCE girls; both NCE and CE girls improved faster across development compared to NCE and CE boys, respectively. Greater cumulative risk was associated with more errors at 7.5 years in the CE and NCE groups. No differences were observed between CE and NCE children on time to complete the Stroop task at 7.5 years. However, NCE children had greater age-related improvements in their time to complete the Stroop interference task relative to their CE counterparts. NCE girls improved the fastest over time relative to NCE boys; a similar trend emerged ($p<0.10$) with CE girls improving faster over time than CE boys. Although all participants improved across development, higher cumulative risk in both groups was associated with slower age-related improvements (i.e., higher slopes) in the time to complete the Stroop task across development. After accounting for gender and cumulative risk, findings in both groups indicated that those who made more errors at 7.5 years of age and/or who had slower age-related changes (i.e., higher slopes) of time to complete the Stroop task across development were more aggressive as rated by caregivers at 14 years of age. Although qualified by gender and cumulative risk, these findings are consistent with reduced cognitive processing efficiency and executive function difficulties in CE children relative to NCE children. Findings suggest that executive function difficulties in CE children may be subtle as development continues to unfold over time. Furthermore, these findings indicate that development of inhibitory control may be an important mechanism linking prenatal cocaine exposure, gender, and cumulative risk to later adverse outcomes. Bridgett DJ, Mayes LC. Development of inhibitory control among prenatally cocaine exposed and non-cocaine exposed youths from late childhood to early adolescence: The effects of gender and risk and subsequent aggressive behavior. *Neurotoxicol Teratol.* 2011 Jan-Feb; 33(1): 47-60.

Effects of Acute Caffeine Administration on Adolescents

Acute caffeine administration has physiological, behavioral, and subjective effects. Despite its widespread use, few studies have described the impact of caffeine consumption in children and adolescents. The purpose of this study was to investigate the effects of acute caffeine administration in adolescents. The authors measured cardiovascular responses and snack food intake after acute administration of 0 mg, 50 mg, 100 mg, and 200 mg of caffeine. They also compared usual food intake and subjective effects of caffeine between high- and low-caffeine consumers. Finally, they conducted a detailed analysis of caffeine sources and consumption levels. They found main effects of caffeine dose on heart rate (HR) and diastolic blood pressure (DBP), with HR decreasing and DBP increasing with increasing caffeine dose. There were significant interactions among gender, caffeine use, and time on DBP. High caffeine consumers (>50 mg/day) reported using caffeine to stay awake and drinking coffee, tea, soda, and energy drinks more than low consumers (<50 mg/day). Boys were more likely than girls to report using getting a rush, more energy, or

improved athletic performance from caffeine. Finally, when the authors examined energy and macronutrient intake, they found that caffeine consumption was positively associated with laboratory energy intake, specifically from high-sugar, low-fat foods and also positively associated with protein and fat consumption outside of the laboratory. When taken together, these data suggest that acute caffeine administration has a broad range of effects in adolescents and that the magnitude of these effects is moderated by gender and chronic caffeine consumption. Temple JL, Dewey AM, Briatico LN. Effects of acute caffeine administration on adolescents. *Exp Clin Psychopharmacol.* 2010 Dec; 18(6): 510-520.

Risky Behaviors and the Discrepancy between Mother and Child Reports of Parental Knowledge

The study examined discrepancies in mother and child reports of parental knowledge (PK) of a child's whereabouts, activities, and companions, as well as the extent to which discrepancies in reports of PK are related to child risk-taking behavior concurrently and prospectively across two time points. The sample consisted of 219 mother and early adolescent youth (M age=11.0, SD =.8) dyads. Mother and child reports of PK significantly differed and, at both waves, scores on the risk taking composite related negatively to both mother and child reports of PK and positively to the discrepancy between the two reports. A significant interaction between mother and child reports was found at Wave 2, such that the relation between child reported PK and risk behavior was stronger when mothers reported high levels of parental knowledge versus low levels of parental knowledge. Prospective analyses indicated a main effect of mother report. Reynolds EK, MacPherson L, Matusiewicz AK, Schreiber WM, Lejuez CW. Discrepancy between mother and child reports of parental knowledge and the relation to risk behavior engagement. *J Clin Child Adolesc Psychol.* 2011 Jan; 40(1): 67-79.

Prenatal Cocaine Exposure and Gender Effects on Inhibitory Control and Attention

Children exposed prenatally to cocaine show deficits in emotion regulation and inhibitory control. While controlling for the measures of medical complication in the perinatal period, environmental risk, and prenatal polydrug exposure (alcohol, tobacco, and marijuana), the authors examined the effects of prenatal cocaine exposure and gender on attention and inhibitory control in 203 children at ages 6, 9, and 11. Cocaine exposure affected the performance of males, but not females. Heavily exposed males showed deficits in the attention and the inhibition tasks. In addition, a significantly greater proportion of heavily exposed males (21%) than unexposed males (7%) or heavily exposed females (7%) failed to complete the task ($p < 0.01$). Even without those poorest performing subjects, the overall accuracy for heavily exposed males (81%) was significantly reduced ($p < 0.05$) compared to lightly exposed males (87%) and unexposed males (89%). The findings highlight the importance of considering gender specificity in cocaine exposure effects. Processes by which cocaine effects may be specific to males are discussed. Carmody DP, Bennett DS, Lewis M. The effects of prenatal cocaine exposure and gender on inhibitory control and attention. *Neurotoxicol Teratol.* 2011 Jan-Feb; 33(1): 61-68.

Longitudinal Analysis of Inhibitory Control, Memory and Receptive Language in Adolescents and Prenatal Cocaine Exposure

Preclinical studies of gestational cocaine exposure (GCE) show evidence of changes in brain function at the anatomical, physiological, and behavioral levels, to include effects on developing dopaminergic systems. In contrast, human studies have produced less consistent results, with most showing small

effects or no effects on developmental outcomes. Important changes in brain structure and function occur through adolescence, therefore it is possible that prenatal cocaine exposure has latent effects on neurocognitive (NC) outcome that do not manifest until adolescence or young adulthood. The authors examined NC function using a set of 5 tasks designed to tap 4 different systems: inhibitory control, working memory, receptive language, and incidental memory. For each NC task, data were collected longitudinally at ages 12, 14.5 and 17 years and examined using generalized estimating equations. One hundred and nine children completed at least two of the three evaluations. Covariates included in the final model were assessment number, gender, participant age at first assessment, caregiver depression, and two composites from the Home Observation for Measurement of the Environment (HOME), Environmental Stimulation and Parental Nurturance. The authors found no cocaine effects on inhibitory control, working memory, or receptive language ($p=0.18$). GCE effects were observed on incidental face memory task ($p=0.055$), and GCE by assessment number interaction effects were seen on the incidental word memory task ($p=0.031$). Participant performance on inhibitory control, working memory, and receptive language tasks improved over time. HOME Environmental Stimulation composite was associated with better receptive language functioning. With a larger sample size smaller differences between groups may have been detected. This report shows no evidence of latent effects of GCE on inhibitory control, working memory, or receptive language. GCE effects were observed on the incidental face memory task, and GCE by assessment number interaction effects was seen on the incidental word memory task. Betancourt LM, Yang W, Brodsky NL, Gallagher PR, Malmud EK, Giannetta JM, Farah MJ, Hurt H. Adolescents with and without gestational cocaine exposure: Longitudinal analysis of inhibitory control, memory and receptive language. *Neurotoxicol Teratol*. 2011 Jan-Feb; 33(1): 36-46.

Maternal Cocaine Use and Mother-Infant Interactions

This study examined the associations between prenatal cocaine exposure and quality of mother-infant play interactions at 13 months of infant ages. The authors investigated whether maternal psychological distress and infant reactivity mediated or moderated this association. Participants consisted of 220 (119 cocaine exposed and 101 non-cocaine exposed) mother-infant dyads participating in an ongoing longitudinal study of prenatal cocaine exposure. Results indicated that mothers who used cocaine during pregnancy displayed higher negative affect and lower sensitivity toward their infant during play interactions at 13 months, and that their infants were less responsive toward them. Contrary to hypothesis, this association was not mediated by maternal psychological distress or by infant reactivity. However, results for both the cocaine and non-cocaine exposed infants were supportive of a transactional model where lower maternal sensitivity at 1 month was predictive of higher infant reactivity at 7 months, which in turn was predictive of lower maternal warmth/sensitivity at 13 months, controlling for potential stability in maternal behavior. Results also indicated that as hypothesized, infant reactivity moderated the association between maternal cocaine use during pregnancy and maternal warmth/sensitivity at 13 months of age. Cocaine-using mothers who experienced their infants as being more reactive in early infancy were less warm/sensitive toward them in later infancy. Results have implications for parenting interventions that may be targeted toward improving maternal sensitivity among cocaine-using mothers with more reactive infants. Eiden RD, Schuetze P, Coles CD. Maternal cocaine use and mother-infant interactions: Direct and moderated associations. *Neurotoxicol Teratol*. 2011 Jan-Feb; 33(1): 120-128.

In Utero Cocaine Exposure and Language Development through Early Adolescence

The potential longitudinal effects of prenatal cocaine exposure (PCE) on language functioning were estimated from early childhood through early adolescence in a large, well-retained urban sample of 451 full-term children (242 cocaine-exposed, 209 non-cocaine-exposed) participating in the Miami Prenatal Cocaine Study (MPCS). The sample was enrolled prospectively at birth, with documentation of prenatal drug exposure status through maternal interview, and toxicology assays of maternal and infant urine, and infant meconium. Age-appropriate versions of the Clinical Evaluation of Language Fundamentals (CELF) were used to measure total, expressive, and receptive language at ages 3, 5, and 12 years. Longitudinal latent growth curve (LLGC) modeling of the data revealed an association between PCE (measured dichotomously as yes/no) and lower functioning in expressive and total language scores, after considering other sources of variation including child's age at testing, sex, prenatal exposure to alcohol, marijuana, and tobacco, and additional medical and social-demographic covariates. Analyses of level of PCE showed a gradient, i.e. dose-dependent, relationship between PCE level and expressive, receptive, and total language scores in the models controlling for age, child's sex, and other prenatal drug exposures. With additional covariate control these findings were most stable for the total language score. The evidence supports an inference about an enduring stable cocaine-specific effect on children's language abilities, with no effect on language growth over time in the longitudinal trajectory of language development. Bandstra ES, Morrow CE, Accornero VH, Mansoor E, Xue L, Anthony JC. Estimated effects of in utero cocaine exposure on language development through early adolescence. *Neurotoxicol Teratol.* 2011 Jan-Feb; 33(1): 25-35.

Retrospective Maternal Report of Alcohol Consumption in Pregnancy Predicts Pregnancy and Teen Outcomes

Detecting patterns of maternal drinking that place fetuses at risk for fetal alcohol spectrum disorders (FASDs) is critical to diagnosis, treatment, and prevention but is challenging because information on antenatal drinking collected during pregnancy is often insufficient or lacking. Although retrospective assessments have been considered less favored by many researchers due to presumed poor reliability, this perception may be inaccurate because of reduced maternal denial and/or distortion. The present study hypothesized that fetal alcohol exposure, as assessed retrospectively during child adolescence, would be related significantly to prior measures of maternal drinking and would predict alcohol-related behavioral problems in teens better than antenatal measures of maternal alcohol consumption. Drinking was assessed during pregnancy, and retrospectively about the same pregnancy, at a 14-year follow-up in 288 African-American women using well-validated semistructured interviews. Regression analysis examined the predictive validity of both drinking assessments on pregnancy outcomes and on teacher-reported teen behavior outcomes. Retrospective maternal self-reported drinking assessed 14 years postpartum was significantly higher than antenatal reports of consumption. Retrospective report identified 10.8 times more women as risk drinkers (one drink per day) than the antenatal report. Antenatal and retrospective reports were moderately correlated and both were correlated with the Michigan Alcoholism Screening Test. Self-reported alcohol consumption during pregnancy based on retrospective report identified significantly more teens exposed prenatally to at-risk alcohol levels than antenatal, in-pregnancy reports. Retrospective report predicted more teen behavior problems (e.g., attention problems and externalizing behaviors) than the antenatal report. Antenatal report predicted younger gestational age at birth and retrospective report predicted smaller birth size; neither predicted teen IQ. These results suggest that if only antenatal, in-pregnancy maternal report is used, then a substantial proportion of children exposed prenatally to risk levels of alcohol might be misclassified. The validity of retrospective assessment of prior

drinking during pregnancy as a more effective indicator of prenatal exposure was established by predicting more behavioral problems in teens than antenatal report. Retrospective report can provide valid information about drinking during a prior pregnancy and may facilitate diagnosis and subsequent interventions by educators, social service personnel, and health-care providers, thereby reducing the life-long impact of FASDs. Hannigan JH, Chiodo LM, Sokol RJ, Janisse J, Ager JW, Greenwald MK, Delaney-Black V. A 14-year retrospective maternal report of alcohol consumption in pregnancy predicts pregnancy and teen outcomes. *Alcohol*. 2010 Nov-Dec; 44(7-8): 583-594.

Sex Partnerships, Health, and Social Risks of Young Men Leaving Jail

Young men involved in the criminal justice system face disproportionately high rates of sexual risk behavior, drug use, and violence. Little is known about how their involvement in sex partnerships might mitigate their unique health and social risks. This study explores whether sex partner experience protects against harmful sexual behaviors, drug problems, violence, and recidivism in 16-18-year-old Black and Latino men leaving a US jail. Data were drawn from the Returning Educated African-American and Latino Men to Enriched Neighborhoods (REAL MEN) study conducted between 2003-2007, which tracked 552 adolescents during their time in a New York City jail and 397 of them one year after their release. Logistic regression was used to examine the relationship between sex partner experience and sex behavior, drug use, violence, and recidivism. This study indicates that young men who have long-term sex partners prior to incarceration are less likely to be inconsistent condom users (OR = 0.50, $p = 0.01$), have sex while high on drugs/alcohol (OR = 0.14, $p = 0.001$), use marijuana daily (OR = 0.45, $p = 0.001$), and carry weapons during illegal activity (OR = 0.58, $p = 0.05$), especially compared with peers who simultaneously are involved with long-term and casual "short-term" sex partners. However, the positive effects of having a long-term sex partner generally do not apply over time - in this case, one year after being released from jail. Aside from sexual partners, factors such as employment and housing stability predict whether these young men will experience positive or negative outcomes post-incarceration. This study highlights the importance and potential benefits of health interventions that engage young Black and Latino men who are involved in the criminal justice system in the US, as well as their sex partners, in health promotion programs. The study also confirms the need for programs that address the employment and housing needs of young men after they leave correctional facilities. Ramaswamy M, Freudenberg N. Sex partnerships, health, and social risks of young men leaving jail: analyzing data from a randomized controlled trial. *BMC Public Health*. 2010 Nov 10; 10: 689.

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

Research Findings - Clinical Neuroscience Research

Intronic Polymorphisms Affecting Alternative Splicing of the Human Dopamine D2 Receptor are Associated with Cocaine Abuse

The dopamine receptor D2 (encoded by *DRD2*) is implicated in susceptibility to mental disorders and cocaine abuse, but mechanisms responsible for this relationship remain uncertain. *DRD2* mRNA exists in two main splice isoforms with distinct functions: D2 long (D2L) and D2 short (D2S, lacking exon 6), expressed mainly postsynaptically and presynaptically, respectively. Two intronic single-nucleotide polymorphisms (SNPs rs2283265 (intron 5) and rs1076560 (intron 6)) in high linkage disequilibrium (LD) with each other have been reported to alter D2S/D2L splicing and several behavioral traits in human subjects, such as memory processing. To assess the role of *DRD2* variants in cocaine abuse, the authors measured levels of D2S and D2L mRNA in human brain autopsy tissues (prefrontal cortex and putamen) obtained from cocaine abusers and controls, and genotyped a panel of *DRD2* SNPs (119 abusers and 95 controls). Robust effects of rs2283265 and rs1076560 on reducing formation of D2S relative to D2L were confirmed. The minor alleles of rs2283265/rs1076560 were considerably more frequent in Caucasians (18%) compared with African Americans (7%). Also, in Caucasians, rs2283265/rs1076560 minor alleles were significantly overrepresented in cocaine abusers compared with controls (rs2283265: 25 to 9%, respectively; $p=0.001$; OR=3.4 (1.7-7.1)). Several SNPs previously implicated in diverse clinical association studies are in high LD with rs2283265/rs1076560 and could have served as surrogate markers. These results confirm the role of rs2283265/rs1076560 in D2 alternative splicing and support a strong role in susceptibility to cocaine abuse. Moyer RA, Wang D, Papp AC, Smith RM, Dugue L, Mash DC, Sadee W. Intronic polymorphisms affecting alternative splicing of human dopamine D2 receptor are associated with cocaine abuse. *Neuropsychopharm.* 2010 Dec 8. [Epub ahead of print].

Impaired Cortical-Striatal Connectivity During Simple Motor Performance 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 1 healthy control as they performed a finger-tapping task. Functional coupling was quantified by correlating the time courses of each pair of anatomically-connected regions of

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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*. 2010. [Epub ahead of print].

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Circulating Leptin is Associated with Increased Craving to Smoke in Abstinent Smokers

The adipocyte hormone leptin regulates satiety and energy expenditure. Recent evidence suggests that leptin is associated with increased craving for alcohol and with shorter length of abstinence during alcohol treatment. This study examined leptin's associations with craving for cigarettes and smoking relapse among smokers interested in cessation. Participants (32 smokers; 14 women) attended a laboratory session 24 h following their designated quit day where circulating leptin levels and craving for smoking were assessed. Other Measures of withdrawal symptoms, affect, physical symptoms, as well as neuroendocrine and cardiovascular Measures were collected before and after performing two stress tasks (public speaking and cognitive tasks). High circulating leptin levels were associated with increased craving, withdrawal symptoms, negative affect, physical symptoms, and reduced positive affect. Circulating leptin levels were not related to cardiovascular and neuroendocrine Measures, responses to acute stressors, or to smoking relapse. These results indicate that circulating leptin is a promising biological marker of craving for smoking and warrant further investigation of the links between appetite regulation and nicotine dependence. Al'Absi M, Hooker S, Fujiwara K, Kiefer F, von der Goltz C, Cragin T, Wittmers LE. Circulating leptin levels are associated with increased craving to smoke in abstinent smokers. *Pharm Biochem Behav* 2010; 97: 509-513.

Diffusion Tensor Imaging and Decision Making in Cocaine Dependence

Chronic stimulant abuse is associated with both impairment in decision making and structural abnormalities in brain gray and white matter. Recent data suggest these structural abnormalities may be related to functional impairment in important behavioral processes. In 15 cocaine-dependent and 18 control subjects, the authors examined relationships between decision-making performance on the Iowa Gambling Task (IGT) and white matter integrity as measured by diffusion tensor imaging (DTI). Whole brain voxelwise analyses showed that, relative to controls, the cocaine group had lower fractional anisotropy (FA) and higher mean of the second and third eigenvalues (γ) in frontal and parietal white matter regions and the corpus callosum. Cocaine subjects showed worse performance on the IGT, notably over the last 40 trials. Importantly, FA and γ values in these regions showed a significant relationship with IGT performance on the last 40 trials. The authors concluded that compromised white matter integrity in cocaine dependence may be related to functional impairments in decision making. Lane SD, Steinberg JL, Ma L, Hasan KM, Kramer LA, Zuniga EA, Narayana PA, Moeller FG. Diffusion tensor imaging and decision making in cocaine dependence. *PLoS ONE*. 2011 July 16; 5(7): e11591.

Nerve Growth Factor B Polypeptide (NGFB) Genetic Variability: Association with the Methadone Dose Required for Effective Maintenance Treatment

Opioid addiction is a chronic disease with high genetic contribution and a large inter-individual variability in therapeutic response. The goal of this study was to identify pharmacodynamic factors that modulate methadone dose requirement. The neurotrophin family is involved in neural plasticity, learning, memory and behavior and deregulated neural plasticity may underlie the pathophysiology of drug addiction. Brain-derived neurotrophic factor (BDNF) was shown to affect the response to methadone maintenance treatment. This study explores the effects of polymorphisms in the nerve growth factor (B polypeptide) gene, NGFB, on the methadone doses required for successful maintenance treatment for heroin addiction. Genotypes of 14 NGFB polymorphisms were analyzed for association with the stabilizing methadone dose in 72 former severe heroin addicts with no major co-medications. There was significant difference in methadone doses required by subjects with different genotypes of the NGFB intronic single-nucleotide polymorphism rs2239622 ($P=0.0002$). These results may have clinical importance. Levran O, Peles E., Samon S., Randesi M, Zhao C, Zhang B, Adelson M, Kreek MJ. Nerve growth factor B polypeptide (NGFB) genetic variability: Association with the methadone dose required for effective maintenance treatment. *Pharmacogenomics J.* 2011 March 1. [Epub ahead of print].

Heritability of Delay Discounting in Adolescence: A Longitudinal Twin Study

Delay discounting (DD) refers to the preference for smaller immediate rewards over larger but delayed rewards, and is considered to be a distinct component of a broader "impulsivity" construct. Although greater propensity for discounting the value of delayed gratification has been associated with a range of problem behaviors and substance abuse, particularly in adolescents, the origins of individual differences in DD remain unclear. The authors examined genetic and environmental influences on a real-life behavioral measure of DD using a longitudinal twin design. Adolescent participants were asked to choose between a smaller (\$7) reward available immediately and a larger (\$10) reward to be received in 7 days. Biometrical genetic analysis using linear structural equation modeling showed significant heritability of DD at ages 12 and 14 (30 and 51%, respectively) and suggested that the same genetic factors influenced the trait at both ages. DD was significantly associated with symptoms of conduct disorder, attention deficit hyperactivity disorder, substance use, and with higher novelty seeking and poor self-regulation. This study provides the first evidence for heritability of DD in humans and suggests that DD can be a promising endophenotype for genetic studies of addiction and externalizing disorders. Anokhin, AP, Golosheykin G, Grant JD, Heath AC. Heritability of delay discounting in adolescence: A longitudinal twin study. *Behav Genet.* 2011; 41(2): 175-183.

Gene X Disease Interaction on Orbitofrontal Gray Matter in Cocaine Addiction

Long-term cocaine use has been associated with structural deficits in brain regions having dopamine-receptive neurons. However, the concomitant use of other drugs and common genetic variability in monoamine regulation present additional structural variability. The objective of this study was to examine variations in gray matter volume (GMV) as a function of lifetime drug use and the genotype of the monoamine oxidase A gene, MAOA, in men with cocaine use disorders (CUD) and healthy male controls. The design of the study was a cross-sectional comparison carried out at the Clinical Research Center at

Brookhaven National Laboratory. Forty individuals with CUD and 42 controls who underwent magnetic resonance imaging to assess GMV and were genotyped for the MAOA polymorphism (categorized as high- and low-repeat alleles) served as subjects. The impact of cocaine addiction on GMV, was tested by (1) comparing the CUD group with controls, (2) testing diagnosis x MAOA interactions, and (3) correlating GMV with lifetime cocaine, alcohol, and cigarette smoking, and testing their unique contribution to GMV beyond other factors. Results showed that: (1) Individuals with CUD had reductions in GMV in the orbitofrontal, dorsolateral prefrontal, and temporal cortex and the hippocampus compared with controls. (2) The orbitofrontal cortex reductions were uniquely driven by CUD with low- MAOA genotype and by lifetime cocaine use. (3) The GMV in the dorsolateral prefrontal cortex and hippocampus was driven by lifetime alcohol use beyond the genotype and other pertinent variables. The authors conclude that long-term cocaine users with the low-repeat MAOA allele have enhanced sensitivity to gray matter loss, specifically in the orbitofrontal cortex, indicating that this genotype may exacerbate the deleterious effects of cocaine in the brain. In addition, long-term alcohol use is a major contributor to gray matter loss in the dorsolateral prefrontal cortex and hippocampus, and is likely to further impair executive function and learning in cocaine addiction. Alia-Klein N, Parvaz MH, Woicik PA, Konova AB, Maloney T, Shumay E, Wang R, Telang F, Biegan A, Wang G-J, Fowler JS, Tomasi D, Volkow ND, Goldstein RZ. Gene X disease interaction on orbitofrontal gray matter in cocaine addiction. *Arch Gen Psychiat*. 2011 March; 68(3): 283-294.

Nonmedical Use of Prescription Opioids and Pain in Veterans with and without HIV

Few studies have systematically evaluated nonmedical use of prescription opioids (NMU) among U.S. military veterans, those who report pain, and those with human immunodeficiency virus (HIV). An increased understanding of the factors associated with NMU may help providers to balance maintaining patient access to prescription opioids for legitimate medical reasons and reducing the risks of addiction. The authors analyzed self-report data and electronic medical and pharmacy record data from 4122 participants in the Veterans Aging Cohort Study. Bivariate associations were analyzed using chi-squared tests, t tests, and median tests, and multivariable associations were assessed using logistic regression. Median participant age was 52 years; 95% were men; 65% were black, and 53% were HIV infected. NMU was reported by 13% of participants. In multivariable analysis, NMU was associated with: being Hispanic (adjusted odds ratio [AOR] 1.8); aged 40-44years (AOR 1.6); Alcohol Use Disorders Identification Test score ≥ 20 (AOR 2.0); drug use disorder (AOR 1.9); opioid use disorder (AOR 2.7); past month cigarette use (AOR 1.3); receiving a past-year Veterans Health Administration opioid prescription (AOR 1.9); hepatitis C (AOR 1.5); and pain interference (AOR 1.1). Being overweight (AOR 0.6) or obese (AOR 0.5) and having a higher 12-Item Short-Form Health Survey (SF-12) Mental Component Summary (AOR 0.98) were associated with less NMU. Patients with and without NMU did not differ on HIV status or SF-12 Physical Component Summary. Veterans in care have a high prevalence of NMU that is associated with substance use, medical status, and pain interference, but not HIV status. Nonmedical use of prescription opioids among veterans in care is associated with pain interference, medical and substance use disorder morbidity, but not human immunodeficiency virus status. Barry DT, Goulet JL, Kerns RK, Becker WC, Gordon AJ, Justice AC, Fiellin DA. Nonmedical use of prescription opioids and pain in veterans with and without HIV. *Pain*. 2011 Feb 25. [Epub ahead of print].

Pain Catastrophizing and Pain Coping among Methadone-maintained Patients

The aim of this study was to examine the association of pain catastrophizing

and pain coping strategies with characteristic pain intensity (an average of worst, least, and typical pain intensity in the past week) and recent pain-related disability (an average of three Measures of past week pain interference) in opioid-dependent patients enrolled in a methadone maintenance treatment program (MMTP) who reported recent pain. The design of this study was a cross-sectional survey among 108 MMTP patients who reported recent pain. Participants completed measures of demographics, pain status (i.e., "chronic severe pain" [pain lasting at least 6 months with at least moderate pain intensity or significant pain interference in the past week] vs "some pain" [pain in the past week not meeting the threshold of chronic severe pain]), characteristic pain intensity, recent pain-related disability, somatization, depression, catastrophizing, and pain coping strategies. Catastrophizing explained a significant proportion of the variance in characteristic pain intensity (14%) and recent pain-related disability (11%) after controlling for demographics, pain status, somatization, and depression. Mirroring the findings of studies of non-opioid-dependent chronic pain patients, greater catastrophizing was associated with greater pain intensity and increases in recent pain-related disability. On average, the "chronic severe pain" group reported higher levels of catastrophizing than the "some pain" group. Consistent with studies of patients with chronic pain who are not opioid dependent, the findings emphasize the importance of assessing and addressing catastrophizing in MMTP patients with pain. Garnet B, Beitel M, Cutter CJ, Savant J, Peters S, Schottenfeld RS, Barry DT. Pain catastrophizing and pain coping among methadone-maintained patients. *Pain Med.* 2011 Jan; 12(1): 79-86.

Painful Heat Reveals Hyperexcitability of the Temporal Pole in Interictal and Ictal Migraine States

During migraine attacks, alterations in sensation accompanying headache may manifest as allodynia and enhanced sensitivity to light, sound, and odors. The objective of this study was to identify physiological changes in cortical regions in migraine patients using painful heat and functional magnetic resonance imaging (fMRI) and the structural basis for such changes using diffusion tensor imaging (DTI). In 11 interictal patients, painful heat threshold + 1°C was applied unilaterally to the forehead during fMRI scanning. Significantly greater activation was identified in the medial temporal lobe in patients relative to healthy subjects, specifically in the anterior temporal pole (TP). In patients, TP showed significantly increased functional connectivity in several brain regions relative to controls, suggesting that TP hyperexcitability may contribute to functional abnormalities in migraine. In 9 healthy subjects, DTI identified white matter connectivity between TP and pulvinar nucleus, which has been related to migraine. In 8 patients, fMRI activation in TP with painful heat was exacerbated during migraine, suggesting that repeated migraines may sensitize TP. This article investigates a nonclassical role of TP in migraineurs. Observed temporal lobe abnormalities may provide a basis for many of the perceptual changes in migraineurs and may serve as a potential interictal biomarker for drug efficacy. Moulton EA, Becerra L, Maleki N, Pendse G, Tully S, Hargreaves R, Burstein R, Borsook D. Painful heat reveals hyperexcitability of the temporal pole in interictal and ictal migraine States. *Cereb Cortex.* 2011 Feb; 21(2): 435-448.

Opioids, Chronic Pain, and Addiction in Primary Care

Research has largely ignored the systematic examination of physicians' attitudes towards providing care for patients with chronic noncancer pain. The objective of this study was to identify barriers and facilitators to opioid treatment of chronic noncancer pain patients by office-based medical providers. The authors used a qualitative study design using individual and group interviews. Participants were 23 office-based physicians in New England.

Interviews were audiotaped, transcribed, and systematically coded by a multidisciplinary team using the constant comparative method. Physician barriers included absence of Objective or physiological Measures of pain; lack of expertise in the treatment of chronic pain and coexisting disorders, including addiction; lack of interest in pain management; patients' aberrant behaviors; and physicians' attitudes toward prescribing opioid analgesics. Physician facilitators included promoting continuity of patient care and the use of opioid agreements. Physicians' perceptions of patient-related barriers included lack of physician responsiveness to patients' pain reports, negative attitudes toward opioid analgesics, concerns about cost, and patients' low motivation for pain treatment. Perceived logistical barriers included lack of appropriate pain management and addiction referral options, limited information regarding diagnostic workup, limited insurance coverage for pain management services, and limited ancillary support for physicians, and insufficient time. Addressing these barriers to pain treatment will be crucial to improving pain management service delivery. This article demonstrates that perceived barriers to treating patients with chronic noncancer pain are common among office-based physicians. Addressing these barriers in physician training and in existing office-based programs might benefit both noncancer chronic pain patients and their medical providers. Barry DT, Irwin KS, Jones ES, Becker WC, Tetrault JM, Sullivan LE, Hansen H, O'Connor PG, Schottenfeld RS, Fiellin DA. Opioids, chronic pain, and addiction in primary care. *J Pain*. 2010 Dec; 11(12): 1442-1450.

Exploring Relations among Traumatic, Posttraumatic, and Physical Pain Experiences in Methadone-maintained Patients

Differences in lifetime trauma exposure and screened symptoms of posttraumatic stress disorder (PTSD) were examined in methadone maintenance treatment (MMT) patients with a variety of pain experiences. Parametric and nonparametric statistical tests were performed on data obtained from 150 patients currently enrolled in MMT. In comparison to MMT patients reporting no pain in the previous week, those with chronic severe pain (CSP) (i.e., pain lasting at least 6 months with moderate to severe pain intensity or significant pain interference) exhibited comparable levels of trauma involving sexual assault but reported significantly higher levels of trauma involving physical assault, number of traumatic events, and screened symptoms of PTSD. A third group, non-CSP MMT patients reporting some pain in the past week, differed significantly from the CSP group on number of traumatic events but reported comparable levels of sexual assault and physical assault. In comparison to men, women reported higher levels of sexual assault and were more likely to score above the cutoff on the PTSD screener but reported comparable levels of physical assault and number of traumatic events. Pain-related differences in trauma and screened symptoms of PTSD exist in MMT patients and may have implications for program planning and outreach efforts. This article demonstrates that trauma and screened symptoms of PTSD vary as a function of sex and pain status in methadone-maintained patients. Future studies may benefit from developing and assessing Interventions that address chronic pain, PTSD, and opioid dependence in MMT. Barry DT, Beitel M, Cutter CJ, Garnet B, Joshi D, Rosenblum A, Schottenfeld RS. Exploring relations among traumatic, posttraumatic, and physical pain experiences in methadone-maintained patients. *J Pain*. 2011 Jan 12; (1): 22-28.

The Subjective, Reinforcing, and Analgesic Effects of Oxycodone in Patients with Chronic, Non-malignant Pain Who Are Maintained on Sublingual Buprenorphine/Naloxone

Some sources suggest that significant misuse of opioid drugs exists among patients with chronic pain. However, the risk factors and motivation behind their abuse may differ from those of other opioid abusers. This study sought to

examine the abuse liability of oxycodone among patients with chronic, non-malignant pain who met the DSM-IV criteria for opioid abuse. Eighteen opioid-dependent patients with chronic pain lived on an in-patient unit of the New York State Psychiatric Institute during the 7-week study. Participants were given oral oxycodone (0, 10, 20, 40, and 60 mg/70 kg) while maintained on various doses of sublingual buprenorphine/naloxone (Bup/Nx; 2/0.5, 8/2, and 16/4 mg/day). Doses of both medications were administered under double-blind conditions. Oxycodone produced an overall positive, but less robust, subjective profile than previously reported in recreational opioid users without pain. Furthermore, unlike the authors' findings in recreational opioid users and more similar to effects in non-drug-abusing individuals, oxycodone failed to serve as a reinforcer. As for the maintenance drug, Bup/Nx produced a dose-related reduction in some of the effects of acutely administered oxycodone. These data suggest that sublingual Bup/Nx has the potential as an analgesic medication and further research should investigate its use in treating patients with chronic pain who abuse opioids. Jones JD, Sullivan MA, Manubay J, Vosburg SK, Comer SD. The subjective, reinforcing, and analgesic effects of oxycodone in patients with chronic, non-malignant pain who are maintained on sublingual buprenorphine/naloxone. *Neuropsychopharmacology*. 2011 Jan; 36(2): 411-422.

APOE ϵ 4 Allele and CSF APOE on Cognition in HIV-Infected Subjects

The significance of the cerebrospinal fluid (CSF) Apolipoprotein E (APOE) level and whether it might have differential effects on brain function due to the presence of APOE ϵ 4 allele(s) in HIV-infected patients are unknown. However, APOE ϵ 4 allele has been associated with greater incidence of HIV-associated dementia and accelerated progression of HIV infection. Here, the authors show further evidence for the role of APOE ϵ 4 in promoting cognitive impairment. They measured the APOE levels in the CSF of HIV-infected individuals. HIV+ subjects showed lower CSF APOE proteins than SN controls (-19%, $p=0.03$). While SN subjects with or without ϵ 4 allele showed no difference in CSF APOE levels, ϵ 4+ HIV+ subjects had similar levels to the SN subjects but higher levels than ϵ 4- HIV+ subjects (+34%, $p=0.01$). Furthermore, while HIV+ subjects with ϵ 2 or ϵ 3 allele(s) showed a positive relationship between their CSF APOE levels and cognitive performance on the speed of processing domain ($r=+0.35$, $p=0.05$), ϵ 4+ HIV+ subjects, in contrast, exhibited a negative relationship such that those with higher levels of CSF APOE(4) performed worse on the HIV Dementia Scale ($r=-0.61$, $p=0.02$), had lower Global Cognitive Scores ($r=-0.57$, $p=0.03$), and had poorer performance on tests involving learning (ϵ 4 allele x [APOE] interaction, $p=0.01$). These findings also suggest that the relatively higher levels of CSF APOE in ϵ 4+ HIV+ (having primarily APOE4 isoforms) may negatively impact the brain and lead to poorer cognitive outcomes, while those individuals without the ϵ 4 allele (with primarily APOE2 or APOE3 isoforms) may show compensatory responses that lead to better cognitive performance. Andres MA, Feger U, Nath A, Munsaka S, Jiang CS, Chang L. APOE ϵ 4 allele and CSF APOE on Cognition in HIV-Infected Subjects. *J Neuroimmune Pharmacol*. 2010 Dec 24. [Epub ahead of print].

Neurocognitive Functioning in Acute or Early HIV Infection

The authors examined neurocognitive functioning among persons with acute or early HIV infection (AEH) and hypothesized that the neurocognitive performance of AEH individuals would be intermediate between HIV seronegatives (HIV-) and those with chronic HIV infection. Comprehensive neurocognitive testing was accomplished with 39 AEH, 63 chronically HIV infected, and 38 HIV- participants. All AEH participants were HIV infected for less than 1 year. Average domain deficit scores were calculated in seven neurocognitive domains. HIV-, AEH, and chronically HIV infected groups were

ranked from best (rank of 1) to worst (rank of 3) in each domain. All participants received detailed substance use, neuromedical, and psychiatric evaluations and HIV infected persons provided information on antiretroviral treatment and completed laboratory evaluations including plasma and CSF viral loads. A nonparametric test of ordered alternatives (Page test), and the appropriate nonparametric follow-up test, was used to evaluate level of neuropsychological (NP) functioning across and between groups. The median duration of infection for the AEH group was 16 weeks [interquartile range, IQR: 10.3-40.7] as compared to 4.9 years [2.8-11.1] in the chronic HIV group. A Page test using ranks of average scores in the seven neurocognitive domains showed a significant monotonic trend with the best neurocognitive functioning in the HIV- group (mean rank=1.43), intermediate neurocognitive functioning in the AEH group (mean rank=1.71), and the worst in the chronically HIV infected (mean rank=2.86; L statistic=94, $p<0.01$); however, post-hoc testing comparing neurocognitive impairment of each group against each of the other groups showed that the chronically infected group was significantly different from both the HIV- and AEH groups on neurocognitive performance; the AEH group was statistically indistinguishable from the HIV- group. Regression models among HIV infected participants were unable to identify significant predictors of neurocognitive performance. Neurocognitive functioning was worst among persons with chronic HIV infection. Although a significant monotonic trend existed and patterns of the data suggest the AEH individuals may fall intermediate to HIV- and chronic participants, the authors were not able to statistically confirm this hypothesis. Moore DJ, Letendre SL, Morris S, Umlauf A, Deutsch R, Smith DM, Little S, Rooney A, Franklin DR, Gouaux B, Leblanc S, Rosario D, Fennema-Notestine C, Heaton RK, Ellis RJ, Atkinson JH, Grant I. CHARTER Group. Neurocognitive functioning in acute or early HIV infection. *J Neurovirol.* 2011 Feb 17; (1): 50-57.

HIV-associated Neurocognitive Disorders Persist in the Era of Potent Antiretroviral Therapy: CHARTER Study

This is a cross-sectional, observational study to determine the frequency and associated features of HIV-associated neurocognitive disorders (HAND) in a large, diverse sample of infected individuals in the era of combination antiretroviral therapy (CART). A total of 1,555 HIV-infected adults were recruited from 6 university clinics across the United States, with minimal exclusions. The authors used standardized neuromedical, psychiatric, and neuropsychological (NP) examinations, and recently published criteria for diagnosing HAND and classifying 3 levels of comorbidity (minimal to severe non-HIV risks for NP impairment). Fifty-two percent of the total sample had NP impairment, with higher rates in groups with greater comorbidity burden (40%, 59%, and 83%). Prevalence estimates for specific HAND diagnoses (excluding severely confounded cases) were 33% for asymptomatic neurocognitive impairment, 12% for mild neurocognitive disorder, and only 2% for HIV-associated dementia (HAD). Among participants with minimal comorbidities ($n = 843$), history of low nadir CD4 was a strong predictor of impairment, and the lowest impairment rate on CART occurred in the subset with suppressed plasma viral loads and nadir CD4 ≥ 200 cells/mm³ (30% vs 47% in remaining subgroups). The most severe HAND diagnosis (HAD) was rare, but milder forms of impairment remained common, even among those receiving CART who had minimal comorbidities. Future studies should clarify whether early disease events (e.g., profound CD4 decline) may trigger chronic CNS changes, and whether early CART prevents or reverses these changes. Heaton RK, Clifford DB, Franklin DR Jr, Woods SP, Ake C, Vaida F, Ellis RJ, Letendre SL, Marcotte TD, Atkinson JH, Rivera-Mindt M, Vigil OR, Taylor MJ, Collier AC, Marra CM, Gelman BB, McArthur JC, Morgello S, Simpson DM, McCutchan JA, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I. CHARTER Group. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology.* 2010 Dec 7; 75(23):

2087-2096.

Fulminant Encephalopathy with Basal Ganglia Hyperintensities in HIV-infected Drug Users

The objective of this study was to define a clinical syndrome associated with active drug abuse in HIV-infected individuals. The authors performed a retrospective review to identify individuals treated at the Johns Hopkins Hospital from 1993 to 2008 who were HIV-infected and were actively abusing drugs and had bilateral basal ganglia lesions on MRI. They were identified using a key word search in the radiology database, autopsy database, and the Moore HIV clinic database. Clinical, laboratory, and radiographic findings were correlated to define the syndrome. Ten individuals were identified who presented with a change in mental status or seizures, used cocaine or cocaine with heroin, had uncontrolled HIV infection (>190,000 copies/mL of plasma), elevated CSF protein (63-313 mg/dL), and diffuse hyperintense bilateral basal ganglia lesions on imaging. The majority of patients (8/10) had renal failure and despite supportive therapy most (7/9) ultimately died (median survival 21 days). Postmortem examination in one individual showed the presence of overwhelming microglial activation in the basal ganglia. The 2 surviving individuals were started on combined antiretroviral therapy (CART) during hospitalization. The authors describe a unique clinical syndrome of a fulminant encephalopathy associated with primarily basal ganglia involvement in HIV-infected drug abusers. This syndrome is a rare but serious condition that is associated with a high mortality rate. Early CART institution may be useful and neuroprotective in this disorder, although this requires further investigation. Newsome SD, Johnson E, Pardo C, McArthur JC, Nath A. Fulminant encephalopathy with basal ganglia hyperintensities in HIV-infected drug users. *Neurology*. 2011 Mar 1; 76(9): 787-794.

Spontaneous Strategy Use Protects Against Visual Working Memory Deficits in Older Adults Infected with HIV

Recent studies suggest that older human immunodeficiency virus (HIV)-infected adults are at particular risk for HIV-associated neurocognitive disorders (HAND), including dementia. Deficits in attention/working memory are posited to play a central role in the development of HAND among older adults. The aim of the present study was to examine the possible protective benefits of spontaneous strategy use during a visual working memory task in 46 older and 42 younger adults infected with HIV. Results revealed a significant interaction between age and strategy use, with older adults who used a meta-cognitive strategy demonstrating superior working memory performance versus non-strategy users. This effect was not observed in the younger HIV-infected sample and was not better explained by possible confounding factors, such as education, comorbid medical conditions, or HIV disease severity. Within the older group, strategy use was associated with better executive functions and higher estimated verbal intelligence. Findings from this study suggest that working memory declines in older HIV-infected adults are moderated by the use of higher-level mnemonic strategies and may inform cognitive neurorehabilitation efforts to improve cognitive and everyday functioning outcomes in older persons living with HIV infection. Woods SP, Weber E, Cameron MV, Dawson MS, Delano-Wood L, Bondi MW, Grant I. HIV Neurobehavioral Research Center (HNRC) Group. Spontaneous strategy use protects against visual working memory deficits in older adults infected with HIV. *Arch Clin Neuropsychol*. 2010 Dec 25(8); 724-733.

Structure and Etiology of Co-occurring Internalizing and Externalizing Disorders in Adolescents

Several studies suggest that a two-factor model positing internalizing and externalizing factors explains the interrelationships among psychiatric disorders. However, it is unclear whether the covariation between internalizing and externalizing disorders is due to common genetic or environmental influences. The authors examined whether a model positing two latent factors, internalizing and externalizing, explained the interrelationships among six psychiatric disorders (major depressive disorder, generalized anxiety disorder, separation anxiety disorder, attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder) in adolescents, and whether there are common genetic and environmental influences on internalizing and externalizing latent factors. Multivariate behavior genetic analyses of data from 1162 twin pairs and 426 siblings ascertained from the general population via the Colorado Center for Antisocial Drug Dependence (CADD) were conducted. The authors found support for a model positing two latent factors (internalizing and externalizing). These factors were moderately heritable and influenced by significant common genetic and nonshared environmental influences. These findings suggest that co-occurrence of internalizing and externalizing psychopathology in adolescents results from both genetic and environmental influences. Cosgrove VE, Rhee SH, Gelhorn HL, Boeldt D, Corley RC, Ehringer MA, Young SE, Hewitt JK. Structure and etiology of co-occurring internalizing and externalizing disorders in adolescents. *J Abnorm Child Psychol.* 2011 Jan 39(1): 109-123.

Common and Drug-specific Genetic Influences on Subjective Effects to Alcohol, Tobacco and Marijuana Use

The aim of this study was to examine variation in positive and negative subjective effects to alcohol, tobacco and marijuana and covariation between these three drugs and each effect. Retrospective self-reports of subjective effects were collected to estimate the genetic and environmental influences and the extent of their specificity across three drugs. Data were drawn from 1299 adolescent and young adult same- and opposite sex twin- and sibling-pairs participating in the Colorado Center for Antisocial Drug Dependence (CADD). The study setting was a large, collaborative, longitudinal study of substance use and antisocial behavior in community and clinical adolescents. Subjective effects were assessed using a 13-item questionnaire that included positive and negative responses to alcohol, tobacco and marijuana. Heritable influences contributed moderately (additive genetic effects 16-56%) to positive and negative subjective effects to all three drugs and did not differ for males and females. Genetic and environmental contributions to positive and negative subjective effects are largely non-overlapping for tobacco and marijuana. Multivariate genetic modeling indicated that subjective effects to alcohol, tobacco and marijuana share a common, heritable etiology and that drug-specific genetic influences were an important contributor to individual differences in drug response. Results from these genetic analyses suggest that subjective effects to these commonly used and misused drugs are heritable and that the genetic and environmental influences on effects to one drug also influence subjective effects to other drugs. Haberstick BC, Zeiger JS, Corley RP, Hopfer CJ, Stallings MC, Rhee SH, Hewitt JK. Common and drug-specific genetic influences on subjective effects to alcohol, tobacco and marijuana use. *Addiction.* 2011 Jan; 106(1): 215-224.

Smoking Withdrawal Modulates Right Inferior Frontal Cortex but not Presupplementary Motor Area Activation during Inhibitory Control

Smokers exhibit decrements in inhibitory control (IC) during withdrawal. The objective of this study was to investigate the neural basis of these effects in critical substrates of IC--right inferior frontal cortex (rIFC) and presupplementary motor area (pre-SMA). Smokers were scanned following

smoking as usual and after 24-h smoking abstinence. During scanning they completed a Go/No-Go task that required inhibiting responses to infrequent STOP trials. Event-related brain activation in response to successfully inhibited STOP trials was evaluated in two regions of interest: rIFC (10mm sphere, $x=40$, $y=30$, $z=26$) and pre-SMA (10mm sphere, $x=2$, $y=18$, $z=40$). Smoking abstinence robustly increased errors of commission on STOP trials (37.1 vs 24.8% in the satiated condition, $p<0.001$) while having no effects on GO trial accuracy or reaction time (RT). In rIFC, smoking abstinence was associated with a significantly increased event-related BOLD signal ($p=0.026$). Pre-SMA was unaffected by smoking condition. The results of this preliminary study suggest that successful IC during withdrawal is associated with increased processing demands on a cortical center associated with attention to inhibitory signals. Kozink RV, Kollins SH, McClernon FJ. Smoking withdrawal modulates right inferior frontal cortex but not presupplementary motor area activation during inhibitory control. *Neuropsychopharmacology*. 2010 Dec; 35(13): 2600-2606.

Characterization of Time-course of Withdrawal Symptoms in Abstinent Methamphetamine-dependent Subjects

Withdrawal symptoms have been linked to a propensity for relapse to drug abuse. Inasmuch as this association applies to methamphetamine (MA) abuse, an understanding of the course of MA withdrawal symptoms may help to direct treatment for MA dependence. Previous studies of symptoms manifested during abstinence from MA have been limited in size and scope. The authors asked (i) whether debilitating psychological and/or physical symptoms appear during the first several weeks of MA abstinence, (ii) how craving for MA evolves and (iii) whether psychiatric symptoms (e.g. depression, psychosis) persist beyond a month of abstinence. This research studied MA-dependent participants, who initiated and maintained abstinence from the drug for up to 5 weeks, compared to a matched healthy comparison group and was conducted on an in-patient research hospital ward (MA-dependent subjects) and out-patient (comparison subjects). Participants were 56 MA-dependent and 89 comparison subjects. Measurements consisted of a rater-assessed MA withdrawal questionnaire and self-report assessment of craving (MA-dependent subjects) and self-report assessment of psychiatric symptoms (both groups). At study entry, MA-dependent subjects exhibited a wide range in severity of depressive symptoms, with the average score at a mild-moderate level of severity. Symptoms of psychosis were also prevalent. While depressive and psychotic symptoms largely resolved within a week of abstinence, craving did not decrease significantly from the time of initiating abstinence until the second week, and then continued at a reduced level to the fifth week. Depressive and psychotic symptoms accompany acute withdrawal from methamphetamine but resolve within 1 week. Craving is also present and lasts at least 5 weeks. Zorick T, Nestor L, Miotto K, Sugar C, Hellemann G, Scanlon G, Rawson R, London ED. Withdrawal symptoms in abstinent methamphetamine-dependent subjects. *Addiction*. 2010 Oct; 105(10): 1809-1818.

A Cerebellar Thalamic Cortical Circuit Governs Error-related Cognitive Control

Error detection and behavioral adjustment are core components of cognitive control. Numerous studies have focused on the anterior cingulate cortex (ACC) as a critical locus of this executive function. The authors' previous work showed greater activation in the dorsal ACC and subcortical structures during error detection, and activation in the ventrolateral prefrontal cortex (VLPFC) during post-error slowing (PES) in a stop signal task (SST). However, the extent of error-related cortical or subcortical activation across subjects was not correlated with VLPFC activity during PES. So then, what causes VLPFC activation during PES? To address this question, the authors employed Granger

causality mapping (GCM) and identified regions that Granger caused VLPFC activation in 54 adults performing the SST during fMRI. These brain regions, including the supplementary motor area (SMA), cerebellum, a pontine region, and medial thalamus, represent potential targets responding to errors in a way that could influence VLPFC activation. In confirmation of this hypothesis, the error-related activity of these regions correlated with VLPFC activation during PES, with the cerebellum showing the strongest association. The finding that cerebellar activation Granger causes prefrontal activity during behavioral adjustment supports a cerebellar function in cognitive control. Furthermore, multivariate GCM described the "flow of information" across these brain regions. Through connectivity with the thalamus and SMA, the cerebellum mediates error and post-error processing in accord with known anatomical projections. Taken together, these new findings highlight the role of the cerebello-thalamo-cortical pathway in an executive function that has heretofore largely been ascribed to the anterior cingulate-prefrontal cortical circuit. Ide JS, Li CS. A cerebellar thalamic cortical circuit for error-related cognitive control. *Neuroimage*. 2011 Jan 1; 54(1): 455-464.

Hyperactive Intrinsic Amygdala Network Connectivity is Associated with Impulsivity in Abstinent Heroin Addicts

Impulsivity is a pathological hallmark of drug addiction. However, little is known about the neuropsychological underpinnings of this impaired impulsive control network on drug addiction. Twenty two abstinent heroin dependent (HD) subjects and 15 cognitively normal (CN) subjects participated in this study. Resting-state functional connectivity MRI was employed to measure abnormalities in the intrinsic amygdala functional connectivity (iAFC) network activity and the Barratt Impulsive Scale, 11th version was used to measure impulsivity. Linear regression analysis was applied to detect the neural constructs underlying impulsivity by correlating iAFC network activity with impulsive scores. In the HD group, higher impulsivity scores and significantly enhanced iAFC network activity were found, especially in bilateral thalamus, right insula, and inferior frontal gyrus. Markedly decreased anticorrelated iAFC network activity was seen in the left precuneus, and even switched to positive correlation pattern in right precuneus, relative to the CN group. The iAFC network strengths in the HD group were positively correlated with impulsivity in the right subcallosal gyrus, insula, thalamus and posterior cingulate cortex, and negatively correlated in left fusiform area. In the CN group, the left pre-somatomotor area-amygdala connectivity was positively correlated, and right orbital frontal cortex-amygdala and precuneus-amygdala connectivity were negatively correlated with impulsivity scores. This study demonstrates different constructs of the impulsive network in HD and CN subjects. Altered iAFC network connectivity in HD subjects may contribute to the loss of impulsive control. This further facilitates our understanding of the neural underpinnings of behavior dysfunction in addiction. Xie C, Li SJ, Shao Y, Fu L, Goveas J, Ye E, Li W, Cohen AD, Chen G, Zhang Z, Yang Z. Identification of hyperactive intrinsic amygdala network connectivity associated with impulsivity in abstinent heroin addicts. *Behav Brain Res*. 2011 Jan 20; 216(2): 639-646.

Repeated N-acetyl Cysteine Reduces Cocaine Seeking in Rodents and Craving in Cocaine-dependent Humans

Addiction is a chronic relapsing disorder hypothesized to be produced by drug-induced plasticity that renders individuals vulnerable to craving-inducing stimuli such as re-exposure to the drug of abuse. Drug-induced plasticity that may result in the addiction phenotype includes increased excitatory signaling within corticostriatal pathways that correlates with craving in humans and is necessary for reinstatement in rodents. Reduced cystine-glutamate exchange by system x(c)- appears to contribute to heightened excitatory signaling within the striatum, thereby posing this as a novel target in the treatment of

addiction. In the present report, the authors examined the impact of repeated N-acetyl cysteine, which is commonly used to activate cystine-glutamate exchange, on reinstatement in rodents in a preclinical study and on craving in cocaine-dependent humans in a preliminary, proof-of-concept clinical experiment. Interestingly, repeated administration (7 days) of N-acetyl cysteine (60 mg/kg, IP) produced a significant reduction in cocaine (10mg/kg, IP)-induced reinstatement, even though rats (N=10-12/group) were tested 24h after the last administration of N-acetyl cysteine. The reduction in behavior despite the absence of the N-acetyl cysteine indicates that repeated N-acetyl cysteine may have altered drug-induced plasticity that underlies drug-seeking behavior. In parallel, the authors' preliminary clinical data indicate that repeated administration (4 days) of N-acetyl cysteine (1200-2400mg/day) to cocaine-dependent human subjects (N=4 per group) produced a significant reduction in craving following an experimenter-delivered IV injection of cocaine (20mg/70kg/60s). Collectively, these data demonstrate that N-acetyl cysteine diminishes the motivational qualities of a cocaine challenge injection possibly by altering pathogenic drug-induced plasticity. Amen SL, Piacentine LB, Ahmad ME, Li SJ, Mantsch JR, Risinger RC, Baker DA. Repeated N-acetyl cysteine reduces cocaine seeking in rodents and craving in cocaine-dependent humans. *Neuropsychopharmacology*. 2011 Mar; 36(4): 871-878.

Urges for Food and Money Spill Over into Motor System Excitability before Action is Taken

Much human behavior is driven by urges. Yet research into urges is hampered by a paucity of tools to objectively index their strength, timing and control. Here the authors used transcranial magnetic stimulation (TMS) and concurrent electromyography to examine whether urges for food and money are detectable via motor system excitability. In Experiment 1, they used a naturalistic food paradigm to show that food items that were most strongly wanted elicited the largest motor excitability, even before participants knew which response to make to get them. In Experiment 2a, they replicated the results using money - motor excitability was greater for larger monetary amounts. In Experiment 2b they show that monetary amount does not modulate motor excitability when participants simply observe, without having to take action. As the chief effect occurred prior to the subject knowing which motor response to make, it is not merely related to response preparation, and as the effect was present only when action was required, it is not merely related to increased arousal. Instead, the increased motor excitability likely indexes the degree of motivation a subject has to perform an action. Thus, the authors have used TMS to demonstrate that urges for food and money 'spill over' into the motor system. This is likely mediated by interactions between the limbic system (including the orbital frontal cortex) and the motor system, probably at the level of the basal ganglia. Implications are discussed for theories of embodied cognition and for methodological progress in studying urge control. Gupta N, Aron AR. Urges for food and money spill over into motor system excitability before action is taken. *Eur J Neurosci*. 2011 Jan; 33(1): 183-188.

Intermittent "Real-time" fMRI Feedback Is Superior to Continuous Presentation for a Motor Imagery Task

Real-time functional MRI feedback (RTfMRI) is a developing technique, with unanswered methodological questions. Given a delay of seconds between neural activity and the measurable hemodynamic response, one issue is the optimal method for presentation of neurofeedback to subjects. The primary objective of this preliminary study was to compare the methods of continuous and intermittent presentation of neural feedback on targeted brain activity. Thirteen participants performed a motor imagery task and were instructed to increase activation in an individually defined region of left premotor cortex

using RTfMRI. The fMRI signal change was compared between real and false feedback for scans with either continuous or intermittent feedback presentation. More individuals were able to increase their fMRI signal with intermittent feedback, while some individuals had decreased signal with continuous feedback. The evaluation of feedback itself activated an extensive amount of brain regions, and false feedback resulted in brain activation outside of the individually defined region of interest. As implemented in this study, intermittent presentation of feedback is more effective than continuous presentation in promoting self-modulation of brain activity. Furthermore, it appears that the process of evaluating feedback involves many brain regions that can be isolated using intermittent presentation. Johnson KA, Hartwell K, Lematty T, Borckardt J, Morgan PS, Govindarajan K, Brady K, George MS. Intermittent "Real-time" fMRI Feedback is superior to continuous presentation for a motor imagery task: A pilot study. *J Neuroimaging*. 2010 Oct 26. [Epub ahead of print].

Khat Use and Neurobehavioral Functions: Suggestions for Future Studies

Although there is a rich body of research available regarding the effect of acute and chronic khat dosing in animal models, research on the behavioral and cognitive effects of khat in human subjects is not extensive and several of the available studies have been done only in the context of observational and single-case studies. In light of the absence of a substantial literature on the neurobehavioral deficits associated with khat use and to provide a context that could be used to identify themes for future research the authors review previous research that has focused on other stimulant drugs. This review highlights multiple areas of neurocognitive deficit that have been identified in previous studies of individuals who have been chronic users of stimulants, such as amphetamines and methamphetamines. The review highlights a substantial body of evidence demonstrating a wide range of learning and memory impairments including deficits that persist during abstinence from active drug use. This review does not imply a similar khat effect, but due to some similarities pharmacologically between the active components of khat (cathinone and cathine) and amphetamines, future studies examining these same domains of cognitive functioning in chronic khat users and abstinent khat users appears to be warranted, if possible using some of the same or similar laboratory measures. Hoffman R, Al'Absi M. Khat use and neurobehavioral functions: suggestions for future studies. *J Ethnopharmacol*. 2010 Dec 1; 132(3): 554-563.

Body Mass Index is Associated with Brain Metabolite Levels in Alcohol Dependence--A Multimodal Magnetic Resonance Study

Recent studies demonstrated that alcohol dependence and excessive alcohol consumption are associated with increased rates of obesity. In healthy light-drinkers, the authors of this study and others have observed associations between elevated body mass index (BMI) and reductions in brain volumes, lower concentrations of N-acetyl-aspartate (NAA, marker of neuronal viability) and choline-containing compounds (Cho, involved in membrane turnover), and lower glucose utilization, particularly in frontal lobe--a brain region that is particularly vulnerable to the effects of alcohol dependence. Here, the authors evaluated whether BMI in alcohol-dependent individuals was independently associated with regional measures of brain structure, metabolite concentrations, and neocortical blood flow. As part of a study on the effects of alcohol dependence on neurobiology, the authors analyzed retrospectively data from 54 alcohol-dependent males, abstinent from alcohol for about 1 month and with BMI between 20 and 37 kg/m² by structural MRI, perfusion MRI (blood flow), and proton magnetic resonance spectroscopic imaging. After correction for age, smoking status, and various measures of alcohol

consumption, higher BMI was associated with lower concentrations of NAA, Cho, creatine and phosphocreatine (Cr, involved in high energy metabolism), and myo-inositol (m-Ino, a putative marker of astrocytes) primarily in the frontal lobe, in subcortical nuclei, and cerebellar vermis ($p < 0.004$). Regional brain volumes and perfusion were not significantly related to BMI. Furthermore, comorbid conditions, clinical laboratory measures, and nutritional assessments were not significant predictors of these MR-based measures. The results suggest that BMI, independent of age, alcohol consumption, and common comorbidities, is related to regional NAA, Cho, Cr, and m-Ino concentrations in this cohort of alcohol-dependent individuals. Additionally, as some common comorbid conditions in alcohol dependence such as cigarette smoking are associated with BMI, their associations with regional brain metabolite levels in alcohol-dependent individuals may also be influenced by BMI. Gazdzinski S, Durazzo TC, Mon A, Meyerhoff DJ. Body mass index is associated with brain metabolite levels in alcohol dependence--a multimodal magnetic resonance study. *Alcohol Clin Exp Res.* 2010 Dec; 34(12): 2089-2096.

Dopamine and Serotonin Transporter Availability in Chronic Heroin Users: A [¹²³I]B-CIT SPECT Imaging Study

Dopamine (DA) and serotonin (5-HT) transporter availability in heroin users and healthy controls was measured using [¹²³I]B-CIT and SPECT imaging. Heroin users had statistically similar striatal DA and brainstem and diencephalon 5-HT transporter availability compared with controls. No associations between transporter availability and heroin use characteristics were found. Cosgrove KP, Tellez-Jacques K, Pittman B, Petrakis I, Baldwin RM, Tamagnan G, Seibyl J, Kosten T, Staley JK. Dopamine and serotonin transporter availability in chronic heroin users: a [¹²³I]B-CIT SPECT imaging study. *Psychiatry Res.* 2010 Dec 30; 184(3): 192-195.

Genetics of Caffeine Consumption and Responses to Caffeine

Caffeine is widely consumed in foods and beverages and is also used for a variety of medical purposes. Despite its widespread use, relatively little is understood regarding how genetics affects consumption, acute response, or the long-term effects of caffeine. This paper reviews the literature on the genetics of caffeine from the following: (1) twin studies comparing heritability of consumption and of caffeine-related traits, including withdrawal symptoms, caffeine-induced insomnia, and anxiety, (2) association studies linking genetic polymorphisms of metabolic enzymes and target receptors to variations in caffeine response, and (3) case-control and prospective studies examining relationship between polymorphisms associated with variations in caffeine response to risks of Parkinson's and cardiovascular diseases in habitual caffeine consumers. Twin studies find the heritability of caffeine-related traits to range between 0.36 and 0.58. Analysis of polysubstance use shows that predisposition to caffeine use is highly specific to caffeine itself and shares little common disposition to use of other substances. Genome association studies link variations in adenosine and dopamine receptors to caffeine-induced anxiety and sleep disturbances. Polymorphism in the metabolic enzyme cytochrome P-450 is associated with risk of myocardial infarction in caffeine users. Modeling based on twin studies reveals that genetics plays a role in individual variability in caffeine consumption and in the direct effects of caffeine. Both pharmacodynamic and pharmacokinetic polymorphisms have been linked to variation in response to caffeine. These studies may help guide future research in the role of genetics in modulating the acute and chronic effects of caffeine. Yang A, Palmer AA, de Wit H. Genetics of caffeine consumption and responses to caffeine. *Psychopharmacology (Berl).* 2010 Aug; 211(3): 245-257.

Combined Effects of Acute, Very-Low-Dose Ethanol and Delta(9)-Tetrahydrocannabinol in Healthy Human Volunteers

Previous studies examining the combined effects of ethanol and cannabis, or its primary psychoactive ingredient, Δ^9 -tetrahydrocannabinol (THC), have provided mixed results. Data from an in vitro study suggests that combined, sub-threshold doses of these drugs may interact to produce synergistic effects. Very low doses of the two drugs in combination have not been tested in humans. This study assessed whether combinations of acute, very low doses of ethanol and THC produce synergistic effects on subjective, cognitive, and physiological measures. Healthy volunteers (n=11) received capsules containing placebo or THC (2.5 mg), and beverages containing placebo or ethanol (0.1 and 0.2 g/kg) alone, and in combination, across separate sessions, in a within-subjects, randomized, double-blind design. During each session, participants completed measures of working memory, psychomotor ability, and simple reaction time, and provided subjective mood and drug effect ratings. Cardiovascular measures were obtained at regular intervals. As intended, when administered alone, these very low doses of ethanol and THC had only moderate effects on isolated measures. The combined effects of these drugs were not synergistic, and in some cases appeared to be less-than-additive. These data provide no evidence for synergistic effects of acute combinations of very-low-dose ethanol and THC on subjective or physiologic response, or on cognitive performance. Ballard ME, de Wit H. Combined effects of acute, very-low-dose ethanol and delta(9)tetrahydro cannabinol in healthy human volunteers. *Pharmacol Biochem Behav.* 2011 Feb; 97(4): 627-631.

Self-Related Neural Response to Tailored Smoking-Cessation Messages Predicts Quitting

Tailored health interventions can be more effective in eliciting positive behavior change than generic interventions, but the underlying neural mechanisms are not yet understood. Here, 91 smokers participated in a functional magnetic resonance imaging session and a tailored smoking-cessation program. The authors found that increases in activation in self-related processing regions, particularly dorsomedial prefrontal cortex, to tailored messages predicted quitting during a 4-month follow-up. Chua HF, Ho SS, Jasinska AJ, Polk TA, Welsh RC, Liberzon I, Strecher VJ. Self-related neural response to tailored smoking-cessation messages predicts quitting. *Nat Neurosci.* 2011 Apr; 14(4): 426-427.

Brain Metabolite Concentrations Across Cortical Regions in Healthy Adults

Magnetic resonance spectroscopy (MRS) can provide in vivo information about metabolite levels across multiple brain regions. This study used MRS to examine concentrations of N-acetylaspartate (NAA), a marker of neuronal integrity and function, and choline (Cho), which is related to the amount of cell membrane per unit volume, in anterior cingulate cortex (ACC) and parieto-occipital cortex (POC) in healthy individuals. Data were drawn from two experiments which examined glutamatergic and GABAergic signaling in schizophrenia and bipolar disorder. After controlling for gray matter percentages, NAA/creatine (Cr) was 18% higher in POC than in ACC ($p < 0.001$); Cho/Cr was 46% lower in POC than in ACC ($p < 0.001$). There was an effect of study ($p < 0.001$ for both metabolites), but no region by study interaction (NAA $p = 0.101$, Cho $p = 0.850$). Since NAA is localized to the intracellular space, these data suggest that ACC neuronal compartment is reduced as compared with POC, or that there is a lower concentration of NAA per cell in the ACC than POC, or both. Since elevated Cho suggests more cell membrane per unit volume, reduced NAA in ACC appears to be coupled with

increases in overall cell membrane compartment. These findings are consistent with a number of previous studies using proton MRS which found increasing NAA and decreasing Cho moving caudally, and with postmortem anatomical studies which found neurons in more widely spaced bundles in ACC when compared to parietal and occipital cortices. MRS may be a useful tool for studying physical properties of the living human brain. Bracken BK, Jensen JE, Prescott AP, Cohen BM, Renshaw PF, Ong Yr D. Brain metabolite concentrations across cortical regions in healthy adults. *Brain Res.* 2011 Jan 19; 1369: 89-94.

Correlates of At-Risk/Problem Internet Gambling in Adolescents

The Internet represents a new and widely available forum for gambling. However, relatively few studies have examined internet gambling in adolescents. This study sought to investigate the correlates of at-risk or problem gambling in adolescents acknowledging or denying gambling on the internet. Survey data from 2,006 Connecticut high school student gamblers were analyzed using χ^2 and logistic regression analyses. At-risk/problem gambling was found more frequently in adolescent internet gamblers than in non-internet gamblers. Compared with at-risk/problem gambling in the non-Internet gambling group, at-risk/problem gambling in the Internet gambling group was more strongly associated with poor academic performance and substance use (particularly current heavy alcohol use; odds ratio 2.99; $p = .03$) and less strongly associated with gambling with friends (odds ratio 0.32; $p = .0003$). At-risk/problem gambling in the internet and non-internet gambling groups, respectively, was associated at $p < .05$, each with multiple adverse measurements including dysphoria/depression (odds ratios 1.76 and 1.96), getting into serious fights (odds ratios 2.50 and 1.93), carrying weapons (odds ratios 2.11 and 1.90), and use of tobacco (odds ratios 2.05 and 1.88 for regular use), marijuana (odds ratios 2.02 and 1.39), and other drugs (odds ratios 3.24 and 1.67). Clinically, it is important to assess for teenagers' involvement in internet gambling, particularly because adolescent at-risk/problem internet gambling appears specifically associated with non-peer involvement, heavy alcohol use, and poor academic functioning. Potenza MN, Wareham JD, Steinberg MA, Rugle L, Cavallo DA, Krishnan-Sarin S, Desai RA. Correlates of at-risk/problem internet gambling in adolescents. *J Am Acad Child Adolesc Psychiatry.* 2011 Feb ; 50(2): 150-159.e3.

Perceptual Load-Dependent Neural Correlates of Distractor Interference Inhibition

The load theory of selective attention hypothesizes that distractor interference is suppressed after perceptual processing (i.e., in the later stage of central processing) at low perceptual load of the central task, but in the early stage of perceptual processing at high perceptual load. Consistently, studies on the neural correlates of attention have found a smaller distractor-related activation in the sensory cortex at high relative to low perceptual load. However, it is not clear whether the distractor-related activation in brain regions linked to later stages of central processing (e.g., in the frontostriatal circuits) is also smaller at high rather than low perceptual load, as might be predicted based on the load theory. The authors studied 24 healthy participants using functional magnetic resonance imaging (fMRI) during a visual target identification task with two perceptual loads (low vs. high). Participants showed distractor-related increases in activation in the midbrain, striatum, occipital and medial and lateral prefrontal cortices at low load, but distractor-related decreases in activation in the midbrain ventral tegmental area and substantia nigra (VTA/SN), striatum, thalamus, and extensive sensory cortices at high load. Multiple levels of central processing involving midbrain and frontostriatal circuits participate in suppressing distractor interference at either low or high perceptual load. For suppressing distractor interference, the processing of sensory inputs in both early and late stages of central processing are enhanced

at low load but inhibited at high load. Xu J, Monterosso J, Kober H, Balodis IM, Potenza MN. Perceptual load-dependent neural correlates of distractor interference inhibition. *PLoS One*. 2011 Jan 18; 6(1): e14552.

Imaging Dopamine Transmission in Cocaine Dependence: Link Between Neurochemistry and Response to Treatment

Previous research has shown that dopamine signaling in the limbic striatum is crucial for selecting adaptive, motivated behavior and that disrupted dopamine transmission is associated with impulsive and maladaptive behavior. In humans, positron emission tomography (PET) imaging studies have shown that cocaine dependence is associated with the dysregulation of striatal dopamine signaling, which is linked to cocaine-seeking behavior. The goal of the present study was to investigate whether this association applies to the treatment setting. The authors hypothesized that dopamine signaling in the limbic striatum would be associated with response to a behavioral treatment that uses positive reinforcement to replace impulsive cocaine use with constructive personal goals. Prior to treatment, cocaine-dependent subjects underwent two PET scans using [¹¹C]raclopride, before and after the administration of a stimulant (methylphenidate), for measurement of striatal dopamine D2/3 receptor binding and presynaptic dopamine release. Both of the outcome Measures were lower in the volunteers who did not respond to treatment than in those who experienced a positive treatment response. These findings provide insight into the neurochemistry of treatment response and show that low dopamine transmission is associated with treatment failure. In addition, these data suggest that the combination of behavioral treatment with methods that increase striatal dopamine signaling might serve as a therapeutic strategy for cocaine dependence. Martinez D, Carpenter KM, Liu F, Slifstein M, Broft A, Friedman AC, Kumar D, Van Heertum R, Kleber HD, Nunes E. Imaging dopamine transmission in cocaine dependence: Link between neurochemistry and response to treatment. *Am J Psychiatry* 2011 Mar 15. [Epub ahead of print].

Brain Metabolite Normalization In MA-Dependent Subjects Across Sustained Abstinence: A Proton MRS Study

The goal of the present study was to extend the authors' previous findings on long-term methamphetamine (MA) use and drug abstinence on brain metabolite levels in an expanded group of MA-dependent individuals. Seventeen MA abusers with sustained drug abstinence (1-5 years), 30 MA abusers with short-term drug abstinence (1-6 months) and 24 non-substance using controls were studied using MR spectroscopy (MRS). MRS Measures of NAA/Cr, Cho/Cr and Cho/NAA were obtained in the anterior cingulate cortex (ACC) and in the primary visual cortex (PVC). ACC-Cho/NAA values were abnormally high in the short-term abstinent group compared to controls [$F(1,52) = 18.76, p < 0.0001$]. No differences were observed between controls and the long-term abstinent group [$F(1,39) = 0.97, p = 0.97$]. New evidence of lower ACC-NAA/Cr levels were observed in the short-term abstinent MA abusers compared to controls [$F(1,52) = 23.05, p < 0.0001$] and long-term abstinent MA abusers [$F(1,45) = 7.06, p = 0.01$]. No differences were observed between long-term abstinent MA abusers and controls [$F(1,39) = 0.48, p = 0.49$]. The new findings of relative NAA/Cr normalization across periods of abstinence suggest that adaptive changes following cessation of MA abuse may be broader than initially thought. These changes may contribute to some degree of normalization of neuronal function in the ACC. Salo R, Buonocore MH, Leamon M, Natsuaki Y, Waters C, Moore CD, Galloway GP, Nordahl TE. Extended findings of brain metabolite normalization in MA-dependent subjects across sustained abstinence: A proton MRS study. *Drug Alcohol Depend* 2011; 113(2-3): 133-138.

PET Imaging of Dopamine D_{2/3} Receptors in the Human Cortex with [¹¹C]FLB 457

In a recent PET study, the authors demonstrated the ability to measure amphetamine-induced DA release in the human cortex with the relatively high affinity dopamine D_{2/3} radioligand [¹¹C]FLB 457 (Narendran et al., [2009] *Synapse* 63:447-461). The aim of this study was to evaluate the reproducibility and reliability of [¹¹C]FLB 457 in the same imaging paradigm they used to measure amphetamine-induced DA transmission. Six healthy human subjects (three males/three females) were studied twice with [¹¹C]FLB 457, once at baseline and again 3 h following the end of the baseline scan. D_{2/3} receptor binding parameters were estimated using a two-tissue compartment kinetic analysis in the cortical regions of interest and cerebellum (reference region). The test-retest variability and intraclass correlation coefficient were assessed for distribution volume (VT), binding potential relative to plasma concentration (BP(P)), and binding potential relative to non-displaceable uptake (BP(ND)) of [¹¹C]FLB 457. The test-retest variability of [¹¹C]FLB 457 VT, BPP, and BP(ND) were 15%, consistent with the published test-retest variability for this ligand in other brain regions (Sudo et al., [2001] *Nucl Med Commun* 22:1215-1221; Vilkmann et al., [2000] *Eur J Nucl Med* 27:1666-1673). In addition, no significant decrease in [¹¹C]FLB457 BP(ND) was observed in the second scan compared to the first one. This suggests that the contribution of carryover mass of [¹¹C]FLB 457 to the measured reduction in [¹¹C]FLB 457 BP(ND) following amphetamine was relatively low. These data support the further validation of [¹¹C]FLB 457 as a tool to measure amphetamine-induced dopamine release in the human cortex. Narendran R, Mason NS, May MA, Chen C-M, Kendro S, Ridler K, Rabiner EA, Laruelle M, Mathis CA, Frankle WG. Positron emission tomography imaging of dopamine D_{2/3} receptors in the human cortex with [¹¹C]FLB 457: reproducibility studies. *Synapse* 2011; 65(1): 35-40.

The Insula and Evaluative Processes

The insula has been implicated as a component of central networks subserving evaluative and affective processes. This study examined evaluative valence and arousal ratings in response to picture stimuli in patients with lesions of the insula and two contrast groups: a control-lesion group (the primary contrast group) and an amygdala-lesion group. Patients rated the positivity and negativity of picture stimuli (from very unpleasant to very pleasant) and how emotionally arousing they found the pictures to be. Compared with patients in the control-lesion group, patients with insular lesions reported reduced arousal in response to both unpleasant and pleasant stimuli, as well as marked attenuation of valence ratings. In contrast, the arousal ratings of patients with amygdala lesions were selectively attenuated for unpleasant stimuli, and these patients' positive and negative valence ratings did not differ from those of the control-lesion group. Results support the view that the insular cortex may play a broad role in integrating affective and cognitive processes, whereas the amygdala may have a more selective role in affective arousal, especially for negative stimuli. Berntson GG, Norman GJ, Bechara A, Bruss J, Tranel D, Cacioppo JT. The insula and evaluative processes. *Psychol Sci* 2011; 22(1): 80-86.

Neuroscience of Self and Self-Regulation

As a social species, humans have a fundamental need to belong that encourages behaviors consistent with being a good group member. Being a good group member requires the capacity for self-regulation, which allows

people to alter or inhibit behaviors that would place them at risk for group exclusion. Self-regulation requires four psychological components. First, people need to be aware of their behavior so as to gauge it against societal norms. Second, people need to understand how others are reacting to their behavior so as to predict how others will respond to them. This necessitates a third mechanism, which detects threat, especially in complex social situations. Finally, there needs to be a mechanism for resolving discrepancies between self-knowledge and social expectations or norms, thereby motivating behavior to resolve any conflict that exists. This article reviews recent social neuroscience research on the psychological components that support the human capacity for self-regulation. Heatherton TF. Neuroscience of self and self-regulation. *Annu Rev Psychol* 2011; 62: 363-390.

Emotion Dysregulation and Deliberate Self-Harm among Inpatients with Substance Use Disorders

Despite the emphasis on the role of emotion dysregulation in deliberate self-harm (DSH), no studies have examined this association among patients with substance use disorders (SUD). This study examined if emotion dysregulation is heightened among SUD inpatients with (vs. without) DSH, and if the association between DSH and emotion dysregulation remains significant when controlling for their shared association with risk factors for both, including borderline personality disorder (BPD), posttraumatic stress disorder (PTSD), childhood abuse, and substance use severity. Findings indicate heightened emotion dysregulation among SUD patients with (vs. without) DSH, and provide evidence of a unique association between emotion dysregulation and DSH when controlling for BPD, PTSD, childhood abuse, and substance use severity. Findings also highlight the particular relevance of three dimensions of emotion dysregulation to DSH among SUD patients: limited access to effective emotion regulation strategies, difficulties engaging in goal-directed behaviors when distressed, and emotional nonacceptance. Gratz KL, Tull MT. The relationship between emotion dysregulation and deliberate self-harm among inpatients with substance use disorders. *Cognit Ther Res* 2010 Dec; 34(6): 544-553.

Influence of Positive Mood on Different Aspects of Cognitive Control

Some evidence suggests that positive mood influences cognitive control. The current research investigated whether positive mood has differential effects on two aspects of cognitive control, working memory and prepotent response inhibition. In Study 1, following a positive or neutral mood induction, participants completed the Running Memory Span (RMS), a measure primarily of working memory storage capacity, and the Stroop task, a measure of prepotent response inhibition. Results were that the positive mood group performed worse on the RMS task but not on the Stroop task. In Study 2, participants completed the RMS and another measure of prepotent response inhibition, the Flanker task. Results were that when in a positive mood state participants performed worse on the RMS but not on the Flanker task. Overall, this research suggests that positive mood has differential effects on cognitive control, impairing working memory but having no effect on prepotent response inhibition. Martin EA, Kerns JG. The influence of positive mood on different aspects of cognitive control. *Cogn Emot* 2011 Feb; 25(2): 265-279.

Psychiatric Comorbidity in Methamphetamine Dependence

The primary aim of the present study was to assess the prevalence of psychiatric comorbidity in a large sample of methamphetamine (MA)-dependent subjects using a validated structured clinical interview, without

limitation to sexual orientation or participation in a treatment program. The secondary aim was to assess whether the prevalence of psychiatric comorbidities varied by gender. Structured clinical interviews (SCIDs) were administered to 189 MA-dependent subjects and lifetime prevalence of DSM-IV diagnoses was assessed. Across the sample, 28.6% had primary psychotic disorders, 23.8% of which were substance-induced; 13.2% had MA-induced delusional disorders and 11.1% had MA-induced hallucinations. A substantial number of lifetime mood disorders were identified that were not substance-induced (32.3%), whereas 14.8% had mood disorders induced by substances, and 10.6% had mood disorders induced by amphetamines. Of all participants, 26.5% had anxiety disorders and 3.7% had a substance-induced anxiety disorder, all of which were induced by MA. Male subjects reported a higher percentage of MA-induced delusions compared to female abusers. Given the impact of MA psychosis and other drug-induced symptoms on hospitals and mental health services, the description and characterization of comorbid psychiatric symptoms associated with MA use is of paramount importance. Salo R, Flower K, Kielstein A, Leamon MH, Nordahl TE, Galloway GP. Psychiatric comorbidity in methamphetamine dependence. *Psychiatry Res* 2011 Apr; 186(2-3): 356-361.

Spontaneous Action Representation in Smokers when Watching Movie Characters Smoke

Do smokers simulate smoking when they see someone else smoke? For regular smokers, smoking is such a highly practiced motor skill that it often occurs automatically, without conscious awareness. Research on the brain basis of action observation has delineated a frontoparietal network that is commonly recruited when people observe, plan, or imitate actions. Here, the authors investigated whether this action observation network would be preferentially recruited in smokers when viewing complex smoking cues, such as those occurring in motion pictures. Seventeen right-handed smokers and 17 nonsmokers watched a popular movie while undergoing functional magnetic resonance imaging. Using a natural stimulus, such as a movie, allowed the authors to keep both smoking and nonsmoking participants naive to the goals of the experiment. Brain activity evoked by movie scenes of smoking was contrasted with nonsmoking control scenes that were matched for frequency and duration. Compared with nonsmokers, smokers showed greater activity in left anterior intraparietal sulcus and inferior frontal gyrus, regions involved in the simulation of contralateral hand-based gestures, when viewing smoking versus control scenes. These results demonstrate that smokers spontaneously represent the action of smoking when viewing others smoke, the consequence of which may make it more difficult to abstain from smoking. Wagner DD, Dal Cin S, Sargent JD, Kelley WM, Heatherton TF. Spontaneous action representation in smokers when watching movie characters smoke. *J. Neurosci* 2011; 31(3): 894-898.

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. The authors investigated effects of abstinence on cue-induced craving in cigarette smokers. Eighty-six non-treatment-seeking, adult smokers (10 cigarettes daily) were paid to abstain for 7 (Group 1), 14 (Group 2), or 35 (Groups 3 and 4) days. Abstinence was verified daily. Groups 1, 2, and 3 underwent a single cue session on the final abstinence day (7, 14, or 35). Group 4 viewed cues on Days 7, 14, and 35. Between and within groups, smoking-cue-induced craving increased with

abstinence on some Measures: Cue-induced craving was greater in Group 3 (35-day) compared with Group 1 (7-day). Within Group 4, cue-induced craving was greater at 35 than 14 days. Cue-induced craving did not decrease with abstinence on any measure. The authors present initial evidence of incubation of cue-induced craving in humans. The observation that cue-induced craving increases with abstinence, even as "background" craving and withdrawal symptoms subside, might have treatment implications. Bedi G, Preston KL, Epstein DH, Heishman SJ, Marrone GF, Shaham Y, de Wit H. Incubation of cue-induced cigarette craving during abstinence in human smokers. *Biol. Psychiatry* 2011 Apr; 69(7): 708-711.

Effect of Bupropion Treatment on Brain Activation Induced by Cigarette-Related Cues 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 study design was a randomized, double-blind, before-after controlled trial conducted at 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 were 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. The authors conclude that 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, Shulenberg S, Mandelkern MA, Brody AL. Effect of bupropion treatment on brain activation induced by cigarette-related cues in smokers. *Arch Gen Psychiatry* 2011 Jan 3. [Epub ahead of print].

Effects of Varenicline on Smoking Cue-Triggered Neural and Craving Responses

Varenicline, an effective smoking cessation medication, functions as an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist. It indirectly affects the dopaminergic reward system by reducing withdrawal symptoms during abstinence and by decreasing the reinforcement received from nicotine while smoking. The authors hypothesize that varenicline would have a third mechanism to blunt responses to smoking cues in the reward-related ventral striatum and medial orbitofrontal cortex and would be associated with a reduction in smoking cue-elicited craving. A laboratory model of conditioned responding and arterial spin-labeled perfusion functional magnetic resonance imaging, a biomarker of regional brain activity, was used to test the authors' hypothesis. Perfusion functional magnetic resonance imaging is quantitative and stable across time, facilitating the measurement of medication-induced neural modifications in the brain in response to a challenge (smoking cue exposure) and in the brain in the resting condition (without provocation).

Smokers were imaged during rest and during smoking cue exposure before and after a 3-week randomized placebo-controlled medication regimen. Subjects were nonabstinent to explicitly examine the effects of varenicline on cue reactivity independent of withdrawal. The setting in which the study was conducted was the Center for the Study of Addictions, University of Pennsylvania, Philadelphia. Subjects were nicotine-dependent smokers who responded to advertisements placed on local radio and listserves to participate in a medication-related research study that specifically stated "this is not a Quit Smoking Study" and "smokers may be contemplating but not currently considering quitting." Prerandomization smoking cues vs nonsmoking cues activated the ventral striatum and medial orbitofrontal cortex ($t = 3.77$) and elicited subjective reports of craving ($P = .006$). Craving reports correlated with increased activity in the posterior cingulate ($t = 4.11$). Administration of varenicline diminished smoking cue-elicited ventral striatum and medial orbitofrontal cortex responses (t values from -3.75 to -5.63) and reduced self-reported smoking cue-elicited craving, whereas placebo-treated subjects exhibited responses similar to those observed prior to randomization. Varenicline-induced activation of lateral orbitofrontal cortex in the brain at rest ($t = 5.63$) predicted blunting of smoking cue responses in the medial orbitofrontal cortex ($r = -0.74$). The authors conclude that Varenicline's reciprocal actions in the reward-activated medial orbitofrontal cortex and in the reward-evaluating lateral orbitofrontal cortex underlie a diminished smoking cue response, revealing a distinctive new action that likely contributes to its clinical efficacy. Franklin T, Wang Z, Suh JJ, Hazan R, Cruz J, Li Y, Goldman M, Detre JA, O'Brien CP, Childress AR. Effects of varenicline on smoking cue-triggered neural and craving responses. *Arch Gen Psychiatry* 2011 Jan 3. [Epub ahead of print].

Nicotine as a Factor in Stress Responsiveness among Detoxified Alcoholics

The effect of transdermal nicotine on stress reactivity was investigated in currently smoking, detoxified, substance-dependent individuals (65% alcohol dependent, $n = 51$; 31 male) following a psychosocial stressor. Using a randomized, double-blind, placebo-controlled design, subjects were assigned to receive either active transdermal nicotine (low or high dose) or placebo. Six hours following nicotine administration, subjects performed a laboratory psychosocial stressor consisting of two 4-min public-speaking sessions. Consistent with prior reports, substance-dependent individuals displayed a blunted stress response. However, a review of the cortisol distribution data encouraged additional analyses. Notably, a significant minority of the substance-dependent individuals (33%) demonstrated elevated poststress cortisol levels. This group of responders was more likely to be alcohol dependent and to have received the high dose of nicotine [$\chi^2(2) = 32$, $P < 0.0001$], [$\chi^2(2) = 18.66$, $P < 0.0001$]. Differences in salivary cortisol responses between responders and nonresponders could not be accounted for by the length of sobriety, nicotine withdrawal levels, anxiety or depressive symptomatology at the time of the psychosocial stressor. These results suggest that nicotine administration may support a normalization of the salivary cortisol response following psychosocial stress in subgroups of substance-dependent individuals, particularly those who are alcohol dependent. Given the association between blunted cortisol levels and relapse, and the complex actions of nicotine at central and peripheral sites, these findings support the systematic study of factors including nicotine, which may influence stress reactivity and the recovery process in alcohol-dependent individuals. Gilbertson R, Frye RF, Nixon SJ. Nicotine as a factor in stress responsiveness among detoxified alcoholics. *Alcohol Alcohol* 2011 Feb; 46(1): 39-51.

Gender Effects of Marijuana on Cognition

Despite the knowledge that many drugs affect men and women differently, few studies exploring the effects of marijuana use on cognition have included women. Findings from both animal and human studies suggest marijuana may have more marked effects in women. This study examined sex differences in the acute effects of marijuana on cognition in 70 (n=35 male, 35 female) occasional users of marijuana. Tasks were chosen to tap a wide variety of cognitive domains affected by sex and/or marijuana including attention, cognitive flexibility, time estimation, and visuospatial processing. As expected, acute marijuana use impaired performance on selective and divided attention, time estimation, and cognitive flexibility. While there did not appear to be sex differences in marijuana's effects on cognition, women requested to discontinue the smoking session more often than men, likely leading to an underestimation of differences. Further study of psychological differences in marijuana's effects on men and women following both acute and residual effects of marijuana is warranted. Anderson BM, Rizzo M, Block RI, Pearlson GD, O'Leary DS. Sex, drugs, and cognition: Effects of marijuana. *J Psychoactive Drugs* 2010 Dec; 42(4): 413-424.

Poor Decision-Making by Chronic Marijuana Users is Associated with Decreased Functional Responsiveness to Negative Consequences

Chronic marijuana users (MJ Users) perform poorly on the Iowa Gambling Task (IGT), a complex decision-making task in which monetary wins and losses guide strategy development. This functional magnetic resonance imaging (MRI) study sought to determine if the poor performance of MJ Users was related to differences in brain activity while evaluating wins and losses during the strategy development phase of the IGT. MJ Users (16) and Controls (16) performed a modified IGT in an MRI scanner. Performance was tracked and functional activity in response to early wins and losses was examined. While the MJ Users continued to perform poorly at the end of the task, there was no difference in group performance during the initial strategy development phase. During this phase, before the emergence of behavioral differences, Controls exhibited significantly greater activity in response to losses in the anterior cingulate cortex, medial frontal cortex, precuneus, superior parietal lobe, occipital lobe and cerebellum as compared to MJ Users. Furthermore, in Controls, but not MJ Users, the functional response to losses in the anterior cingulate cortex, ventral medial prefrontal cortex and rostral prefrontal cortex positively correlated with performance over time. These data suggest MJ Users are less sensitive to negative feedback during strategy development. Wesley MJ, Hanlon CA, Porrino LJ. Poor decision-making by chronic marijuana users is associated with decreased functional responsiveness to negative consequences. *Psychiatry Res* 2011; 191(1): 51-59.

An fMRI Study of Risk-Taking Following Wins and Losses

Human decision-making involving independent events is often biased and affected by prior outcomes. Using a controlled task that allows us to manipulate prior outcomes, the present study examined the effect of prior outcomes on subsequent decisions in a group of young adults. The authors found that participants were more risk-seeking after losing a gamble (riskloss) than after winning a gamble (riskwin), a pattern resembling the gambler's fallacy. Functional MRI data revealed that decisions after riskloss were associated with increased activation in the frontoparietal network, but decreased activation in the caudate and ventral striatum. The increased risk-seeking behavior after a loss showed a trend of positive correlation with activation in the frontoparietal network and the left lateral orbitofrontal cortex but a trend of negative correlation with activation in the amygdala and caudate. In addition, there was a trend of positive correlation between feedback-related activation in the left lateral frontal cortex and subsequent

increased risk-seeking behavior. These results suggest that a strong cognitive control mechanism but a weak affective decision-making and reinforcement learning mechanism that usually contribute to flexible, goal-directed decisions can lead to decision biases involving random events. This has significant implications for our understanding of the gambler's fallacy and human decision making under risk. Xue G, Lu Z, Levin IP, Bechara A. An fMRI study of risk-taking following wins and losses: Implications for the gambler's fallacy. *Hum Brain Mapp* 2011 Feb; 32(2): 271-281.

Neural Response to Action and Reward Prediction Errors

The error-related negativity (ERN) is thought to index an anterior cingulate (ACC) behavioral monitoring system. The feedback ERN (FRN) is elicited to error feedback when the correct response is not known, but also when a choice outcome is suboptimal and to passive reward prediction violation, suggesting that the monitoring system may not be restricted to actions. This study used principal components analysis to show that the ERN consists of a single central component whereas the reward prediction violation FRN is comprised of central and prefrontal components. A prefrontal component is also present in action monitoring but occurs later, at the error positivity latency. This suggests that ACC monitors both actions and events for reward prediction error. Prefrontal cortex may update reward expectation based on the prediction violation with the latency difference due to differential processing time for motor and perceptual information. Potts GF, Martin LE, Kamp S-M, Donchin E. Neural response to action and reward prediction errors: Comparing the error-related negativity to behavioral errors and the feedback-related negativity to reward prediction violations. *Psychophysiology* 2011 Feb; 48(2): 218-228.

Variations of Response Time in a Selective Attention Task are Linked to Variations of Functional Connectivity in the Attentional Network

Although variations of response time (RT) within a particular experimental condition are typically ignored, they may sometimes reflect meaningful changes in the efficiency of cognitive and neural processes. In the present study, the authors investigated whether trial-by-trial variations of response time (RT) in a cross-modal selective attention task were associated with variations of functional connectivity between brain regions that are thought to underlie attention. Sixteen healthy young adults performed an audiovisual selective attention task, which involved attending to a relevant visual letter while ignoring an irrelevant auditory letter, as the investigators recorded their brain activity using functional magnetic resonance imaging (fMRI). In line with predictions, variations of RT were associated with variations of functional connectivity between the anterior cingulate cortex and various other brain regions that are posited to underlie attentional control, such as the right dorsolateral prefrontal cortex and bilateral regions of the posterior parietal cortex. They were also linked to variations of functional connectivity between anatomically early and anatomically late regions of the relevant-modality visual cortex whose communication is thought to be modulated by attentional control processes. By revealing that variations of RT in a selective attention task are linked to variations of functional connectivity in the attentional network, the present findings suggest that variations of attention may contribute to trial-by-trial fluctuations of behavioral performance. Prado J, Carp J, Weissman DH. Variations of response time in a selective attention task are linked to variations of functional connectivity in the attentional network. *Neuroimage* 2011; 54(1): 541-549.

Functional Heterogeneity of Conflict, Error, Task-Switching, and Unexpectedness Effects within Medial Prefrontal Cortex

The last decade has seen considerable discussion regarding a theoretical account of medial prefrontal cortex (mPFC) function with particular focus on the anterior cingulate cortex. The proposed theories have included conflict detection, error likelihood prediction, volatility monitoring, and several distinct theories of error detection. Arguments for and against particular theories often treat mPFC as functionally homogeneous, or at least nearly so, despite some evidence for distinct functional subregions. Here the authors used functional magnetic resonance imaging (fMRI) to simultaneously contrast multiple effects of error, conflict, and task-switching that have been individually construed in support of various theories. They found overlapping yet functionally distinct subregions of mPFC, with activations related to dominant error, conflict, and task-switching effects successively found along a rostral-ventral to caudal-dorsal gradient within medial prefrontal cortex. Activations in the rostral cingulate zone (RCZ) were strongly correlated with the unexpectedness of outcomes suggesting a role in outcome prediction and preparing control systems to deal with anticipated outcomes. The results as a whole support a resolution of some ongoing debates in that distinct theories may each pertain to corresponding distinct yet overlapping subregions of mPFC. Nee DE, Kastner S, Brown JW. Functional heterogeneity of conflict, error, task-switching, and unexpectedness effects within medial prefrontal cortex. *Neuroimage* 2011; 54(1): 528-540.

Medial Prefrontal Cortex Predicts and Evaluates the Timing of Action Outcomes

The medial prefrontal cortex (mPFC) is active in conditions of performance monitoring including error commission and response conflict, but the mechanisms underlying these effects remain in dispute. Recent work suggests that mPFC learns to predict the value of actions, and that error effects represent a discrepancy between actual and expected outcomes of an action. In general, expectation signals regarding the outcome of an action may have a temporal structure, given that outcomes are expected at specific times. Nonetheless, it is unknown whether and how mPFC predicts the timing as well as the valence of expected action outcomes. Here the authors show with fMRI that otherwise correct feedback elicits apparent error-related activity in mPFC when delivered later than expected, suggesting that mPFC predicts not only the valence but also the timing of expected outcomes of an action. Results of a model-based analysis of fMRI data suggested that regions in the caudal cingulate zone, dorsal mPFC, and dorsal anterior cingulate cortex were jointly responsive to unexpectedly delayed feedback and negative feedback outcomes. These results suggest that regions in anterior cingulate and mPFC may be more broadly responsive to outcome prediction errors, signaling violations of both predicted outcome valence and predicted outcome timing, and the results further constrain theories of performance monitoring and cognitive control pertaining to these regions. Forster SE, Brown JW. Medial prefrontal cortex predicts and evaluates the timing of action outcomes. *Neuroimage* 2011 Mar; 55(1): 253-265.

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

Research Findings - Epidemiology and Etiology Research

The Relatedness of HIV Epidemics in the United States-Mexico Border Region

Phylogeography can improve the understanding of local and worldwide HIV epidemics, including the migration of subepidemics across national borders. Researchers analyzed HIV-1 sequences sampled from Mexico and San Diego, California to determine the relatedness of these epidemics. They sampled the HIV epidemics in (1) Mexico by downloading all publicly available HIV-1 pol sequences from antiretroviral-naive individuals in GenBank (n = 100) and generating similar sequences from cohorts of IDUs and female sex workers in Tijuana, Mexico (n = 27) and (2) in San Diego, California by pol sequencing well-characterized primary (n = 395) and chronic (n = 267) HIV infection cohorts. Estimates of population structure (F(ST)), genetic distance cluster analysis, and a cladistic measure of migration events (Slatkin-Maddison test) were used to assess the relatedness of the epidemics. Both a test of population differentiation (F(ST) = 0.06; p < 0.01) and a cladistic estimate of migration events (84 migrations, p < 0.01) indicated that the Tijuana and San Diego epidemics were not freely mixing. A conservative cluster analysis identified 72 clusters (two or more sequences), with two clusters containing both Mexican and San Diego sequences (permutation p < 0.01). Analysis of this very large dataset of HIV-1 sequences suggested that the HIV-1 epidemics in San Diego, California and Tijuana, Mexico are distinct. Larger epidemiological studies are needed to quantify the magnitude and associations of cross-border mixing. Mehta S, Delpont W, Brouwer K, Espitia S, Patterson T, Pond S, Strathdee S, Smith D. The relatedness of HIV epidemics in the United States-Mexico Border Region. *J AIDS Res Hum Retroviruses*. 2010; 26 (12): 1273-1277.

The Cost-Effectiveness and Population Outcomes of Expanded HIV Screening and Antiretroviral Treatment in the United States

Although recent guidelines call for expanded routine screening for HIV, resources for antiretroviral therapy (ART) are limited, and all eligible persons are not currently receiving treatment. Researchers sought to evaluate the effects on the U.S. HIV epidemic of expanded ART, HIV screening, or interventions to reduce risk behavior. They used a dynamic mathematical model of HIV transmission and disease progression and conducted a cost-effectiveness analysis, drawing data from the published literature. The target population in the U.S. for their study included high-risk injection drug users and men who have sex with men and low-risk persons aged 15 to 64 years and the time horizon was twenty years and lifetime (costs and quality-adjusted life-years [QALYs]). The interventions in the model were expanded HIV screening and counseling, treatment with ART, or both, and their outcome measures were new HIV infections, discounted costs and QALYs, and incremental cost-

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effectiveness ratios. The results of the base analysis were that one-time HIV screening of low-risk persons coupled with annual screening of high-risk persons could prevent 6.7% of a projected 1.23 million new infections and cost \$22,382 per QALY gained, assuming a 20% reduction in sexual activity after screening. Expanding ART utilization to 75% of eligible persons would prevent 10.3% infections and cost \$20,300 per QALY gained. A combination strategy prevents 17.3% of infections and costs \$21,580 per QALY gained. The sensitivity analysis showed that, with no reduction in sexual activity, expanded screening would prevent 3.7% of infections. Earlier ART initiation when a CD4 count is greater than 0.350×10^9 cells/L would prevent 20% to 28% of infections. Additional efforts to halve high-risk behavior could reduce infections by 65%. Although the analysis is limited by the use of a simplified model of disease progression and treatment, and the exclusion of acute HIV screening, these results suggest that expanding HIV screening and treatment simultaneously offers the greatest health benefit and is cost-effective. However, even with substantial expansion of HIV screening and treatment programs, markedly reducing the U.S. HIV epidemic would also require substantial reductions in risk behavior. Recent guidelines call for expanded routine screening for HIV, but resources for antiretroviral therapy (ART) are limited, and all eligible persons are not currently receiving treatment. Long E, Brandeau M, Owens D. The cost-effectiveness and population outcomes of expanded HIV screening and antiretroviral treatment in the United States. *Ann Intern Med.* 2010; 153 (12): 778-789.

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Ambient Temperature and Risk of Death from Accidental Drug Overdose in New York City, 1990-2006

Mortality increases as ambient temperature increases. Because cocaine affects core body temperature, ambient temperature may play a role in cocaine-related mortality in particular. This study examined the association between ambient temperature and fatal overdoses in New York City. Mortality data were obtained from the Office of the Chief Medical Examiner for 1990 to 2006, and temperature data from the National Oceanic and Atmospheric Association. Generalized additive models were used to test the relationship between weekly average temperatures and counts of accidental overdose deaths in New York City, controlling for year and average length of daylight hours. A significant relationship was found between ambient temperature and accidental overdose fatality for all models where the overdoses were due in whole or in part to cocaine (all $P < 0.05$), but not for non-cocaine overdoses. Risk of accidental overdose deaths increased for weeks when the average temperature was above 24 degrees Celsius. There is a strong relationship between temperature and accidental overdose mortality that is driven by cocaine-related overdoses rising at temperatures above 24 degrees Celsius, which is a substantially lower temperature than prior estimates. To put this into perspective, approximately seven weeks a year between 1990 and 2006 had an average weekly temperature of 24 degrees Celsius or above in New York City. Heat-related mortality presents a considerable public health concern in general. These findings provide an additional reason why cocaine users constitute a particularly high-risk group. Bohnert A, Prescott M, Vlahov D, Tardiff K, Galea S. Ambient temperature and risk of death from accidental drug overdose in New York City, 1990-2006. *Addiction.* 2010; 105 (6): 1049-1054.

Spatial Access to Syringe Exchange Programs and Pharmacies Selling Over-the-Counter Syringes as Predictors of Drug Injectors' Use of Sterile Syringes

Researchers examined relationships among spatial access to syringe exchange programs (SEPs) and pharmacies selling over-the-counter (OTC) syringes and New York City drug injectors' needle use practices. The analyses used data collected from 4,003 active IDU in NYC, 1995-2006 (79% male, 51%

Latino/Hispanic, 21% non-Hispanic/African American, 28% White, average age 38 years, 11% HIV+). Each year from 1995 to 2006, they measured the percentage of 42 city health districts' surface area that was within 1 mile of an SEP or OTC pharmacy. They applied hierarchical generalized linear models to investigate relationships between these exposures and the odds that any of the 4,003 IDUs used a sterile syringe for at least 75% of injections in the past 6 months. They found that a 1-unit increase in the natural log of the percentage of a district's surface area within a mile of an SEP in 1995 was associated with a 26% increase in the odds of injecting with a sterile syringe; a 1-unit increase in this exposure over time increased these odds 23%. A 1-unit increase in the natural log of OTC pharmacy access improved these odds 15%. These findings show that greater spatial access to SEPs and OTC pharmacies improved IDUs' capacity to engage in risk reduction practices that reduce HIV and HCV transmission. Cooper HL, Des Jarlais DC, Ross Z, Tempalski B, Bossak B, Friedman SR. Spatial Access To Syringe Exchange programs and pharmacies selling over-the-counter syringes as predictors of drug injectors' use of sterile syringes. *Am J Public Health*. 2010; e1-e8.

Familial Transmission and Heritability of Childhood Disruptive Disorders

There is substantial evidence of a link between parental substance use disorders and antisocial behavior and childhood disruptive disorders in offspring, but it is unclear whether this transmission is specific to particular disorders or if a general liability accounts for familial resemblance. The authors examined whether the association between parental externalizing disorders and childhood disruptive disorders in preadolescent offspring is a result of the transmission of general or disorder-specific liabilities and estimated the genetic and environmental contributions to variation in these general and specific liability indicators. Participants were 1,069 families consisting of 11-year-old twins and their biological mother and father. Structural equation modeling was used to simultaneously estimate the general and specific transmission effects of four parental externalizing disorders (conduct disorder, adult antisocial behavior, alcohol dependence, and drug dependence) on childhood disruptive disorders (attention deficit hyperactivity disorder, conduct disorder, and oppositional defiant disorder). Parent-child resemblance was accounted for by the transmission of a general liability to externalizing disorders, and this general liability was highly heritable. Specific effects were also detected, but for sibling rather than parental transmission. Specific genetic and non-shared environmental effects were detected for each childhood disruptive disorder, but only conduct disorder exhibited a significant shared environmental effect. A highly heritable general liability accounts for the parent-child transmission of externalizing psychopathology from parents to their preadolescent offspring. This general liability should be a focus of research for both etiology and intervention. Bornovalova M, Hicks B, Iacono W, McGue M. Familial transmission and heritability of childhood disruptive disorders. *Am J Psychiatry*. 2010; 167 (9): 1066-7104.

The Economic Burden of Late Entry into Medical Care for Patients with HIV Infection

A large proportion of people with HIV enter care late in the HIV disease course. Late entry can increase expenditures for care. This study estimated direct medical care expenditures for HIV patients as a function of disease status at initial presentation to care. Late entry was defined as initial CD4 test result 200 cells/mm³, intermediate entry as initial CD4 counts >200, and 500 cells/mm³; and early entry as initial CD4 count >500. The study included 8,348 patients who received HIV primary care and who were newly enrolled between 2000 and 2006 at one of 10 HIV clinics participating in the HIV Research Network, in which this project participates. Medical record data were

reviewed from 2000 to 2007. Costs were estimated per outpatient visit and inpatient day, and monthly medication costs (antiretroviral and opportunistic illness prophylaxis). Unit costs were multiplied by utilization measures to estimate expenditures for inpatient days, outpatient visits, HIV medications, and laboratory tests, and then the association was analyzed between cumulative expenditures and initial CD4 count, stratified by years in care. Late entrants to care comprised 43.1% of new patients. The number of years receiving care after enrollment did not differ significantly across initial CD4 groups. Mean cumulative treatment expenditures ranged from \$27,275 to \$61,615 higher for late than early presenters. After 7 to 8 years in care, the difference was still substantial. Notably, injection drug users had significantly higher cumulative costs ($p < 0.01$). These findings show that patients who enter medical care late in their HIV disease have substantially higher direct medical treatment expenditures than those who enter at earlier stages. Successful efforts to link patients with medical care earlier in the disease course are likely to yield cost savings. Fleishman J, Yehia B, Moore R, Gebo K, Gebo K. The economic burden of late entry into medical care for patients with HIV infection. *Med Care*. 2010; 48 (12): 1071-1079.

The Role of a Prescription in Anxiety Medication Use, Abuse, and Dependence

Prescriptions for anxiety medications have increased substantially in recent years. Individuals with anxiety disorders are at risk of nonmedical use of these medications, but information about whether this risk is elevated among patients with a prescription for such medications is lacking. The authors compared risk of nonmedical use in individuals in a national sample with and without a prescription for anxiety medication and identified characteristics associated with nonmedical use. Data were drawn from face-to-face surveys of 34,653 adult participants in the National Epidemiologic Survey on Alcohol and Related Conditions. The risk of nonmedical use of prescription anxiety medication and associated drug use disorders was computed for individuals who had or had not ever received a prescription for anxiety medication; among those who had received a prescription, characteristics associated with nonmedical use were analyzed. Prescription of anxiety medication was associated with lifetime and past-year nonmedical use (odds ratios, 1.6 and 1.9, respectively) and lifetime DSM-IV abuse or dependence (odds ratio, 2.6). Among respondents who received a prescription ($N=4,294$), nonmedical use was associated with male sex, younger age, white race, history of use of illicit drugs, history of other drug use disorders, and history of illegal behaviors. These results indicate that prescription for anxiety medications is associated with nonmedical use of these medications, although the direction of causality cannot be determined in this study. Fenton M, Keyes K, Martins S, Hasin D. The role of a prescription in anxiety medication use, abuse, and dependence. *Am J Psychiatry*. 2010; 167 (10): 1247-1253.

A Prospective Study of Alcohol Consumption and HIV Acquisition among Injection Drug Users

Researchers sought to estimate the effect of alcohol consumption on HIV acquisition while appropriately accounting for confounding by time-varying risk factors. Participants were African-American injection drug users in the AIDS Link to Intravenous Experience (ALIVE) cohort study, recruited and followed with semiannual visits in Baltimore, Maryland between 1988 and 2008. The researchers used marginal structural models to estimate the effect of alcohol consumption on HIV acquisition. At study entry, 28% of 1525 participants were women with a median (quartiles) age of 37 (32-42) years and 10 (10-12) years of formal education. During follow-up, 155 participants acquired HIV, and alcohol consumption was 24%, 24%, 26%, 17%, and 9% for 0, 1-5, 6-20, 21-50, and 51-140 drinks per week over the prior 2 years, respectively. In

analyses accounting for socio-demographic factors, drug use, and sexual activity, hazard ratios for participants reporting 1-5, 6-20, 21-50, and 51-140 drinks per week in the prior 2 years compared to participants who reported 0 drinks per week were 1.09 (0.60-1.98), 1.18 (0.66-2.09), 1.66 (0.94-2.93), and 2.12 (1.15-3.90), respectively. A trend test indicated a dose-response relationship between alcohol consumption and HIV acquisition (P value for trend = 9.7×10^{-5}). This study found a dose-response relationship between alcohol consumption and subsequent HIV acquisition, independent of measured known risk factors, indicating the importance of enhancing HIV risk reduction strategies with alcohol-specific interventions tailored for substance users and for prevention programs among HIV positives. Howe C, Cole S, Ostrow D, Mehta S, Kirk G. A prospective study of alcohol consumption and HIV acquisition among injection drug users. *AIDS*. 2011; 25 (2): 221-228.

The Dimensionality of Alcohol Use Disorders: Results from Israel

To prepare for DSM-V, the structure of DSM-IV alcohol dependence and abuse criteria and a proposed additional criterion, at-risk drinking, require study in countries with low per-capita consumption, and comparison of current and lifetime results within the same sample. Authors investigated DSM-IV Alcohol Use Disorder (AUD) criteria in Israel, where per-capita alcohol consumption is low. Household residents selected from the Israeli population register (N=1338) were interviewed with the AUDADIS. Item response theory analyses were conducted using MPlus, and diagnostic thresholds were examined with the kappa statistic. Dependence and abuse criteria fit a one-dimensional model interspersed across the severity continuum, for both current and lifetime timeframes. Legal problems were rare and did not improve model fit. Weekly at-risk drinking reflected greater severity than in U.S. samples. When dependence and abuse criteria were combined, a diagnostic threshold of ≥ 3 criteria produced the best agreement with DSM-IV diagnoses ($\kappa > 0.80$). Consistent with other studies, alcohol dependence and abuse criteria reflected a latent variable representing a single AUD. Results suggested little effect in removing legal problems and little gained by adding weekly at-risk drinking. Results contribute to knowledge about AUD criteria by examining them in a low-consumption country. Shmulewitz D, Keyes K, Beseler C, Aharonovich E, Aivadyan C, Spivak B, Hasin D. The dimensionality of alcohol use disorders: results from Israel. *Drug Alcohol Depend*. 2010; 111 (1-2): 146-154.

Telescoping and Gender Differences in Alcohol Dependence: New Evidence from Two National Surveys

The course of alcohol disorders in women is often described as 'telescoped' compared to that in men, with a later age at initiation of alcohol use but shorter times from use to dependence and treatment. This study examined evidence for such a telescoping effect in the general population and tested birth cohort effects for gender differences. Data from two U.S. national surveys conducted 10 years apart (1991-1992 and 2001-2002) using the same diagnostic instrument (the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV) were used to analyze five birth cohorts. Age at initiation of alcohol use, time from first use to dependence, and time from dependence to first treatment were analyzed. Interaction terms (cohort by gender; cohort by gender by time) were tested in Cox proportional hazards models. Little evidence was found for a telescoping effect in women. For alcohol use and dependence, cohort and gender interacted, which suggests that gender differences are diminished in more recent cohorts. A three-way interaction of cohort, gender, and time was significant for time from first use to dependence, suggesting that men have a shorter time to dependence, especially in younger cohorts. A telescoping effect is not evident in the general population. Gender differences in the overall hazard of alcohol use and

dependence are decreasing in more recent cohorts, while gender differences in time from first use to dependence are increasing. These findings challenge the commonly held notion of a gender-specific course of alcohol disorders and suggest the need for a greater clinical focus on problem drinking in women and further research on accelerated time to dependence in men. Keyes K, Martins S, Blanco C, Hasin D. Telescoping and gender differences in alcohol dependence: new evidence from two national surveys. *Am J Psychiatry*. 2010; 167 (8): 969-976.

Alcohol Consumption Among HIV-Infected Women: Impact on Time to Antiretroviral Therapy and Survival

Alcohol use is prevalent among HIV-infected people and is associated with lower antiretroviral adherence and high-risk sexual and injection behaviors. Researchers sought to determine factors associated with alcohol use among HIV-infected women engaged in clinical care and if baseline alcohol use was associated with time to combination antiretroviral therapy (cART) and death in this population. In an observational clinical cohort, alcohol consumption at the initial medical visit was examined and categorized as heavy, occasional, past, or no use. Multinomial logistic regression was used to test preselected covariates and their association with baseline alcohol consumption. The association between alcohol use and time to cART and time to death was examined using Kaplan-Meier statistics and Cox proportional hazards regression. Between 1997 and 2006, 1030 HIV-infected women enrolled in the cohort. Assessment of alcohol use revealed occasional and hazardous consumption in 29% and 17% of the cohort, respectively; 13% were past drinkers. In multivariate regression, heavy drinkers were more likely to be infected with hepatitis C than nondrinkers (relative risk ratios [RRR] 2.06, 95% confidence interval [CI] 1.29-3.44) and to endorse current drug (RRR 3.51, 95% CI 2.09-5.91) and tobacco use (RRR 3.85 95% CI 1.81-8.19). Multivariable Cox regression adjusting for all clinical covariates demonstrated an increased mortality risk (hazard ratio [HR] 1.40, 95% CI 1.00-1.97, $p < 0.05$) among heavy drinkers compared to nondrinkers but no delays in cART initiation (1.04 95% CI 0.81-1.34). Among this cohort of HIV-infected women, heavy alcohol consumption was independently associated with earlier death. Baseline factors associated with heavy alcohol use included tobacco use, hepatitis C, and illicit drug use. Alcohol is a modifiable risk factor for adverse HIV-related outcomes. These findings point to the importance of consistent screening for alcohol consumption and refer HIV-infected women with heavy alcohol use for treatment in the provider setting. Neblett R, Hutton H, Lau B, McCaul M, Moore R, Chander G. Alcohol consumption among HIV-infected women: impact on time to antiretroviral therapy and survival. *J Women's Health (Larchmt)*. 2011; 20 (2): 279-286.

Responses to Discrimination and Psychiatric Disorders among Black, Hispanic, Female, and Lesbian, Gay, and Bisexual Individuals

Authors examined associations between perceived discrimination due to race/ethnicity, sexual orientation, or gender; responses to discrimination experiences; and psychiatric disorders. The sample included respondents in the 2004-2005 National Epidemiologic Survey on Alcohol and Related Conditions (N=34,653). Associations between self-reported past-year discrimination and past-year psychiatric disorders were analyzed, as assessed with structured diagnostic interviews among Black (n= 6587); Hispanic (n= 6359); lesbian, gay, and bisexual (LGB; n = 577); and female (n = 20 089) respondents. Black respondents reported the highest levels of past-year discrimination, followed by LGB, Hispanic, and female respondents. Across groups, discrimination was associated with 12-month mood (odds ratio [ORs] = 2.1-3.1), anxiety (ORs = 1.8-3.3), and substance use (ORs = 1.6-3.5) disorders. Respondents who

reported not accepting discrimination and not discussing it with others had higher odds of psychiatric disorders (ORs = 2.9-3.9) than did those who did not accept discrimination but did discuss it with others. Black respondents and women who accepted discrimination and did not talk about it with others had elevated rates of mood and anxiety disorders, respectively. Psychiatric disorders are more prevalent among individuals reporting past-year discrimination experiences. Certain responses to discrimination, particularly not disclosing it, are associated with psychiatric morbidity. McLaughlin K, Hatzenbuehler M, Keyes K. Responses to discrimination and psychiatric disorders among black, hispanic, female, and lesbian, gay, and bisexual individuals. *Am J Public Health*. 2010; 100 (8): 1477-1484.

The Effect of Social Networks and Social Support on Common Mental Disorders Following Specific Life Events

This study examined the association between life events and common mental disorders while accounting for social networks and social supports. Participants included 1920 adults in the Baltimore Epidemiologic Catchment Area Cohort who were interviewed in 1993-1996, of whom 1071 were re-interviewed in 2004-2005. Generalized estimating equations were used to analyze the data. Social support from friends, spouse or relatives was associated with significantly reduced odds of panic disorder and psychological distress, after experiencing specific life events. Social networks or social support had no significant stress-buffering effect. Social networks and social support had almost no direct or buffering effect on major depressive disorder, and no effect on generalized anxiety disorder and alcohol abuse or dependence disorder. The significant association between social support and psychological distress, rather than diagnosable mental disorders, highlights the importance of social support, especially when the severity of a mental health related problem is low. Maulik P, Eaton W, Bradshaw C. The effect of social networks and social support on common mental disorders following specific life events. *Acta Psychiatr Scand*. 2010; 122 (2): 118-128.

Personal Network Correlates of Alcohol, Cigarette, and Marijuana Use among Homeless Youth

Youth who are homeless are among the most marginalized individuals in the United States and face multiple risks, including use of substances. This study investigates how the use of alcohol, cigarettes, and marijuana among homeless youth may be influenced by characteristics of their social networks. Homeless youth aged 13-24 were randomly sampled from 41 service and street sites in Los Angeles County (N=419). Predictors of substance use were examined using linear regression analysis (for average number of drinks and average number of cigarettes per day) and negative binomial regression analysis (for frequency of past month marijuana use). Youth with more substance users in their networks reported greater alcohol, cigarette, and marijuana consumption regardless of whether these network members provided tangible or emotional support. Marijuana use was more frequent for youth who met more network members through homeless settings, but less frequent among those who met more network members through treatment or AA/NA. Greater alcohol use occurred among youth who met more network members through substance use-related activities. Youth having more adults in positions of responsibility in their networks consumed less alcohol, and those with more school attendees in their networks consumed less alcohol and cigarettes. Findings highlight the importance of social context in understanding substance use among homeless youth. Results also support the relevance of network-based interventions to change social context for substance-using youth, in terms of both enhancing pro-social influences and reducing exposure to substance use. Wenzel S, Tucker J, Golinelli D, Green H, Zhou A. Personal network correlates of alcohol, cigarette, and marijuana use among homeless youth. *Drug Alcohol Depend*.

2010; 112 (1-2): 140-149.

Expanded Highly Active Antiretroviral Therapy Coverage among HIV-positive Drug Users to Improve Individual and Public Health Outcomes

This paper reviews recent scientific evidence on the use of highly active antiretroviral therapy (HAART) to treat and prevent HIV and discusses the need for an expansion in the provision of HAART to those in medical need, including drug users. HAART represents the single most significant advance in the fight against HIV/AIDS. The vast majority of patients treated with HAART will experience long-term remission of HIV disease. Although HAART does not cure HIV, it changes the disease into a chronic and manageable condition in most people. It is significantly associated with decreased HIV/AIDS-related morbidity, fewer opportunistic infections, and reduced mortality. Evidence has also shown that HAART can reduce HIV transmission, as is most clearly illustrated in studies of vertical or mother-to-child HIV transmission, wherein use of HAART by infected mothers has helped to virtually eliminate HIV transmission to their infants. Moreover, HAART use among heterosexual discordant couples (i.e., one partner is HIV positive while the other is not) in Africa was found to be associated with a 92% reduction in HIV transmission. Until recently, the use of HAART among drug-using populations has remained controversial. However, HAART has been shown to produce similar survival benefit when individuals with and without history of drug use are compared. An effort to expand the use of HAART among drug users should include the full promotion of human rights and respect for each patient's privacy and autonomy. Public health programs to expand HAART use to those in medical need, including drug users, should be carried out within a comprehensive 'combination prevention' framework. For drug users, such an approach would emphasize the importance of drug addiction treatment. It would also emphasize HIV prevention, including HIV testing and counseling and behavioral risk reduction interventions, and more broadly, it would work toward the removal of structural barriers, including the effects of stigma and social marginalization, to treating HIV-infected drug users and retaining them in care. Montaner J, Wood E, Kerr T, Lima V, Barrios R, Shannon K, Harrigan R, Hogg R. Expanded highly active antiretroviral therapy coverage among HIV-positive drug users to improve individual and public health outcomes. *J Acquir Immune Defic Syndr.* 2010; 55 Suppl 1: S5-S9.

Virologic and Immunologic Response to HAART, by Age and Regimen Class

Researchers sought to determine the impact of age and initial HAART regimen class on virologic and immunologic response within 24 months after initiation. They pooled and analyzed data from 19 prospective cohort studies in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Antiretroviral-naïve adults (N=12,196) who initiated HAART between 1998 and 2008 using a boosted protease inhibitor-based regimen or a nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen were included in the study. Discrete time-to-event models were used to estimate adjusted hazard odds ratios (aHOR) and 95% confidence intervals (CIs) for suppressed viral load (d500 copies/ml) and, separately, at least 100 cells/ μ l increase in CD4 cell count. Truncated, stabilized inverse probability weights accounted for selection biases from discontinuation of initial regimen class. Among the 12,196 eligible participants (mean age = 42 years), 50% changed regimen classes after initiation (57 and 48% of whom initiated protease inhibitor and NNRTI-based regimens, respectively). Mean CD4 cell count at initiation was similar by age. Virologic response to treatment was less likely in those initiating using a boosted protease inhibitor [aHOR = 0.77 (0.73, 0.82)], regardless of age. Immunologic response decreased with increasing age [18-<30: ref; 30-

<40: aHOR = 0.92 (0.85, 1.00); 40-<50: aHOR = 0.85 (0.78, 0.92); 50-<60: aHOR = 0.82 (0.74, 0.90); e60: aHOR = 0.74 (0.65, 0.85)], regardless of initial regimen. This study found no evidence of an interaction between age and initial antiretroviral regimen on virologic or immunologic response to HAART; however, decreased immunologic response with increasing age may have implications for age-specific when-to-start guidelines. Althoff K, Justice A, Gange S, Deeks S, Saag M, Silverberg M, Gill M, Lau B, Napravnik S, Tedaldi E, Klein M, Gebo K, Gebo K. Virologic and immunologic response to HAART, by age and regimen class. *AIDS*. 2010; 24 (16): 2469-2479.

HIV Prevalence Rates Among Men Who Have Sex with Men in the Southern US: Population-Based Estimates by Race/Ethnicity

States across the U.S. lack effective ways to quantify HIV prevalence rates among men who have sex with men (MSM). Researchers estimated population-based HIV prevalence rates among MSM in 17 southern states in the US by race/ethnicity. In 2007, there were a total of 172,166 black, Hispanic, and white MSM living with HIV in the South. Through 2007, estimated HIV prevalence rates per 100,000 MSM ranged from 2,607.6 among white (non-Hispanic) MSM in Maryland to 41,512.9 among black (non-Hispanic) MSM in the District of Columbia. Black MSM rates significantly exceeded Hispanic and white MSM rates in each state. Significant racial/ethnic disparities in rates persisted in a sensitivity analysis examining the possibility that minority MSM populations had been underestimated in each state. Rates at the regional level were 25.2 times higher for black MSM (one out of 5), 43.0 times higher for Hispanic MSM (one of 16), and 106.0 times higher for white MSM (one of 22). State-level analyses of racial/ethnic-specific MSM HIV prevalence rates like these can help guide resource allocation for targeted intervention programs. Lieb S, Prejean J, Thompson R, Fallon SJ, Cooper H, Gates GJ, Liberti TM, Friedman SR, Malow RM. HIV Prevalence rates among men who have sex with men in the southern United States: Population-based estimates by race/ethnicity. *AIDS Behav*. 2011; 15: 596-606.

Motivations for Non-Medical Prescription Drug Use

Despite a concerning increase in the nonmedical use of prescription drugs among illicit drug users, their motives for abusing prescription drugs are still largely unknown. The objective of this study was to (a) determine the motivations for engaging in the nonmedical use of prescription opioids and sedatives among street-based illicit drug users, methadone maintenance patients, and residential drug treatment clients; (b) examine associations between prescription drug abuse motivations and gender, age, race/ethnicity, and user group; and (c) examine associations between specific motivations and prescription drug abuse patterns. Quantitative surveys (n = 684) and in-depth interviews (n = 45) were conducted with a diverse sample of prescription drug abusers in South Florida between March 2008 and November 2009. The three most common motivations reported were 'to get high,' 'to sleep,' and 'for anxiety/stress.' There were age, race/ethnicity, and gender differences by motives. Prescription drug abuse patterns were also found to be associated with specific motivations. For example, participants who reported getting high as a primary motivation for their abuse tended to engage in non-oral methods of ingestion, such as shooting, smoking, and snorting their pills. The authors urge drug treatment professionals not only to inquire about motives but also to give special attention to individuals who report getting high as a chief motivation, as they may be at increased risk for addiction and health complications. Although additional research will be needed, these findings highlight the necessity for prevention and treatment initiatives for prescription drug abusers. Rigg K, Ibañez G. Motivations for non-medical prescription drug use: a mixed methods analysis. *J Subst Abuse Treat*. 2010; 39 (3): 236-247.

Associations between First Use of Substances and Change in Internalizing Symptoms among Girls

This study examined how girls' initial use of alcohol, cigarettes, and marijuana related to changes in depressive, generalized anxiety, and social anxiety symptoms, and whether these changes varied based on which internalizing symptom trajectories the girls were on. Data came from the Pittsburgh Girls Study, a community-based study of girls (52% African-American and 1% Caucasian) assessed at ages 5 to 8 and followed for 6 years. Growth mixture modeling was used to identify trajectory groups. The results indicated that for girls on a 'high depressive symptom' trajectory, initial use of marijuana was related to further increases in depressive symptoms. Initial uses of alcohol and cigarettes were associated with overall increases in depressive symptoms, and the initial use of cigarettes was associated with an overall increase in generalized anxiety symptoms. Initial use of all substances was related to change in social anxiety, but the direction of change varied by trajectory group and substance. Links between initial use and internalizing symptoms depended on the type of substance, type of internalizing symptom, and trajectory group. Such findings have important prevention implications to identify those at risk and to challenge 'self-medication' assumptions. Marmorstein N, White H, Chung T, Hipwell A, Stouthamer-Loeber M, Loeber R. Associations between first use of substances and change in internalizing symptoms among girls: differences by symptom trajectory and substance use type. *J Clin Child Adolesc Psychol.* 2010; 39 (4): 545-558.

Changes in Blood-borne Infection Risk Among Injection Drug Users

Population-level hepatitis C virus (HCV) infection incidence is a surrogate for community drug-related risk. Researchers characterized trends in HIV and HCV infection incidence and HCV infection prevalence among IDUs recruited over 4 periods: 1988-1989, 1994-1995, 1998, and 2005-2008. They calculated HIV and HCV infection incidence within the first year of follow-up among IDUs whose test results were negative for these viruses at baseline (n = 2061 and n = 373, respectively). They then used Poisson regression to compare trends across groups. HIV infection incidence declined significantly from 5.5 cases/100 person-years (py) in the 1988-1989 group to 2.0 cases/100 py in the 1994-1995 group to 0 cases/100 py in the 1998 and 2005-2008 groups. Concurrently, HCV infection incidence declined but remained robust (22.0 cases/100 py in the 1988-1989 cohort to 17.2 cases/100 py in the 1994-1995 cohort, 17.9 cases/100 py in the 1998 cohort, and 7.8 cases/100 py in the 2005-2008 cohort; P = .07). Likewise, HCV infection prevalence declined, but chiefly in younger IDUs. For persons aged <39 years, relative to the 1988-1989 cohort, all groups exhibited significant declines (adjusted prevalence ratio [PR] for the 2005-08 cohort, .73; 95% confidence interval [CI], .65-.81). However, for persons aged 39 years and older, only the 2005-2008 cohort exhibited declining prevalence compared with the 1988-1989 cohort (adjusted PR, .87; 95% CI, .77-.99). These findings suggest that, although efforts to reduce blood-borne infection incidence have had impact, they will need to be intensified for the most transmissible viruses, such as HCV. Mehta S, Astemborski J, Kirk G, Strathdee S, Nelson K, Vlahov D, Thomas D. Changes in blood-borne infection risk among injection drug users. *J Infect Dis.* 2011; 203 (5): 587-594.

Trajectories of Injection Drug Use Over 20 Years (1988-2008) in Baltimore, Maryland

The objective of this study was to identify longitudinal patterns of injection drug use over 20 years in the AIDS Linked to the Intravenous Experience

(ALIVE) Study, a community-based cohort of injection drug users (IDUs) in Baltimore, Maryland, with a focus on injection cessation. Starting in 1988, persons over 18 years of age with a history of injection drug use were recruited into the study. Participants provided information on their injection drug use semiannually through 2008. The analysis was restricted to 1,716 IDUs with at least 8 study visits. Finite mixture models were used to identify trajectories and predictors of injection patterns over time. The mean age of participants was 35 years; 75% were male, and 95% were African-American. Five distinct patterns were identified: 2 usage patterns (32% engaged in persistent injection and 16% had frequent relapse) and 3 cessation patterns (early cessation (19%), delayed cessation (16%), and late cessation (18%)). A history of drug treatment, no recent use of multiple substances, and less frequent injection distinguished the early cessation group from the other groups. This study demonstrated multiple trajectories of drug injection behaviors, with a substantial proportion of IDUs stopping injection over extended time frames. For maximum effectiveness, public health programs for IDUs should be long-term, comprehensive, and targeted toward individual patterns of use. Genberg BL, Gange SJ, Go VF, Celentano DD, Kirk GD, Mehta SH. Trajectories of injection drug use over 20 years (1988-2008) In Baltimore, Maryland. *Am J Epidemiol.* 2011; 173(7): 829-836.

Cost-effectiveness of Antiretroviral Regimens in the World Health Organization's Treatment Guidelines: a South African Analysis

The World Health Organization (WHO) recently changed its first-line antiretroviral treatment guidelines in resource-limited settings. The cost-effectiveness of the new guidelines is unknown. Researchers conducted a comparative effectiveness and cost-effectiveness analysis using a model of HIV disease progression and treatment. They used a simulation of HIV disease and treatment in South Africa to compare the life expectancy, quality-adjusted life expectancy, lifetime costs, and cost-effectiveness of five initial regimens. Four are currently recommended by the WHO: tenofovir/lamivudine/efavirenz; tenofovir/lamivudine/nevirapine; zidovudine/lamivudine/efavirenz; and zidovudine/lamivudine/ nevirapine. The fifth is the most common regimen in current use: stavudine/lamivudine/ nevirapine. Virologic suppression and toxicities were the determinants of regimen effectiveness and cost-effectiveness in this analysis. The results indicated that choice of first-line regimen is associated with a difference of nearly 12 months of quality-adjusted life expectancy, from 135.2 months (tenofovir/lamivudine/efavirenz) to 123.7 months (stavudine/lamivudine/nevirapine). Stavudine/lamivudine/nevirapine is more costly and less effective than zidovudine/lamivudine/ nevirapine. Initiating treatment with a regimen containing tenofovir/lamivudine/nevirapine is associated with an incremental cost-effectiveness ratio of \$1,045 per quality-adjusted life year compared with zidovudine/lamivudine/ nevirapine. Using tenofovir/lamivudine/efavirenz was associated with the highest survival, fewest opportunistic diseases, lowest rate of regimen substitution, and an incremental cost-effectiveness ratio of \$5,949 per quality-adjusted life year gained compared with tenofovir/lamivudine/nevirapine. Zidovudine/lamivudine/efavirenz was more costly and less effective than tenofovir/lamivudine/nevirapine. Results were sensitive to the rates of toxicities and the disutility associated with them. These findings show that, among the options recommended by WHO, only three should be considered under normal circumstances. Choice among those depends on available resources and willingness to pay. Stavudine/ lamivudine/nevirapine is associated with the poorest quality-adjusted survival and higher costs than zidovudine/lamivudine/nevirapine. Bendavid E, Grant P, Talbot A, Owens D, Zolopa A. Cost-effectiveness of antiretroviral regimens in the world health organization's treatment guidelines: A South African analysis. *AIDS.* 2011; 25(2): 211-220.

Elevated Overdose Mortality Rates among First Nations Individuals in a Canadian Setting: A Population-Based Analysis

Reviewers examined coroner case files to determine the total burden of illicit drug overdose mortality in the province of British Columbia over the period 2001 to 2005. They also sought to investigate possible population-level determinants by estimating overdose rates among subgroups, including First Nations individuals. They calculated age-adjusted mortality rates, standardized mortality ratios (SMR) and years of potential life lost (YPLL), stratified by major population groups. Over the study period, 909 individuals died from illicit drug overdoses, including 104 (11.4%) First Nations individuals. Compared to the general population, First Nations males and females suffered from substantially elevated SMR and YPLL. In a multivariate logistic regression analysis, First Nations deaths were significantly more likely to be among women, related to injection drug use, and to have occurred in the Downtown Eastside area of Vancouver, the local epicenter of HIV infection and public drug use (all $P < 0.05$). This study found highly elevated overdose death rates and levels of premature mortality among First Nations Canadians in British Columbia compared to the general population. While previously unidentified, the results are consistent with the poorer population health profile of First Nations Canadians. Although further research is needed to identify the causes of the elevated death rates, the findings support increased availability of evidence-based overdose prevention measures. Milloy M, Wood E, Reading C, Kane D, Montaner J, Kerr T. Elevated overdose mortality rates among First Nations individuals in a Canadian setting: A population-based analysis. *Addiction*. 2010; 105 (11): 1962-1970.

Understanding Physical Aggression in Rural Girls and Boys from Methamphetamine-Involved Families

This study examines the mental health and experiences of physical aggression in 41 children aged 6 to 14 years from rural families involved with methamphetamine misuse and the child welfare system. Each child was seen for a minimum of 3 hours total by experienced clinicians on at least three sessions conducted at the child's home. Fifty percent of children scored in the clinical range on externalizing and 26 percent on aggression scales of the Child Behavior Checklist (CBCL). More girls (75 percent) scored in the clinical range on CBCL externalizing behaviors than did boys (32 percent). During individual, semi-structured interviews, 17 children spontaneously produced 58 narratives of past physical aggression. These were primarily set at home and involved adults and the children themselves. Children primarily attributed physical aggression to anger and adult substance misuse, and described negative outcomes of the aggression. In contrast, a subgroup of girls with clinically significant levels of CBCL externalizing behaviors characterized their own physical aggression as appropriate retaliation with emotionally satisfying consequences. Many of these girls also scored in the clinically significant range on CBCL internalizing behaviors and total problems. Clinicians who collected the data expressed concern about these girls, in particular because they were ostracized from non-delinquent peer groups, viewed others' continuing physical aggression against them as an inevitable part of their future, and described their own physical aggression as unavoidably driven by that violence. The authors stress these findings have implications for intervention. Haight W, Marshall J, Hans S, Black J, Sheridan K. "They mess with me, I mess with them": Understanding physical aggression in rural girls and boys from methamphetamine-involved families. *Child Youth Serv Rev*. 2010; 32 (10): 1223-1234.

Contemporary Costs of HIV Healthcare in the HAART Era

The delivery of HIV healthcare historically has been expensive. The most recent national data regarding HIV healthcare costs were from 1996-1998. In this study, researchers provide updated estimates of expenditures for HIV management. They performed a cross-sectional review of medical records at 10 sites in the HIV Research Network, a consortium of high-volume HIV care providers across the United States in which they participate through their NIDA study. They assessed inpatient days, outpatient visits, and prescribed antiretroviral and opportunistic illness prophylaxis medications for 14,691 adult HIV-infected patients in primary HIV care in 2006. They estimated total care expenditures, stratified by the median CD4 cell count obtained in 2006 (< 50, 51-200, 201-350, 351-500, >500 cells/ μ l). Per-unit costs of care were based on Healthcare Cost and Utilization Project (HCUP) data for inpatient care, discounted average wholesale prices for medications, and Medicare physician fees for outpatient care. Findings indicated that, averaging over all CD4 strata, the mean annual total expenditures per person for HIV care in 2006 in three sites was \$19,912, with an interquartile range from \$11,045 to \$22,626. Average annual per-person expenditures for care were greatest for those with CD4 cell counts 50 cell/ μ l or less (\$40,678) and lowest for those with CD4 cell counts more than 500 cells/ μ l (\$16,614). The majority of costs were attributable to medications, except for those with CD4 cell counts 50 cells/ μ l or less, for whom inpatient costs were highest. While HIV healthcare in the U.S. continues to be expensive, the majority of expenditures are attributable to medications. With improved HIV survival, these costs will likely increase and should be monitored in the future. Gebo K, Fleishman J, Conviser R, Hellinger J, Hellinger F, Josephs J, Keiser P, Gaist P, Moore R, Moore R. Contemporary costs of HIV healthcare in the HAART era. *AIDS*. 2010; 24 (17): 2705-2715.

Epidemiological Evidence on Count Processes in the Formation of Tobacco Dependence

This work delves into the earliest stages of smoking involvement, focusing on newly incident tobacco cigarette smokers in the very recent past, and examines hypothesized subgroup variation in count processes that become engaged once smoking starts. Here, the term 'count process' has two components: (a) whether smoking will be persistent and (b) the rate of smoking, conditional upon membership in a latent class of smokers who will persist, as estimated under the zero-inflated Poisson (ZIP) model for complex survey data. Authors estimate these ZIP parameters for nationally representative samples of newly incident smokers in the United States (all with smoking initiation within 24 months of assessment). Data are from the 2004-2007 National Surveys on Drug Use and Health. Once cigarette smoking started, roughly 40%-45% persisted, and the estimated median rate was five smoking days/30 days, conditional on membership in the latent class of persistent smokers. Among non-Hispanic recent-onset cigarette smokers, Whites, Black/African Americans, Asians, and Native American/Alaskan Natives did not differ, but recent-onset smokers of Hispanic origin and those of Pacific Islander background had comparatively less cigarette involvement. Tobacco prevention and control initiatives may require elaboration in the form of brief interventions, including interpersonal and social transactions that might constrain a mounting frequency of days of smoking before daily smoking starts, and until conventional smoking cessation medication aids become indicated. These very-early stage interventions (VESI) might be mounted within family or peer groups or in the primary care or school settings, but randomized trials to evaluate VESI interventions will be required. Barondess D, Meyer E, Boinapally P, Fairman B, Anthony J. Epidemiological evidence on count processes in the formation of tobacco dependence. *Nicotine Tob Res*. 2010; 12 (7): 734-741.

Drug Arrests and Injection Drug Deterrence

Researchers tested the hypothesis that higher rates of previous hard drug-

related arrests predict lower rates of injection drug use. They analyzed drug-related arrest data from the FBI's Uniform Crime Reporting Program for 93 large US metropolitan statistical areas in 1992 to 2002 to predict previously published annual estimates of the number of IDUs per 10000 individuals. To control for potential confounding of the relationship between hard drug arrests and IDU population rates, they included selected variables representing economic context (unemployment rate) and social cohesion (rate of religious congregations per 10,000 people in 1990). In linear mixed-effects regression, they found that hard drug-related arrest rates were positively associated (parameter = +1.59; SE = 0.57) with the population rate of IDUs in 1992 but were not associated with change in the IDU rate over time (parameter = -0.15; SE = 0.39). To assess this relationship further, the researchers added a variable to estimate the number of non-IDUs entering drug treatment for methamphetamine use per 10,000 people. They found that this variable did not change the relationship between arrests and injection drug use rates. These findings show that deterrence-based approaches to reducing drug use have little if any influence on reducing IDU prevalence. Evidence-based alternatives include interventions that focus on risk reduction to prevent HIV transmission and increase referrals, entry, and retention in drug and HIV treatment programs. Friedman S, Pouget E, Chatterjee S, Cleland C, Tempalski B, Brady J, Cooper H. Drug arrests and injection drug deterrence. *Am J Public Health*. 2011; 101 (2): 344-349.

Social Structural Factors that Shape Assisted Injecting Practices among Injection Drug Users in Vancouver, Canada: A Qualitative Study

IDUs commonly seek manual assistance with illicit drug injections, a practice known to be associated with various health-related risks. Researchers investigated the social structural factors that shape risks related to assisted injection and the outcomes that may result. They conducted 20 semi-structured qualitative interviews with IDU enrolled in the ACCESS or Vancouver Injection Drug Users Study (VIDUS) who reported requiring assistance injecting in the past six months. Audio-recorded interviews were transcribed verbatim and a thematic analysis was conducted. Barriers to self-injecting included a lack of knowledge of proper injecting technique, a loss of accessible veins, and drug withdrawal. The exchange of money or drugs for assistance with injecting was common. Problems experienced by IDU requiring assistance injecting included theft of the drug, missed injections, overdose, and risk of blood-borne disease transmission. Increased vulnerability to HIV/HCV infection within the context of intimate relationships was represented in participant narratives. IDU identified a lack of services available for those who require assistance injecting, with notable mention of restricted use of Vancouver's supervised injection facility. This study documents numerous severe outcomes that can arise from assisted injecting. Social structural factors that shape the risks related to assisted injection in the Vancouver context included intimate partner relations and social conventions requiring an exchange of goods for provision of injecting assistance. Health services for IDU who need help injecting should include targeted interventions, and supervised injection facilities should attempt to accommodate individuals who require assistance with injecting. Fairbairn N, Small W, Van Borek N, Wood E, Kerr T. Social Structural Factors that shape assisted injecting practices among injection drug users in Vancouver, Canada: A qualitative study. *Harm Reduct J*. 2010; 7: 20-27.

Unsafe Sex Reported by Women Receiving HIV Prevention Services in Los Angeles County

This study examined reported unsafe heterosexual intercourse in a sample of 682 women (42% Latina, 28% African American, mean age of 30) recruited from HIV prevention providers in Los Angeles County. The women were

sexually active, with 63% saying they had sex with one person who was their main partner, and 33% saying they had sex with someone they did not consider as their main partner. Among the 535 women who responded to questions about unsafe intercourse, 22% reported having engaged in high risk, unsafe heterosexual intercourse. They were almost all Latina, about 33% reported use of condoms some or all of the time except with their main partners, and they were significantly more likely to report both main and other sexual partners compared to other women. In addition, these women were more likely to report polydrug use, including injection drug use, in the past 6 months, and having sex partners who also injected drugs. Significant predictors of high risk, unsafe heterosexual intercourse were use of crystal meth in the past 6 months, use of alcohol before or after sex, and use of dental services at the interview agency. Being African American and endorsing use of condoms for vaginal sex from start to finish were inversely associated with high-risk, unsafe heterosexual intercourse. This study found that these women seek out service providers for help with their addictions, for housing, shelter, and for child welfare and dental services. Substance abuse treatment providers would be good venues to provide targeted intervention counseling and treatment for these women in need. Reynolds G, Fisher D, Napper L, Fremming B, Jansen M. Heterosexual Sex Reported By Women Receiving HIV Prevention Services In Los Angeles County. *Women's Health Issues*. 2010; 20 (6): 414-419.

Does Heavy Adolescent Marijuana Use Lead to Criminal Involvement in Adulthood? Evidence from a Multiwave Longitudinal Study of Urban African Americans

While marijuana use is common during adolescence, it can have adverse long-term consequences, with serious criminal involvement being one of them. In this study, researchers used longitudinal data from the Woodlawn Study of a community cohort of urban African Americans (N=702) to examine the effects of heavy adolescent marijuana use (20 or more times) on adult criminal involvement, including perpetration of drug, property and violent crime, as well as being arrested and incarcerated. Utilizing propensity score matching to take into account the shared risk factors between drug use and crime, regression analyses on the matched samples showed that heavy adolescent marijuana use may lead to drug and property crime and criminal justice system interactions, but not violent crime. The significant associations of early heavy marijuana use with school dropout and the progression to cocaine and/or heroin use only partially accounted for these findings. Results suggest that the prevention of heavy marijuana use among adolescents could potentially reduce the perpetration of drug and property crime in adulthood, as well as the burden on the criminal justice system, but would have little effect on violent crime. Green K, Doherty E, Stuart E, Ensminger M. Does heavy adolescent marijuana use lead to criminal involvement in adulthood? Evidence from a multiwave longitudinal study of urban African Americans. *Drug Alcohol Depend*. 2010; 112 (1-2): 117-125.

Policing and Risk of Overdose Mortality in Urban Neighborhoods

Accidental drug overdose is a major cause of mortality among drug users. Fears of police arrest may deter witnesses of drug overdose from calling for medical help and may be a determinant of drug overdose mortality. Few if any studies have empirically assessed the relationship between levels of policing and drug overdose mortality. Researchers hypothesized that levels of police activity, congruent with fears of police arrest, are positively associated with drug overdose mortality. They assembled cross-sectional time-series data for 74 New York City (NYC) police precincts over the period 1990-1999 using data collected from the Office of the Chief Medical Examiner of NYC, the NYC Police Department, and the US Census Bureau. Misdemeanor arrest rate-reflecting police activity-was the primary independent variable of interest, and overdose

rate the primary dependent variable of interest. The mean overdose rate per 100,000 among police precincts in NYC between 1990 and 1999 was 10.8 (standard deviation=10.0). In a Bayesian hierarchical model that included random spatial and temporal effects and a space-time interaction, the misdemeanor arrest rate per 1000 was associated with higher overdose mortality (posterior median=0.003, 95% credible interval=0.001, 0.005) after adjustment for overall drug use in the precinct and demographic characteristics. Levels of police activity in a precinct were found to be associated with accidental drug overdose mortality. Future research should examine aspects of police-community interactions that contribute to higher overdose mortality. Bohnert A, Nandi A, Tracy M, Cerdá M, Tardiff K, Vlahov D, Galea S. Policing and risk of overdose mortality in urban neighborhoods. *Drug Alcohol Depend.* 2011; 113 (1): 62-68.

HIV-1 Diversity after a Class Switch Failure

The purpose of this study was to evaluate whether the choice of a protease inhibitor (PI)- or an efavirenz (EFV)-based HAART initial regimen impacts HIV diversity after failure from a second, class-switch salvage regimen. Sequential HAART failures after a class switch were identified for which the genotypes showed evidence of signature mutations at each failure. Each second failure was required to be from a viral burden <400 RNA c/ml. Thirteen cases of sequential failure from an initial EFV-containing to a PI-containing regimen (EP), and 19 sequential failures from an initial PI-containing to an EFV-containing regimen (PE) were identified. The persistence of signature mutations from the first failure were evaluated at second failure and compared between the EP and PE groups. Phylogenetic trees were constructed for a subgroup of cases from existing genetic sequence information and branch length analysis was used to determine evidence of viral diversity between groups. For EP sequential therapy, 10 of 12 cases carried forward a key non-nucleoside reverse transcriptase inhibitor (NNRTI) mutation in the second failure compared to 5 of 13 cases for PE sequential therapy ($p = 0.041$). Phylogenetic analysis demonstrated that there was more viral diversity in the PE group as compared to the EP group, consistent with the interpretation that mutations at the second failure added to an ancestral virus closer to baseline rather than to the dominant virus at first failure. These findings show that the development of HIV viral diversity after multiple HAART failures is determined by the sequence in which the regimens are ordered. Kolber M, Buendia P, Degruittola V, Moore R. HIV-1 diversity after a class switch failure. *AIDS Res Hum Retroviruses.* 2010; 26 (11): 1175-1180.

Associations Between Multiple Pregnancies and Health Risk Behaviors among U.S. Adolescents

This study examined associations between health risk behaviors (i.e., substance use behaviors, physical violence, or carried a weapon) and multiple adolescent pregnancies (i.e., experiencing or causing more than one pregnancy). Researchers analyzed 1999-2003 data (3 years: 1999, 2001, and 2003) from the National Youth Risk Behavior Survey, a nationally representative survey of high school students (N = 14,211 participants). Multinomial logistic regression was used to compare one and multiple pregnancies versus no pregnancies. Logistic regression was used to compare multiple pregnancies versus one pregnancy. A dose-response relationship was observed between multiple adolescent pregnancies and health risk behaviors; the more risk behaviors endorsed, the greater likelihood of experiencing or causing multiple adolescent pregnancies. Participants who engaged in a 'high' degree of risk behaviors were significantly more likely to have experienced or caused multiple adolescent pregnancies than no pregnancies (or only one pregnancy) versus youth who endorsed no risk behaviors. Earlier sexual debut and more lifetime sexual partners were also associated with increased risk of

endorsing multiple adolescent pregnancies. These health risk behaviors can serve as warning signs to influential persons who may be able to deliver important prevention messages to at-risk adolescents. Cavazos-Rehg P, Krauss M, Spitznagel E, Schootman M, Cottler L, Bierut L. Associations between multiple pregnancies and health risk behaviors among U.S. adolescents. *J Adolesc Health*. 2010; 47 (6): 600-603.

Cannabis Involvement in Individuals with Bipolar Disorder

In a study of 471 bipolar disorder (BD) cases and 1761 controls, individuals with BD were 6.8 times more likely to report a lifetime history of cannabis use. Rates of DSM-IV cannabis use disorders in those with BD were 29.4% and were independently and significantly associated with increased suicide attempts, greater likelihood of mixed episodes and greater disability attributable to BD. Agrawal A, Nurnberger J, Lynskey MT. Cannabis involvement in individuals with bipolar disorder. *Psychiatry Res*. 2011; 185 (3): 459-461.

Exploring the Link between Racial Discrimination and Substance Use: What Mediates? What Buffers?

The relationship between perceived racial discrimination and substance use was examined in 2 studies that were based on the prototype-willingness model. Study 1, using structural equation modeling, revealed prospective relationships between discrimination and use five years later in a panel of African American adolescents (median age 10.5 years, Time 1 [T1]) and their parents. For both groups, the relationship was mediated by anger and/or hostility. For the adolescents, it was also mediated by behavioral willingness, and it was moderated by supportive parenting. Study 2 was a lab experiment in which a subset of the Study 1 adolescents (median age = 18.5 years) was asked to imagine a discriminatory experience, and then their affect and drug willingness were assessed. As in the survey study, discrimination was associated with more drug willingness, and that relationship was again mediated by anger and moderated by supportive parenting. Implications of the results for research and interventions involving reactions to racial discrimination are discussed. Gibbons F, Etcheverry P, Stock M, Gerrard M, Weng C, Kiviniemi M, O'Hara R. Exploring the link between racial discrimination and substance use: What mediates? What buffers? *J Pers Soc Psychol*. 2010; 99 (5): 785-801.

HIV Heterosexual Sexual Risk From Injecting Drug Users Among HIV-Seronegative Noninjecting Heroin Users

Noninjecting heroin users (NIUs) were recruited in New York City during 1996-2003. Cumulative logistic regression was used to analyze the correlates of HIV sexual risk from IDUs among HIV seronegative NIUs engaging in heterosexual sex in the past 30 days (N = 347). Participants were 67% male and 70% African American or Latino, with a mean age of 32.6 years. Hierarchical categories of IDU partner sexual risk included (1) no unprotected sex and no IDU sex partners (21%), (2) unprotected sex but not with IDUs (55%), (3) IDU sex partners but no unprotected sex with them (6%), and (4) unprotected sex with IDUs (17%). Independent correlates ($p < .05$) of HIV sexual risk from IDU partners included female versus male gender (adjusted odds ratio [AOR] = 2.01), ex-IDU versus never IDU (AOR = 1.90), and lower versus higher perceived social distance from IDUs (AOR = 1.60). These findings point to the need for interventions that target female NIUs, ex-IDUs, and NIU members of IDU social and sexual networks. Neaigus A, Miller M, Gyarmathy V, Friedman S. HIV heterosexual sexual risk from injecting drug users among HIV-seronegative noninjecting heroin users. *Subst Use Misuse*. 2011; 46 (2-3): 208-217.

Herpes Simplex Virus Type 2 Associated with HIV Infection among New York Heterosexuals Living in High-Risk Areas

Herpes simplex virus type 2 (HSV-2) has been shown to increase the risk of sexual HIV transmission. A matched case-control design was used to examine the association between HSV-2 and HIV infection among heterosexuals in 'high-risk areas'(HRAs) in New York City (NYC). Researchers identified NYC HRAs using HIV surveillance data on heterosexual-related adult HIV diagnoses and US census data on household poverty. Heterosexuals who were socially or geographically linked to a HRA were recruited using respondent-driven sampling. HIV prevalence was 8.6% and HSV-2 prevalence was 80.1%. Only 6% of HIV-positives knew they were infected. HIV-positive cases were matched to HIV-negative controls on gender, race/ethnicity and age, and tested for antibody to HSV-2. In a multivariate model, HIV infection was associated with HSV-2 infection (adjusted odds ratio [AOR] = 3.5, 95% confidence interval 1.1-11.7) and non-HSV-related STI diagnosis in the previous year (AOR = 2.6, 1.1-6.2). Effective approaches to HIV risk reduction for individuals with HSV-2 remain uncertain, and these are urgently needed in high-risk communities where multiple social, behavioral and biological factors that facilitate HIV infection coexist. Hagan H, Jenness S, Wendel T, Murrill C, Neaigus A, Gelpi-Acosta C. Herpes simplex virus type 2 associated with HIV infection among New York heterosexuals living in high-risk areas. *Int J STD AIDS*. 2010; 21 (8): 580-583.

Prescription Drug Abuse and Diversion: Role of the Pain Clinic

This study sought to better understand the role that South Florida pain management clinics may be playing in the abuse and diversion of prescription drugs. It explored 1) the characteristics and practices of pain clinics that may be facilitating the drug-seeking behaviors of prescription drug abusers and 2) the drug-seeking behaviors of prescription drug abusers who use pain clinics as a primary source for drugs. Thirty in-depth interviews were conducted with prescription drug abusers in South Florida. Interviews were transcribed verbatim and codes were generated based on thematic analyses of the data. Using grounded theory strategies, the analysis revealed six main themes: 'pill mills,' on-site pharmacies, liberal prescribing habits, "sponsoring" drug diversion, pain doctor/pharmacy shopping, and faking symptoms/documentation. The authors discuss these themes and conclude that both the practices of some pain clinics and the drug seeking efforts of prescription drug abusers are contributing to the diversion and abuse of prescription drugs. The data shed new light on how drug abusers have been obtaining controlled prescription drugs from pain clinics. The findings should provide insights for law enforcement, regulatory agencies, and industry as they attempt to develop appropriate policy initiatives and recommendations for best practices. Rigg KK, March SJ, Inciardi JA. Prescription drug abuse and diversion: Role of the pain clinic. *J Drug Issues*. 2010; 40 (3): 681-702.

Childhood Physical Punishment and Later Alcohol Drinking Consequences: Evidence from a Chinese Context

The aim of this study was to examine the association between physical punishment in early childhood and later alcohol use disorder outcomes, taking family history of drinking problems into account and utilizing epidemiological data from China. Data were from the World Mental Health Survey-Metropolitan China Study, with a cross-sectional representative sample of adult household residents living in two metropolitan areas, Beijing and Shanghai. The 1,611 participants were asked about early life experiences, including parental alcohol or other drug problems (AODP) and childhood conduct disorder symptoms, as well as their own adult drinking behaviors. Analyses found robust associations

between childhood physical punishment and adult alcohol abuse outcomes, even when controlling for parental AODP and childhood conduct disorder symptoms. These results from a cross-sectional survey serve as a foundation for further prospective and longitudinal research to examine the relationship between childhood physical punishment and later alcohol and substance use disorders. Cheng H, Huang Y, Anthony J. Childhood physical punishment and later alcohol drinking consequences: Evidence from a Chinese context. *J Stud Alcohol Drugs*. 2010; 72 (1): 24-33.

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

Research Findings - Prevention Research

Impact of Family-Centered Intervention in Public Middle Schools

This study examined the impact of the Family Check-Up (FCU) and linked intervention services on reducing health-risk behaviors and promoting social adaptation among middle school youth. The FCU offers family assessment and support to identify families at risk for problem behavior and substance use who may be referred for additional services. These interventions, along with a family resource center directed to all parents in the school, make up this comprehensive intervention model. A total of 593 students and their families from three public middle schools were randomly assigned to receive either the intervention or middle school services as usual. Forty-two percent of intervention families engaged in the service and received the FCU. Students in both conditions completed a self-report survey measuring alcohol, tobacco, and marijuana use as well as antisocial behavior in 6th, 7th, and 8th grades. Using complier average causal effect analyses, engagement in the intervention moderated intervention outcomes. Families who engaged in the intervention had youth who reported lower rates of antisocial behavior and substance use over time than did a matched control sample. Results extend previous research indicating that a family-centered approach to supporting youth in the public school setting reduced the growth of antisocial behavior, alcohol use, tobacco use, and marijuana use throughout the middle school years. Stormshak E, Connell A, Véronneau M, Myers M, Dishion T, Kavanagh K, Caruthers A. An ecological approach to promoting early adolescent mental health and social adaptation: Family-centered intervention in public middle schools. *Child Dev.* 2011; 82 (1): 209-225.

Preventive Intervention for Rural Emerging Adults Buffers Impact of Life Stress on Risk Behaviors

This study focused on the buffering effects of Adults in the Making (AIM), a family-centered preventive intervention, on the link between life stress and increases in risk behaviors among 347 rural, southern African Americans as they left high school. The intervention was designed to increase family emotional and instrumental support and provide vocational coaching and advocacy along with racial socialization. In addition, the program was intended to enhance youths' self-regulatory competence. Of the families in the study, 174 were assigned to the prevention condition and 173 to a control condition. The investigators measured life stress as a combination of a negative stressful events measure and a perceived discrimination measure. Risk behaviors included risky alcohol use, marijuana use, and sexual behaviors. Measures were collected at pretest, posttest (7 months after pretest), and long-term follow-up (10 months after posttest). Results indicated that life stress was predictive of increases in risk behavior. Furthermore, participation in the

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intervention was related to reduce rates of increase in risk behaviors. Finally, the impact of life stress on risk behavior was reduced for individuals who participated in the intervention. Brody GH, Chen Y, Kogan SM, Smith K, Brown AC. Buffering effects of family-based intervention for African American emerging adults. *J Marriage Fam.* 2010; 72 (5): 1426-1435.

Does Implementation of Universal Prevention Interventions Produce Universal Effects?

This study tested the universality of the effects of the Communities That Care (CTC) prevention system. CTC is being examined in a larger study called the Community Youth Development Study (CYDS). CYDS is a randomized controlled trial of 24 small-to-medium sized communities matched on demographics and randomly assigned to CTC for the implementation of evidence-based prevention programs, or to prevention as usual condition. Testing the universality of the effects of an intervention that was designed to be universal is important because it provides information about how the program operates and for whom and under what conditions it is most effective. The present study examined whether the previously established significant effects of the universal, community-based Communities That Care (CTC) prevention program on the prevalence of substance use and the variety of delinquent behaviors held equally for boys and girls and in risk-related subgroups defined by early substance use, early delinquency, and high levels of community-targeted risk at baseline. Interaction analyses of data from a panel of 4,407 students followed from Grade 5 to Grade 8 in the first randomized trial of CTC in 12 matched community pairs suggests that CTC reduced students' substance use and delinquency equally across risk-related subgroups and gender, with two exceptions: 1) the effect of CTC on reducing substance use in 8th grade was stronger for boys than girls and, 2) the impact of CTC on reducing 8th-grade delinquency was stronger for students who were non-delinquent at baseline. Implications of these differential effects as well as the broad impacts of CTC are discussed. Oesterle S, Hawkins J, Fagan A, Abbott R, Catalano R. Testing the universality of the effects of the Communities That Care prevention system for preventing adolescent drug use and delinquency. *Prev Sci.* 2010; 11 (4): 411-423.

KEEP Foster-Parent Training Intervention: Model Description and Effectiveness

This paper describes the development and history of the Keeping Foster Parents Trained and Supported (KEEP) foster-parent training intervention. KEEP intervention represents a modified version of the Multidimensional Treatment Foster Care intervention developed by interventionists at the Oregon Social Learning Center and is designed to provide training and support for children ages 5-11 in regular foster care. Initial findings are reported from a program of research focused on determining the effectiveness of the intervention. Thus far, the results indicate that the intervention is effective in reducing child behavior problems and that the effects of the intervention are mediated through changes in parenting behavior. There is also evidence that the KEEP foster-parent training intervention increases the chances of a positive change of placement (e.g. child reunited with biological parents) and mitigates the negative risk enhancing effect of a history of multiple placements. Price JM, Chamberlain P, Landsverk J, Reid J. KEEP Foster-Parent Training Intervention: Model description and effectiveness. *Child & Family Social Work.* 2009; 14 (2): 233-242.

Systematic Review of Drug Prevention Programs for Children in Elementary School

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This article is a systematic review of substance use prevention programs targeting elementary school (K-6th grades). Previous studies evaluating such programs among elementary school students showed mixed effects on subsequent substance use and related psychosocial factors. Thirty published evaluation studies of 24 elementary school-based substance use prevention programs were reviewed. The study selection criteria included program evaluations from 1980 to 2008. Among 27 evaluation studies that examined program effects on substance use, 56% (n = 15) found significant decreases. In addition, programs most often demonstrated effects on increasing negative substance use attitudes, increasing knowledge, decreasing perceptions of prevalence rates (i.e., descriptive norms), and improving resistance skills. Implications for the appropriateness and value of introducing substance use prevention programs to youth in elementary school are discussed. Hopfer S, Davis D, Kam J, Shin Y, Elek E, Hecht M. A review of elementary school-based substance use prevention programs: Identifying program attributes. *J Drug Educ.* 2010; 40 (1): 11-36.

Child's Inhibitory Control and Caregiver Involvement as Mediators of Maltreatment History and Early School Adjustment

This study examined whether disparities in school adjustment can be observed in maltreated foster children as early as kindergarten and first grade, and to identify factors that mediate the association between a history of maltreatment and foster placement and early school adjustment. Participants in this study were a subsample of children from a randomized controlled efficacy trial designed to evaluate a treatment foster care program for preschool-aged children, to increase positive outcomes during the transition to school, and to decrease risk for problem behaviors. The entire sample included a foster care (FC) group (n=117 maltreated foster children) and a community comparison (CC) group of non-maltreated children living with their biological families (n=60; matched on age and SES). In this study, 85 maltreated foster children and 56 non-maltreated community children (M age=3-6 years) were assessed across kindergarten and first grade to examine the hypothesis that inhibitory control and caregiver involvement mediate associations between a history of maltreatment and foster placement and early school adjustment. Specifically, academic and social-emotional competences were evaluated. The maltreated foster children performed more poorly in academic and social-emotional competence as compared to the control children. Inhibitory control fully mediated the association of maltreatment and foster placement with academic competence, whereas inhibitory control and caregiver involvement mediated the association with social-emotional competence. The results suggest that inhibitory control and caregiver involvement might be promising targets for school readiness interventions for foster preschoolers. Pears K, Fisher P, Bruce J, Kim H, Yoerger K. Early elementary school adjustment of maltreated children in foster care: The roles of inhibitory control and caregiver involvement. *Child Dev.* 2010; 81 (5): 1550-1564.

Influences on Prevention Program Effectiveness for Latino Students

This study examined how ethnic composition and linguistic acculturation within schools affected the efficacy of a youth substance use prevention model program. Data come from a randomized trial of the keepin' it REAL program, using a predominantly Mexican American sample of middle school students in Phoenix, Arizona. Thirty-five schools were randomly assigned to a control group or to one of three culturally tailored intervention versions. The authors hypothesized that school ethnic and linguistic acculturation composition (percent Latino, percent non-English speaking at home) and individual level of linguistic acculturation jointly would moderate the efficacy of the prevention

program, as indicated by students' alcohol, marijuana, and cigarette use. Using multilevel linear modeling and multiple imputation techniques to manage clustered data and attrition, results showed that desired program effects varied by the linguistic acculturation level of the school, the program version, and individual acculturation level. The Latino intervention version was more efficacious in schools with larger percentages of non-English speaking families, but only among less linguistically acculturated Latino students. There were no significant school level program effects connected to the percentage of Latino students at school, the other versions of the program, or among more linguistically acculturated students. Marsiglia FF, Yabiku ST, Kulis S, Nieri T, Lewin B. Influences of school Latino composition and linguistic acculturation on a prevention program for youth. *Soc Work Res.* 2010; 34 (1): 6-19.

Integrative Multiple Health Behavior Intervention for Youth

This study evaluated the efficacy of a brief integrative multiple behavior intervention and assessed risk factors as mediators of behavioral outcomes among older adolescents. A randomized controlled trial was conducted with participants randomly assigned to either a brief intervention or standard care control with 3-month follow-up. The standard care control condition received a commercially available booklet on wellness. A total of 479 students attending two public high schools participated. Participants receiving the intervention showed a significant reduction in quantity x frequency of alcohol use, and increases in fruit and vegetable consumption and frequency of relaxation activities, compared to those receiving the control, $P = .01$. No effects were found on cigarette and marijuana use, exercise and sleep. Effect sizes were small with alcohol use cessation effects reaching medium size. Intervention effects were mediated by changes in peer influence ability for alcohol use, and self-efficacy and self-image for health promoting behaviors. Findings suggest that the brief intervention resulted in modest changes in some health risk and promoting behaviors for adolescents, with outcomes mediated by several risk factors. Werch C, Bian H, Carlson J, Moore M, Diclemente C, Huang I, Ames S, Thombs D, Weiler R, Pokorny S. Brief integrative multiple behavior intervention effects and mediators for adolescents. *J Behav Med.* 2011; 34 (1): 3-12.

Pharmacy Staff See Roles for Pharmacies in HIV Prevention

Increased access to sterile syringes among injection drug users (IDUs) has been correlated with reduced syringe sharing. Many states, including Rhode Island, have legalized non-prescription (NP) sale of syringes in pharmacies. Previous studies have suggested that training pharmacists to provide HIV-related services to IDUs may be an important opportunity to engage IDUs and provide them with such services. However, it is not clear to what extent pharmacy staffs are willing to expand their roles in providing services to IDUs who come in to purchase syringes. Pharmacists and pharmacy staff were recruited from the 48 pharmacies indicating NP sale of syringes in the greater Providence, RI area, to participate in an online survey. One hundred and forty-six individuals completed the online survey (32 pharmacies, 114 pharmacy staff), most of whom were employed by chain pharmacies (92%). Most participants thought that pharmacies were important resources for IDU customers (77%) and that they would be willing to provide health and prevention information/ referrals to IDU customers who purchase NP syringes (59%). With respect to willingness to offer HIV prevention-related services, access to confidential space and concern about personal safety had the strongest associations with willingness to provide HIV prevention services (OR 4.3 and 0.1, respectively). As the nature of the retail pharmacy shifts, researchers, pharmacy executives, and health care officials can build upon the willingness of pharmacists and pharmacy staff to address the health needs of injection drug users and other underserved populations. Zaller N, Jeronimo A, Bratberg J, Case P, Rich J. Pharmacist and pharmacy staff experiences with

non-prescription (np) sale of syringes and attitudes toward providing HIV prevention services for injection drug users (IDUs) in Providence, RI. *J Urban Health*. 2010; 87 (6): 942-953.

Long-term Outcomes for Participants in a Family Prevention Intervention involving Parents in Treatment for Opioid Addiction

Few studies follow the lives of opiate-addicted parents. The authors examined a 12-year follow-up of 144 parents in methadone treatment in the Seattle area and their children (3- to 14-years-old at baseline) who enrolled in a prevention study. In the original sample, 74% of study participants were women and 78% were Caucasian. At the follow up, 142 participants were located, and 24% of those located were deceased. Among survivors, drug use, drug treatment, incarceration, residential and family disruptions, and health problems were common. Only 33 participants met the study definition for recovery. Moderate and long-term recoveries were associated with consistent methadone treatment, further education, employment, and fewer relationship disruptions. Earlier depression, deviant friends, and poor coping skills predicted continued drug problems. The authors conclude that interventions should include treatment for depression and build skills for avoiding and refusing drugs, coping with stress, and maintaining recovery-supportive friendships. Skinner M, Haggerty K, Fleming C, Catalano R, Gainey R. Opiate-addicted parents in methadone treatment: long-term recovery, health, and family relationships. *J Addict Dis*. 2011; 30 (1): 17-26.

The Relationship between Marijuana Use and School Dropout

In this study, the authors reconsider the relationship between heavy and persistent marijuana use and high school dropout status. Using a unique prospective panel study of over 4,500 7th grade students from South Dakota who are followed through high school, they developed propensity score weights to adjust for baseline differences found to exist before marijuana initiation occurs for most students (7th grade). They then used weighted logistic regression that incorporates these propensity score weights to examine the extent to which time-varying factors, including substance use, also influence the likelihood of dropping out of school. They found a positive association between marijuana use and dropping out (OR=5.6, RR=3.8), over half of which was explained by prior differences in observational characteristics and behaviors. The remaining association (OR=2.4, RR=1.7) became statistically non-significant when measures of cigarette smoking were included in the analysis. Because cigarette smoking is unlikely to seriously impair cognition, the authors interpret this result as evidence that the association between marijuana use and high school dropout is unlikely to be due to its adverse effects on cognition. They then explored which constructs drive this result, determining that they are time-varying parental and peer influences. McCaffrey D, Pacula R, Han B, Ellickson P. Marijuana use and high school dropout: The influence of unobservables. *Health Econ*. 2010; 19 (11): 1281-1299.

The Relationship between School Climate and Student Behavior Problems

This study used an ecological framework to examine how adolescents' perceptions of school climate in 6th grade covaried with the probability and frequency of their engagement in problem behaviors in 7th and 8th grades. Tobit analysis was used to address the issue of having a highly skewed outcome variable with many zeros and yet account for censoring. The 677 participating students from 8 schools were followed from 6th through 8th grades. The proportions of students reporting a positive school climate perception decreased over the middle school years for both genders, while the

level of problem behavior engagement increased. The findings suggested that students who perceived higher levels of school discipline and order or more positive student-teacher relationships were associated with lower probability and frequency of subsequent behavioral problems. Wang M, Selman RL, Dishion TJ, Stormshak EA. A tobit regression analysis of the covariation between middle school students' perceived school climate and behavioral problems. *J Res Adolesc.* 2010; 20 (2): 274-286.

Multilevel Modeling Methods to Understand the Link between Peer Group Aggression and Adjustment

This study examined the association between affiliating with aggressive peers and behavioral, social and psychological adjustment. Students in grades 3, 4, and 5 (N = 427) were followed biannually through 7th grade. Students' peer-nominated groups were identified (based on reports of whom they hang around with the most) Multilevel modeling was used to examine the independent contributions of adolescents' typical peer context (between-person effect) and changes in peer context (within-person effects) to adolescents' adjustment. Typically affiliating with aggressive groups and affiliating with more aggressive groups than usual predicted higher aggression for all youth. Typically, affiliating with aggressive groups predicted negative adjustment (lower social preference and self-worth, higher victimization) for girls but neutral or positive adjustment for boys. Although typical peer context was consistently associated with adjustment, changes in peer context predicted small changes in adjustment for several outcomes. Results underscored the need to adopt a more differentiated picture of adolescents' dynamic peer context and its association with normative development. Rulison K, Gest S, Loken E, Welsh J. Rejection, feeling bad, and being hurt: Using multilevel modeling to clarify the link between peer group aggression and adjustment. *J Adolesc.* 2010; 33 (6): 787-800.

The Influence of Adolescent Substance Co-Use with Friends on Future Individual Use

The influence of using substances with friends on future individual use was examined in the context of parental monitoring rules and the ecology of peer activities. A one-year longitudinal study design included a combined sample of North Italian and French Canadian adolescents (N = 285, 53% girls, M = 14.25 years). Data analyses were conducted using structural equation modeling and multiple regression analyses. As expected, the covariation between parental monitoring and adolescent substance use was mediated by 'co-use' with friends. Moreover, the relation between substance use with friends and individual substance use was moderated by parental monitoring rules and the peer activity context. Specifically, the relation between substance co-use with friends and individual substance use was stronger when the level of parental monitoring rules was low and when friends spent their time together primarily in unstructured contexts such as on the street or in park settings. These findings underline the importance of adults' use of rules to monitor adolescents prone to substance use, and the role of context in facilitating or reducing peer influence. Kiesner J, Poulin F, Dishion TJ. Adolescent substance use with friends: moderating and mediating effects of parental monitoring and peer activity contexts. *Merrill Palmer Q (Wayne State University Press).* 2010; 56 (4): 529-556.

The Impact of Changes in Romantic Relationships on Alcohol and Drug Use Behaviors

Changes in romantic relationship status are common in emerging adulthood and may be linked to changes in substance use. This study tested the hypothesis that entry into relationships or transitioning to a more committed

status leads to decreases in substance use and that dissolution of relationships or transitioning to a less committed status results in increases in substance use. Data were from a community sample of 939 individuals. Substance use (heavy drinking, marijuana use, and cigarette smoking) and relationship status (single, in a romantic relationship but not cohabiting, cohabiting, or married) were assessed at the beginning and end of three 6-month intervals for participants between the ages of 18 and 20 years. Models were estimated to assess the association between transitions in relationship status and substance use, adjusting for prior levels of use. There were increases in heavy drinking, marijuana use, and cigarette smoking associated with dissolution of a romantic relationship, as well as increases in marijuana use and cigarette smoking associated with switching partners within a 6-month interval. Mediation analyses found some support for increases in both depressive symptoms and exposure to substance-using peers partially accounting for these associations. Decreases in substance use were not found for individuals entering into a new relationship or transitioning to a more committed relationship status. In fact, cigarette smoking increased among those who went from being single to being in a romantic relationship compared with those whose relationship status did not change. Emerging adults who experience dissolution of romantic relationships or quickly move from one relationship to another experience increased substance use. Both depressive symptoms and changes in peer environments may partially account for these changes in use. Fleming C, White H, Oesterle S, Haggerty K, Catalano R. Romantic relationship status changes and substance use among 18- to 20-year-olds. *J Stud Alcohol Drugs*. 2010; 71 (6): 847-856.

Reflective Functioning of Mothers with Drug Use Disorders

This study examined maternal reflective functioning as a bi-dimensional construct in a sample of 47 mothers with drug use disorders caring for infants and toddlers. First, a two-factor solution was tested with scale items from the Parent Development Interview and confirmed the presence of two related but distinct dimensions: self-mentalization and child-mentalization. Second, the following predictions were tested (a) self-mentalization would be associated with overall quality of maternal caregiving, and (b) child-mentalization would be associated with (i) maternal contingent behavior and (ii) child communication. Results partially supported hypotheses (a) and (bii). Unexpectedly, self-mentalization alone was associated with maternal contingent behavior. Findings suggest that self-mentalization may be a critical first step in improving mother-child relations involving mothers with drug use disorders. Suchman N, DeCoste C, Leigh D, Borelli J. Reflective functioning in mothers with drug use disorders: implications for dyadic interactions with infants and toddlers. *Attach Hum Dev*. 2010; 12 (6): 567-585.

The Emergence of Maternal Harsh Parenting During Infancy and Toddlerhood Among At-Risk Families

This study examined developmental patterns in maternal harsh parenting behavior from birth to age 3 years and their related longitudinal risk factors (contextual and intrapersonal). Partner aggression was also tested as a time-varying predictor to examine its time-specific influence on maternal harsh parenting. Longitudinal data from 4 assessments of a community sample of 488 at-risk mothers were analyzed using latent growth curve modeling. Maternal risk factors and harsh parenting behaviors were assessed at birth and at ages 1, 2, and 3 years. Results showed a significant increase in maternal harsh parenting from birth to age 3, particularly between ages 1 and 2. Also, there was a significant direct effect of maternal alcohol use and abuse history on maternal harsh parenting at age 3, and maternal age was positively associated with change in maternal harsh parenting over time. In addition, partner aggression was significantly and positively associated with maternal

harsh parenting at each time point. The authors note that the findings suggest possible developmental trends in the emergence of maternal harsh parenting during infancy and toddlerhood. Individual differences in the developmental patterns, differentiation of predictive factors that persist across time, and factors that are unique to specific developmental stages need further elucidation. Kim H, Pears K, Fisher P, Connelly C, Landsverk J. Trajectories of maternal harsh parenting in the first 3 years of life. *Child Abuse Negl.* 2010; 34 (12): 897-906.

Cascading Peer Dynamics underlying the Progression from Problem Behavior to Violence

This study examined the peer dynamics linking early adolescent problem behavior, school marginalization, and low academic performance to multiple indices of late adolescent violence (arrests, parent report, and youth report) in an ethnically diverse sample of 998 males and females. A cascade model was proposed in which early adolescent risk factors assessed at ages 11 to 12 predict gang involvement at ages 13 to 14, which, in turn, predict deviance training with friends at ages 16 to 17, which then predicts violence by ages 18 to 19. Each construct in the model was assessed with multiple measures and methods. Structural equation modeling revealed that the cascade model fit the data well, with problem behavior, school marginalization, and low academic performance significantly predicting gang involvement 2 years later. Gang involvement, in turn, predicted deviance training with a friend, which predicted violence. The best fitting model included an indirect and direct path between early adolescent gang involvement and later violence. These findings suggest the need to carefully consider peer clustering into gangs in efforts to prevent individual and aggregate levels of violence, especially in youths who may be disengaged, marginalized, or academically unsuccessful in the public school context. Dishion T, Véronneau M, Myers M. Cascading peer dynamics underlying the progression from problem behavior to violence in early to late adolescence. *Dev Psychopathol.* 2010; 22 (3): 603-619.

Lack of Support for the Gateway Hypothesis of Drug Use

The gateway drug model is a popular conceptualization of a progression most substance users are hypothesized to follow as they try different legal and illegal drugs. Most forms of the gateway hypothesis are that 'softer' drugs lead to 'harder,' illicit drugs. However, the gateway hypothesis has been notably difficult to directly test - i.e., to test as competing hypotheses in a single model that licit drug use might lead to illicit drug use, or the reverse. This article presents a novel statistical technique, dual-process discrete-time survival analysis, which enables this comparison. This method uses mixture-modeling software to estimate two concurrent time-to-event processes and their effects on each other. Using this method, support for the gateway hypothesis in the National Longitudinal Survey of Youth 1997 was weak. The licit-to-illicit progression was not significantly stronger than the illicit-to-licit progression, violating one of the key implications of the gateway hypothesis, although these findings were constrained by the low prevalence of early illicit drug use and the resultant large confidence intervals. Malone PS, Lanis DA, Masyn KE, Northrup TF. A dual-process discrete-time survival analysis model: Application to the Gateway Drug Hypothesis. *Multivariate Behav Res.* 2010; 45 (5): 790-805.

Variation in the Applicability of the Gateway Hypothesis of Drug Use Progression

It is unclear whether the commonly observed sequence of drug use initiation, beginning with tobacco and alcohol, progressing to cannabis and then other illicit drugs, is due to causal effects of specific earlier drug use promoting

progression, or to influences of other variables such as drug availability and attitudes. One way to investigate this is to see whether risk of later drug use in the sequence, conditional on use of drugs earlier in the sequence, changes according to time-space variation in use prevalence. This study compared patterns and order of initiation of alcohol, tobacco, cannabis, and other illicit drug use across 17 countries with a wide range of drug use prevalence. Findings suggest that progression among these substances varies substantially across countries and that availability, background prevalence of use, as well as attitudes may play significant roles in attenuating relationships among different substances of use, as well as patterns of progression. Degenhardt L, Dierker L, Chiu W, Medina-Mora M, Neumark Y, Sampson N, Alonso J, Angermeyer M, Anthony J, Bruffaerts R, de Girolamo G, de Graaf R, Gureje O, Karam A, Kostyuchenko S, Lee S, Lépine J, Levinson D, Nakamura Y, Posada-Villa J, Stein D, Wells J, Kessler R. Evaluating the drug use. *Drug Alcohol Depend.* 2010; 108 (1-2): 84-97.

Alcohol Use Interrelated with Early Nicotine Use

This study evaluated the association between alcohol use, abuse and dependence and cigarette smoking to determine whether alcohol may signal greater sensitivity to nicotine dependence at very low levels of smoking. Data were drawn from five annual National Surveys on Drug Use and Health and included individuals aged 12 to 21 who reported first exposure to smoking within the past two years and smoking at least once in the past month. Both alcohol abuse and alcohol dependence were associated with increased likelihood of symptoms that seem to tap tolerance for nicotine. These included items such as 'the amount you smoke has increased'; 'needing to smoke a lot more now in order to be satisfied'; and 'smoking much more before starting to feel anything'. Alcohol dependence, but not abuse was associated with the remaining symptoms, 'after not smoking for a while, needing to smoke to feel less restless and irritable'; 'craving cigarettes after not smoking for a while'; and 'worrying about running out of cigarettes'. Associations were not better accounted for by either alcohol use or amount smoked. If causally associated, treatment of alcohol-use disorders may prevent or reduce the early emergence of nicotine dependence symptoms among new smokers, very early in the smoking uptake process. If instead alcohol disorders are a signal of sensitivity for nicotine dependence best accounted for by a third variable, then adolescents with alcohol dependence and/or abuse during early exposures to smoking represent an important subgroup that may benefit from interventions directly targeting this association. Dierker L, Rose J, Donny E, Tiffany S. Alcohol use as a signal for sensitivity to nicotine dependence among recent onset smokers. *Addict Behav.* 2011; 36 (4): 421-426.

Infrequent Smoking May Signal Differing Levels of Risk for Nicotine Dependence

The prevalence of individual nicotine dependence symptoms among recent onset smokers was evaluated across the continuum of nondaily and daily cigarette smoking behavior in a nationally representative sample of recent onset smokers from the National Surveys on Drug Use and Health (NSDUH). Rates of endorsement for 17 symptoms drawn primarily from the Nicotine Dependence Symptom Scale (Shiffman et al., 2004) were calculated for four levels of nondaily (smoked 1-3, 4-10, 11-20, or 21-29 days in the past 30 days) and daily (smoked 1, 2-5, 6-15, or >15 cigarettes per day in the past 30 days) smoking. Logistic and linear regression analyses with polynomial contrasts controlling for age, gender, length of exposure, and smoking quantity tested trends in symptom endorsement across levels of smoking. Significant linear and quadratic trends indicated that increasing rates of endorsement differed most between the lowest levels of nondaily and daily smoking. Results suggest that, for some, infrequent smoking may not represent benign

experimentation. Recognizing early symptoms of nicotine dependence may assist in early identification and intervention of those at risk for heavier smoking in the future. Adolescents can be taught to recognize the early symptoms of nicotine dependence to increase awareness of the rapidity at which these symptoms may appear. Rose J, Dierker L, Donny E. Nicotine dependence symptoms among recent onset adolescent smokers. *Drug Alcohol Depend.* 2010; 106 (2-3): 126-132.

Genetic Vulnerability Affects Relationship between Early Substance Use and Subsequent Sexual Behavior

A longitudinal, prospective design was used to investigate a moderation effect in the association between early adolescent substance use and risky sexual behavior 2 years later. A genetic vulnerability factor, a variable nucleotide repeat polymorphism (VNTR) in the promoter region of the serotonin transporter gene SLC6A4, known as 5-HTTLPR, was hypothesized to moderate the link between substance use at age 14 and risky sexual behavior at age 16. This VNTR has been associated with risk-taking behavior. African American youths in rural Georgia (N=185) provided 2 waves of data on their substance use and sexual behavior. Genetic data were obtained via saliva samples. Substance use and sexual risk behavior were assessed using youth self-report items developed for this investigation. Multiple regression analyses indicated that the presence of 1 or 2 copies of the short allele of the VNTR interacted with substance use to predict sexual behavior. Substance use had little effect on sexual behavior for youths without the short allele; this effect was greatly increased for youths with the short allele. Genetic vulnerability affected the implications of early onset substance use for later sexual behavior. Kogan S, Beach S, Philibert R, Brody G, Chen Y, Lei M. 5-HTTLPR status moderates the effect of early adolescent substance use on risky sexual behavior. *Health Psychol.* 2010; 29 (5): 471-476.

Relationships between Conduct Problems, Substance Use, and Risky Sexual Behaviors in Youth At Risk for Conduct Disorder

Conduct problems, substance use, and risky sexual behavior have been shown to coexist among adolescents, which may lead to significant health problems. The current study was designed to examine relationships among these problem behaviors in a community sample of children at high risk for conduct disorder. A latent growth model of childhood conduct problems showed a decreasing trend from grades K to 5. During adolescence, four concurrent conduct problem and substance use trajectory classes were identified (high conduct problems and high substance use, increasing conduct problems and increasing substance use, minimal conduct problems and increasing substance use, and minimal conduct problems and minimal substance use) using a parallel process growth mixture model. Across all substances (tobacco, binge drinking, and marijuana use), higher levels of childhood conduct problems during kindergarten predicted a greater probability of classification into more problematic adolescent trajectory classes relative to less problematic classes. For tobacco and binge drinking models, increases in childhood conduct problems over time also predicted a greater probability of classification into more problematic classes. For all models, individuals classified into more problematic classes showed higher proportions of early sexual intercourse, infrequent condom use, receiving money for sexual services, and ever contracting an STD. Specifically, tobacco use and binge drinking during early adolescence predicted higher levels of sexual risk-taking in late adolescence. Wu J, Witkiewitz K, McMahon R, Dodge K, Dodge K. A parallel process growth mixture model of conduct problems and substance use with risky sexual behavior. *Drug Alcohol Depend.* 2010; 111 (3): 207-214.

Design Elements in Implementation Research: A Structured Review of Child Welfare and Child Mental Health Studies

Implementation science is an emerging field of research with considerable penetration in physical medicine and less in the fields of mental health and social services. There remains a lack of consensus on methodological approaches to the study of implementation processes and tests of implementation strategies. This paper addresses the need for methods development through a structured review that describes design elements in nine studies testing implementation strategies for evidence-based interventions addressing mental health problems of children in child welfare and child mental health settings. Randomized trial designs were dominant with considerable use of mixed method designs in the nine studies published since 2005. The findings are discussed in reference to the limitations of randomized designs in implementation science Landsverk J, Brown CH, Reutz JR, Palinkas L, Horwitz SM. Design elements in implementation research: A structured review of child welfare and child mental health studies. *Adm Policy Ment Health*. 2011; 38: 54-633.

A Strategy for Assessing Costs of Implementing New Practices in the Child Welfare System

In decisions to adopt and implement new practices or innovations in child welfare, costs are often a bottom-line consideration. The cost calculator, a method developed in England that can be used to calculate unit costs of core case work activities and associated administrative costs, is described as a potentially helpful tool for assisting child welfare administrators to evaluate the costs of current practices relative to their outcomes and could impact decisions about whether to implement new practices. The process by which the cost calculator is being adapted for use in US child welfare systems in two states is described and an illustration of using the method to compare two intervention approaches is provided. Chamberlain P, Snowden LR, Padgett C, Saldana L, Roles J, Holmes L, Ward H, Soper J, Reid J, Landsverk J. A strategy for assessing costs of implementing new practices in the child welfare system: Adapting the English cost calculator in the United States. *Adm Policy Ment Health*. 2011; 38 (24): 24-31.

Viral Load and Costs of HIV Care

The global prevalence of HIV infection continues to grow, as a result of increasing incidence in some countries and improved survival where highly active antiretroviral therapy (HAART) is available. Growing healthcare expenditure and shifts in the types of medical resources used have created a greater need for accurate information on the costs of treatment. The objectives of this review were to compare published estimates of direct medical costs for treating HIV and to determine the impact of disease stage on such costs, based on CD4 cell count and plasma viral load. A literature review was conducted to identify studies meeting pre-specified criteria for information content, including an original estimate of the direct medical costs of treating an HIV-infected individual, stratified based on markers of disease progression. Three unpublished cost-of-care studies were also included, which were applied in the economic analyses published in this supplement. A two-step procedure was used to convert costs into a common price year (2004) using country-specific health expenditure inflators and, to account for differences in currency, using health-specific purchasing power parities to express all cost estimates in US dollars. In all nine studies meeting the eligibility criteria, infected individuals were followed longitudinally and a 'bottom-up' approach was used to estimate costs. The same patterns were observed in all studies: the lowest CD4 categories had the highest cost; there was a sharp decrease in costs as CD4

cell counts rose towards 100 cells/mm³; and there was a more gradual decline in costs as CD4 cell counts rose above 100 cells/mm³. In the single study reporting cost according to viral load, it was shown that higher plasma viral load level (> 100,000 HIV-RNA copies/mL) was associated with higher costs of care. The results demonstrate that the cost of treating HIV disease increases with disease progression, particularly at CD4 cell counts below 100 cells/mm³. The suggestion that costs increase as the plasma viral load rises needs independent verification. This review of the literature further suggests that publicly available information on the cost of HAART by disease stage is inadequate. To address the information gap, multiple stakeholders (governments, pharmaceutical industry, private insurers and non-governmental organizations) have begun to establish and support an independent, high quality and standardized multicountry data collection for evaluating the cost of HIV management. An accurate, representative and relevant cost-estimate data resource would provide a valuable asset to healthcare planners that may lead to improved policy and decision-making in managing the HIV epidemic. Levy A, Johnston K, Annemans L, Tramarin A, Montaner J. The impact of disease stage on direct medical costs of HIV management: A review of the international literature. *Pharmacoeconomics*. 2010; 28 Suppl 1: 35-47.

All Cause Mortality among IDU in Vietnam is 13-fold Greater than General Population

A prospective cohort study in Vietnam enrolled and followed community-dwelling IDUs at 3-month intervals for up to 2 years. The sample included 894 male IDUs (median age of 32 years, 22.8% HIV-positive, all having injected opioids). Deaths were confirmed by family members and by reviewing government records. Marginal Cox proportional hazards models for clustered data were constructed to determine the independent predictors of all-cause mortality, using both fixed baseline measurements and time-dependent repeated measurements. During 710.1 person-years of follow-up, 45 (5.0%) drug injectors died. The causes of deaths were AIDS-related (14 cases, 31%), drug overdose (12, 27%), suicide (3, 7%), traffic accident (3, 7%), violence (2, 4%), pneumonia (2, 4%), non-traffic accident (1, 2%) and unknown causes (8, 18%). The all-cause mortality rate was 6.3% (95% CI=4.6-8.5) per 100 person-years. The standardized mortality ratio was 13.4. The HIV incidence rate was 5.2 (95% CI=3.5-7.6) per 100 person-years. In multi-factorial analysis, HIV infection (hazard ratio [HR]=3.5, 95% CI=1.9-6.3) and previous diagnosis of tuberculosis (HR=10.0, 95% CI=4.1-24.3) were associated significantly with increased hazard of death. The all-cause, age- and sex-standardized mortality among Vietnamese IDUs was 13-fold higher than the general population and substantially higher than IDUs studied in developed countries. Effective prevention and control of HIV infection and tuberculosis are needed urgently. Quan V, Minh N, Ha T, Ngoc N, Vu P, Celentano D, Mo T, Go V. Mortality and HIV transmission among male Vietnamese injection drug users. *Addiction*. 2011; 106 (3): 583-589.

Stigma and Family and the Experience of HIV Seropositivity in Vietnam

The full impact of secondary stigma (stigma directed at family) on an HIV-positive individual is unknown. This qualitative research explores perceptions of secondary stigma in the Vietnamese context and its influence on the ways in which an injection drug user (IDU) copes with HIV infection. Data on experiences learning one's HIV status, disclosure decisions, family reactions, and stigma from family and community were collected through in-depth interviews with 25 HIV-positive IDUs recruited through a health center in Thai Nguyen, Vietnam. Participants felt despair when learning they were HIV-

positive and expressed concerns focused on the emotional burden and the consequences of HIV stigma that extended to family. Many participants engaged in self-isolating behaviors to prevent transmission and minimize secondary stigma. Data illustrated the strong value given to family in Vietnam and underscored the importance of secondary stigma in the coping process including gaining social support and engaging in risk reduction. Salter M, Go V, Minh N, Gregowski A, Ha T, Rudolph A, Latkin C, Celentano D, Quan V. Influence of perceived secondary stigma and family on the response to hiv infection among injection drug users in Vietnam. *AIDS Educ Prev.* 2010; 22 (6): 558-570.

Access to Condoms Relates to Condom Use among Sex Workers

To determine whether condom access is associated with consistent condom use among female sex workers (FSWs) in Tijuana and Ciudad Juarez, Mexico, between 2004 and 2006 questionnaires were administered to 924 FSWs who reported unprotected sex with a client in the past 2 months. Of these women, 43% reported consistent ('often' or 'always') condom use, 74% said condoms were available, and 38% reported having access to free condoms. In a logistic regression, factors positively associated with consistent condom use were condom availability (adjusted odds ratio [AOR] = 2.00; 95% confidence interval [CI]: 1.32-3.03), condom affordability (AOR = 1.72; 95% CI: 1.25-2.38) and self-efficacy (AOR = 2.16; 95% CI: 1.54-3.04). Factors inversely associated with consistent condom use included poor financial status (AOR = 0.65; 95% CI: 0.47-0.90), methamphetamine use (AOR = 0.58; 95% CI: 0.40-0.83), alcohol use (AOR = 0.68; 95% CI: 0.49-0.96), and recent injection drug use (AOR = 0.62; 95% CI: 0.39-0.97). While increased condom availability may improve condom use among FSWs in general, interventions to broaden condom use among lower income and drug-using FSWs are critically needed. Muñoz F, Pollini R, Zœñiga M, Strathdee S, Lozada R, Mart'nez G, Valles-Medina A, Sirotin N, Patterson T. Condom access: Associations with consistent condom use among female sex workers in two northern border cities of Mexico. *AIDS Educ Prev.* 2010; 22 (5): 455-465.

HIV Risks of Male Clients of Female Sex Workers

Male clients of female sex workers (FSWs) may act as a bridge to the general population contributing to the spread of HIV and other sexually transmitted infections (STIs) in the USA and Mexico. This study used cross-sectional data to identify psychosexual and social-cognitive factors associated with sexual risk behavior in a bi-national sample of 300 male clients of FSWs recruited in Tijuana, Mexico from June to October 2008. In a multiple regression analysis, the number of unprotected vaginal sex acts with FSWs was associated with higher sexual compulsivity scores, lower self-efficacy for condom use, greater use of illicit drugs, and more financial need. Behavioral interventions are urgently needed to assist clients of FSWs in reducing high-risk behaviors in an effort to prevent the spread of HIV/STIs in this high-risk population and their sexual partners. Semple S, Strathdee S, Gallardo Cruz M, Robertson A, Goldenberg S, Patterson T. Psychosexual and social-cognitive correlates of sexual risk behavior among male clients of female sex workers in Tijuana, Mexico. *AIDS Care.* 2010; 22 (12): 1473-1480.

Correlates of Unprotected Sex with FSWs in Tijuana

Tijuana, situated adjacent to San Diego, CA on the US-Mexico border, is experiencing an emerging HIV epidemic, with prevalence among female sex workers (FSWs) having risen in recent years from <1% to 6%. Comparable data on FSWs' clients are lacking. Correlates of unprotected sex were explored with FSWs among male clients in Tijuana. In 2008, males from San Diego (N =

189) and Tijuana (N = 211) aged 18 or older who had paid or traded for sex with a FSW in Tijuana during the past 4 months were recruited in Tijuana's red light district. Participants underwent psychosocial interviews, and were tested for HIV, syphilis (*Treponema pallidum*), gonorrhea (*Neisseria gonorrhoeae*), and Chlamydia (*Chlamydia trachomatis*). Of 394 men with complete data, median age was 36 years, 42.1% were married, and 39.3% were unemployed. Ethnic composition was 13.2% white, 79.4% Hispanic, and 7.4% black or other. Half (50.3%) reported unprotected vaginal or anal sex with FSWs in Tijuana in the past 4 months. High proportions reported using drugs during sex (66%), and 36% reported frequenting the same FSW. Factors independently associated with unprotected sex with FSWs were using drugs during sex, visiting the same FSW, being married, and being unemployed. Tailored interventions to promote consistent condom use are needed for clients, especially within the context of drug use and ongoing relations with particular FSWs. Goldenberg S, Gallardo Cruz M, Strathdee S, Nguyen L, Semple S, Patterson T. Correlates of unprotected sex with female sex workers among male clients in Tijuana, Mexico. *Sex Transm Dis.* 2010; 37 (5): 319-324.

Registration of Sex Workers is Related to Sexual Risk Behavior

Sex work is partially regulated in Tijuana, but little is known of its health effects. A recent behavioral intervention among female sex workers (FSWs) decreased incidence of HIV/STIs by 40%. The effects of sex worker regulation on condom use were evaluated among FSWs randomized to this intervention. FSWs aged 18 years who reported unprotected sex with 1 client in the last 2 months, and whether they were registered with Tijuana's Municipal Health Department, underwent a brief, theory-based behavioral intervention to increase condom use. At baseline and 6 months, women underwent interviews and testing for HIV, syphilis, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Negative binomial regression was used to determine the effect of registration on numbers of unprotected sex acts and cumulative HIV/STI incidence. Of 187 women, 83 (44%) were registered. Lack of registration was associated with higher rates of unprotected sex (rate ratio: 1.7, 95% CI: 1.2-2.3), compared to FSWs who were registered, after controlling for potential confounders. Registration predicted increased condom use amongst FSWs enrolled in a behavioral intervention. Public health programs designed to improve condom use among FSWs may benefit from understanding the impact of existing regulation systems on HIV risk behaviours. Sirotin N, Strathdee S, Lozada R, Abramovitz D, Semple S, Bucardo J, Patterson T. Effects of government registration on unprotected sex amongst female sex workers in Tijuana; Mexico. *Int J Drug Policy.* 2010; 21 (6): 466-470.

Cross-Border Contacts Associated with HIV Risk Behavior

International borders are unique social and environmental contexts characterized by high levels of mobility. Among drug users, mobility increases risk for human immunodeficiency virus (HIV) in part through its effects on the social environment. However, the social dynamics of drug users living in border regions are understudied. 1056 injection drug users (IDUs) residing in Tijuana, Mexico were recruited using respondent-driven sampling (RDS) from 2006 to 2007, and underwent surveys and testing for HIV, syphilis, and tuberculosis (TB). Using logistic regression on baseline data, correlates of having ever injected drugs with someone from the US were identified. Almost half (48%) reported ever injecting drugs with someone from the US. In RDS-adjusted logistic regression, factors independently associated with having ever injected with someone from the US included: having greater than middle school education (Adjusted Odds Ratio [AOR] 2.91; 95% confidence interval [C.I.] 1.52, 5.91), speaking English (AOR 3.24, 95% C.I. 1.96, 5.36), age (AOR 1.10 per year; 95% C.I. 1.07, 1.14), age at initiation of injection drug use (AOR 0.90 per year; 95% C.I. 0.86, 0.94), homelessness (AOR 2.61; 95% C.I. 1.27,

5.39), and having ever been incarcerated (AOR 11.82; 95% C.I., 5.22, 26.77). No associations with HIV, syphilis, TB, drug use, or injection risk behavior were observed. Findings suggest that IDU networks in Mexico and the US may transcend international borders, with implications for cross-border transmission of infectious disease. Binational programs and policies need to consider the structure and geographic distribution of drug using networks. Wagner K, Pollini R, Patterson T, Lozada R, Ojeda V, Brouwer K, Vera A, Volkmann T, Strathdee S. Cross-border drug injection among injection drug Users In Tijuana, Mexico. *Drug Alcohol Depend.* 2011; 113 (2-3): 236-241.

Latent TB among Persons At-Risk for HIV Infection

Because there is little routine tuberculosis (TB) screening in Mexico, the prevalence of latent TB infection (LTBI) is unknown. In the context of an increasing HIV epidemic in Tijuana, Mexico, understanding prevalence of LTBI to anticipate emergence of increased LTBI reactivation is critical. Therefore, injection drug users, noninjection drug users, female sex workers, and homeless persons were recruited for a study involving risk assessment, rapid HIV testing, and TB screening. Of 503 participants, the overall prevalences of TB infection, HIV infection, and TB/HIV co-infection were 57%, 4.2%, and 2.2%, respectively; no significant differences by risk group ($p > 0.05$) were observed. Two participants had TB (prevalence 398/100,000). Incarceration in Mexico (odds ratio [OR] 2.28), age (OR 1.03 per year), and years lived in Tijuana (OR 1.02 per year) were independently associated with TB infection ($p < 0.05$). Frequent LTBI in marginalized persons may lead to increases in TB as HIV spreads. Garfein R, Laniado-Laborin R, Rodwell T, Lozada R, Deiss R, Burgos J, Cuevas-Mota J, Cerecer P, Moser K, Volker M, Strathdee S. Latent tuberculosis among persons at risk for infection with HIV, Tijuana, Mexico. *Emerg Infect Dis.* 2010; 16 (5): 757-763.

Microtrial Methods for Translating Gene-Environment Dynamics into Preventive Interventions

Genetically informed research on behavioral outcomes holds substantial promise for guiding efforts to enhance the efficacy and effectiveness of preventive interventions, but it also poses considerable challenges given the complexities of the dynamic interplay between genes and environment. This paper introduces a relatively uncommon research design, called microtrials, to provide a means of translating basic research findings into prevention trials, particularly through introducing genetic effects into prevention models. Microtrials are defined as randomized experiments testing the effects of relatively brief and focused environmental manipulations designed to suppress specific risk mechanisms or enhance specific protective mechanisms, but not to bring about full treatment or prevention effects in distal outcomes. Microtrial methods are described in detail, with discussion of their unique advantages for translating this knowledge base into prevention research. Several important issues to consider when constructing genetically sensitive microtrials are raised. Howe G, Beach S, Brody G. Microtrial methods for translating gene-environment dynamics into preventive interventions. *Prev Sci.* 2010; 11 (4): 343-354.

Advancing Prediction of Foster Placement Disruption using Brief Behavioral Screening

Behavioral difficulties increase the risk that children will experience negative placement disruptions while in foster care. Chamberlain et al. (2006) found that the Parent Daily Report (PDR), a brief measure of parent-reported child behaviors, was a strong predictor of negative placement changes over 1 year among children receiving 'usual case work' services. This paper sought to

replicate and extend original findings regarding the PDR among 359 foster parents participating in a group parent-training intervention. Foster parents of children experiencing a recent foster placement and taking part in the KEEP parenting program were included in analyses. Foster parents completed 16 weekly PDR calls about the behavior of a foster child in their care during the KEEP intervention and about their stress related to the child's behaviors. Multiple strategies, including latent class analysis of weekly PDR counts and continuous moving averages of PDR counts over shorter time frames, were used to test improvements in prediction of negative placement changes. Consistent with prior findings, children with elevated PDR ratings and children living with non-relative foster parents had significantly higher levels of negative placement disruptions. Prediction improved with decision rules relying upon increased amounts of weekly PDR information, although good prediction was achieved with 3-5 weeks of PDR information. Parent-reported stress associated with behavior did not improve prediction. This study confirmed the potential utility of the PDR as a predictor of negative placement changes and illustrates how longitudinal PDR information may aid in improving such prediction. Potential applications of the PDR for improving the timing, type, and quantity of services offered to help foster parents prevent placement disruptions are discussed. Hurlburt MS, Chamberlain P, DeGarmo D, Zhang J, Price JM. Advancing prediction of foster placement disruption using brief behavioral screening. *Child Abuse Negl.* 2010; 34 (12): 917-926.

A Statistical Model for Evaluating Differences in Time Varying Interventions

This paper presents a novel model predictive control (MPC) formulation for linear hybrid systems. The algorithm relies on a multiple-degree-of-freedom formulation that enables the user to adjust the speed of set-point tracking, measured disturbance rejection and unmeasured disturbance rejection independently in the closed-loop system. Consequently, controller tuning is more flexible and intuitive than relying on move suppression weights as traditionally used in MPC schemes. The formulation is motivated by the need to achieve robust performance in using the algorithm in emerging applications, for instance, as a decision policy for adaptive, time-varying interventions used in behavioral health. The proposed algorithm is demonstrated on a hypothetical adaptive intervention problem inspired by the Fast Track program, a real-life preventive intervention for improving parental function and reducing conduct disorder in at-risk children. Simulation results in the presence of simultaneous disturbances and significant plant-model mismatch are presented. These demonstrate that a hybrid MPC-based approach for this class of interventions can be tuned for desired performance under demanding conditions that resemble participant variability that is experienced in practice when applying an adaptive intervention to a population. Nondola NN, Rivera DE. A novel model predictive control formulation for hybrid systems with application to adaptive behavioral interventions. *Proc Am Control Conf.* 2010; 6286-6292.

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

Research Findings - Behavioral and Integrative Treatment Research

Critical Review of HIV Prevention Interventions for Adolescents in Juvenile Justice Settings

The objective of this study was to conduct a critical review of all HIV prevention intervention studies conducted with adolescents in juvenile justice settings to inform future intervention development. PubMed and PsycInfo database searches were conducted for peer-reviewed, published HIV prevention intervention studies with juvenile offenders. Sixteen studies were identified (N=3,700 adolescents). Half of the projects utilized rigorous methodologies to determine intervention effect on behavior change, such as conducting a randomized controlled trial (n=8). Nine studies reported behaviors at least 3 months post-intervention and five out of nine showed decreases in sexual risk behavior. Several HIV prevention programs with juvenile offenders have led to sexual risk reduction, although effect sizes are modest. Most existing programs have neglected to address the impact of family, mental health, and substance use on HIV risk. More work is needed to develop evidence-based interventions that include HIV prevention strategies relevant and appropriate for the juvenile justice setting. Tolou-Shams M, Stewart A, Fasciano J, Brown LK. A review of HIV prevention interventions for juvenile offenders. *J Pediatr Psychol*. 2010 Apr; 35(3): 250-261.

Mother-Child Discrepancies in Perceptions of Mother's Aggression: Implications for Children of Methadone-Maintained Mothers

Despite a long history of documenting discrepancies in parent and child reports of parental care and child psychopathology, it has only been in recent years that researchers have begun to consider these discrepancies as meaningful indicators of parent-child relationship quality and as predictors of long-term child adjustment. Discrepancies in perceptions of parenting may be particularly important for the children of mothers with a history of substance abuse who may be less aware of the impact of their behavior on their child and of their child's internalizing symptoms. This study examined associations between (a) mother-child discrepancies in reports of maternal aggression, and (b) mother and child reports of child internalizing and externalizing symptoms. Data collected from 99 mother-child dyads (with children 4-16 years of age) during the baseline phase of a randomized clinical trial testing a parenting intervention were used in this study. Measures included parent and child versions of the Parental Acceptance-Rejection Questionnaire and the Behavioral Assessment Scale for Children. Findings indicated that as children viewed their mothers as increasingly more aggressive than mothers viewed themselves, children reported more internalizing and externalizing symptoms but mothers only

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reported more child externalizing symptoms. Mother-child discrepancies in reports of parenting behavior have potentially meaningful implications for child emotional and behavioral problems. Borelli JL, Luthar SS, Suchman NE. Discrepancies in perceptions of maternal aggression: implications for children of methadone-maintained mothers. *Am J Orthopsychiatry*. 2010 Jul; 80(3): 412-421.

Review of Pharmacological and Psychosocial Interventions for Cannabis Use Disorders

Cannabis remains the most widely used illicit substance in most developed countries. Its addictive potential has been established and the need for interventions for cannabis-related problems has become apparent. This article provides a review of the research evaluating potential treatments for cannabis use disorders. A search of publication databases identified research studies and reviews of the scientific literature on psychosocial and pharmacological interventions for cannabis use disorders. For adults, behaviorally-based interventions engender significant positive effects on abstinence and reductions in cannabis use. With adolescents, similar treatments and family-based interventions have demonstrated efficacy. Across studies, response rates appear modest even with the most potent psychosocial treatments. Evaluations of pharmacological approaches to cannabis use disorders have yet to provide clinical efficacy data for any specific medication. Agonist and antagonist approaches appear to offer the most promise. Advances in understanding of the neurobiology of the cannabinoid system provide optimism that the synthesis of compounds that alter CB1 receptor site functioning may produce promising medications. Clinical research has identified effective psychosocial treatments, but has yet to yield effective pharmacotherapies. Much work remains to enhance the potency of and access to interventions for those seeking treatment for cannabis use disorders. Budney AJ, Vandrey RG, Stanger C. Pharmacological and psychosocial interventions for cannabis use disorders. Article in Portuguese. *Rev Bras Psiquiatr*. 2010 May; 32 Suppl 1: S46-55.

Traumatic Event History and the Non-Medical Use of Prescription Drugs by Adolescents

The current study examined prevalence and correlates of non-medical use of prescription drugs (NMUPD), with particular emphasis on lifetime history of rape and PTSD as risk associates. Interviews were conducted via telephone using Computer-Assisted Telephone Interviewing technology, resulting in a nationally representative sample of 3001 non-institutionalized, civilian, English or Spanish speaking women (aged 18-86 years) residing in households with a telephone. Demographic characteristics, rape history, general health/mental health, and substance abuse variables were assessed. NMUPD was assessed by asking if, in the past year, participants had misused a prescription drug. Multivariable logistic regressions were conducted for each theoretically derived predictor set. Significant predictors from each set then entered into final multivariable logistic regression to determine significant predictors of past-year NMUPD. NMUPD was endorsed by 5.5% of the sample (n=164). Final multivariable model showed that Lifetime Posttraumatic Stress Disorder, other forms of substance use/abuse, and a history of drug or alcohol facilitated rape were significantly associated with increased likelihood of NMUPD. Risk reduction efforts targeting nonmedical prescription drug use among women who have experienced traumatic events and/or abuse substances are warranted. Trauma-focused interventions for drug or alcohol facilitated rape victims should include treatment or prevention modules that specifically address NMUPD. McCauley JL, Danielson CK, Amstadter AB, Ruggiero KJ, Resnick HS, Hanson RF, Smith DW, Saunders BE, Kilpatrick DG. The role of traumatic event history in non-medical use of prescription drugs among a nationally representative sample of US adolescents. *J Child Psychol Psychiatry*. 2010 Jan; 51(1): 84-93.

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Brief Motivational Intervention Reduced Marijuana Use by Young Women Not Seeking Treatment

The authors randomized 332 women, 18-24 years old, who were not explicitly seeking treatment for their marijuana use to either a two-session motivationally focused intervention or an assessment-only condition. Assessed by timeline follow-back methodology, participants reported using marijuana 57% of days in the 3 months prior to study entry. Intervention effects on the likelihood of marijuana use were not statistically significant at 1 month (odds ratio [OR] = 0.77, $p = .17$), significant at 3 months (OR = 0.53, $p = .01$), and no longer significant at 6 months (OR = 0.74, $p = .20$). Among the 61% of participants endorsing any desire to quit using marijuana at baseline, significant intervention effects on the likelihood of marijuana use days were observed at 1 month (OR = 0.42, $p = .03$), 3 months (OR = 0.31, $p = .02$), and 6 months (OR = 0.35, $p = .03$). A two-session brief motivational intervention reduced marijuana use among young women not seeking treatment. Women with a desire to quit showed a greater and more durable response. Stein MD, Hagerty CE, Herman DS, Phipps MG, Anderson BJ. A brief marijuana intervention for non-treatment-seeking young adult women. *J Subst Abuse Treat.* 2011 Mar; 40(2): 189-198.

Three Subtypes of Female Marijuana Users

This study sought to empirically derive marijuana user subtypes based on DSM abuse and dependence criteria and examine demographic and substance abuse distinctions of derived classes. A community sample of 308 female marijuana users between the ages of 18 and 24 were recruited in the Southern New England region. Latent class analysis was used to derive subgroups based on DSM criteria. The use and demographic characteristics of classes were further analyzed using analysis of variance and the chi-square test. Based on fit criteria, a three-class solution was selected. Class I (37%)—an "unaffected/mild" group—was characterized by very low endorsement rates of abuse and dependence criteria. This class was also found to have significantly lower rates of other substance use problems. Class II (41.6%)—"moderate problem users"—showed moderate endorsement rates of abuse and dependence criteria. Class III (21.4%)—"severe problem users"—showed the greatest levels of abuse and dependence, with 90% meeting DSM criteria for abuse and 100% meeting diagnostic criteria for marijuana dependence. Class III also showed the greatest levels of other substance use problems. Three distinct marijuana abuse and dependence subtypes were derived using latent class analysis. Findings may have implications for the development of more targeted treatment and prevention interventions for young women struggling with varying degrees of marijuana abuse and dependence. de Dios MA, Anderson BJ, Herman DS, Hagerty CE, Caviness CM, Budney AJ, Stein M. Marijuana use subtypes in a community sample of young adult women. *Womens Health Issues.* 2010 May-Jun; 20(3): 201-210.

Exposure to "In Vivo" Marijuana Cues Increased Craving and Skin Conductance Reactivity Among Treatment-Seeking Cannabis-Dependent Adolescents

Cannabis dependence is a common but poorly understood condition in adolescents. Marijuana craving has been posited as a potential contributing factor to continued use and relapse, but relatively few studies have focused on the measurement of craving and reactivity to marijuana cues. The present work sought to explore reactivity to marijuana cues within this age group. Thirty treatment-seeking cannabis-dependent adolescents (age 13-20) completed a cue reactivity session, consisting of exposure to and manipulation

of in vivo marijuana cues ("joint" and lighter) and matching neutral cues (pencil and eraser), in counterbalanced order. Subjective craving and physiological reactivity were assessed. Participants demonstrated increased craving and skin conductance reactivity in response to marijuana cues, relative to neutral cues. In vivo marijuana cues appear to elicit significant subjective and physiological reactivity among treatment-seeking cannabis-dependent adolescents. Further work is needed with a larger sample and with a wider variety of cues. Gray KM, LaRowe SD, Watson NL, Carpenter MJ. Reactivity to in vivo marijuana cues among cannabis-dependent adolescents. *Addict Behav.* 2011 Jan-Feb; 36(1-2): 140-143.

Risky Behaviors and Depression in Adolescents with Sexual Abuse Histories

Posttraumatic stress disorder (PTSD) is often considered the primary problematic outcome of child sexual abuse (CSA). However, a number of other, relatively understudied negative sequelae appear to be prevalent as well. Data from 269 adolescents with a CSA history from the National Survey of Adolescents-Replication study were therefore used to examine the prevalence of risky behaviors (i.e., problematic alcohol and drug use, delinquent behavior) and depression in this sample. The frequencies of these problems in youth with and without a history of PTSD also were examined. Results indicated that risky behaviors and depression were reported as or more frequently than PTSD. Among youth with a history of PTSD, depression and delinquent behavior were more common than among those without a history of PTSD. However, there were no differences between adolescents with and without a history of PTSD in reported problematic substance use. Findings highlight the need for comprehensive trauma-informed interventions for CSA-exposed adolescents. Danielson CK, Macdonald A, Amstadter AB, Hanson R, de Arellano MA, Saunders BE, Kilpatrick DG. Risky behaviors and depression in conjunction with--or in the absence of--lifetime history of PTSD among sexually abused adolescents. *Child Maltreat.* 2010 Feb; 15(1): 101-107.

Expectancies and Self-Efficacy Mediate the Effects of Impulsivity on Marijuana Use Outcomes

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

marijuana use outcomes: an application of the acquired preparedness model. *Addict Behav.* 2011 Apr; 36(4): 389-396.

Improving Treatment Adherence in Patients with Bipolar Disorder and Substance Abuse: Rationale and Initial Development of a Novel Psychosocial Approach

Patients with comorbid bipolar and substance use disorders are at particularly high risk for treatment nonadherence and a host of negative consequences. However, no previous interventions have been designed specifically to address this problem. In the current study, the authors describe the rationale for and initial development of an adjunctive psychosocial intervention that targets adherence in patients with bipolar disorder who are substance abusers. The intervention involves brief in-person sessions and follow-up phone contacts with the patient and a significant other/family member. The authors describe the effects of this novel intervention on adherence and other psychiatric outcomes in a series of cases treated as part of our initial development work. Results suggest that the intervention is feasible and acceptable to patients and could be helpful in enhancing the effects of existing treatments. Given these promising results, they plan to test the intervention further in a randomized clinical trial. Gaudio BA, Weinstock LM, Miller IW. Improving treatment adherence in patients with bipolar disorder and substance abuse: Rationale and initial development of a novel psychosocial approach. *J Psychiatr Pract.* 2011 Jan; 17(1): 5-20.

Homeless MSM with Substance Dependence Discount Delayed Rewards More than Housed Non Substance Abusing MSM

Impulsivity is associated with substance use; however, to date, impulsivity has not been characterized among a sample of homeless, non-treatment seeking, substance-dependent men who have sex with men (MSM). The aim of this study was to utilize the delay-discounting instrument to assess impulsive behaviors among a subsample of homeless, non-treatment seeking, substance-dependent men who have sex with men (S-D MSM) enrolled in a randomized, controlled, contingency management (CM) trial. Twenty S-D MSM participants from the CM parent study were matched on age and ethnicity to 20 non-substance-dependent, non-homeless control participants using propensity scores (N=40) and were administered the delay-discounting procedure. Although discounting values decreased rapidly with time in both groups, the S-D MSM participants consistently discounted rewards more steeply than controls ($p=.05$), particularly at all intermediate measured timeframes. The S-D MSM participants also presented greater median discounting rates (k values) compared with the control group ($m(S-D\ MSM)=2.39$ ($SD=3.72$) vs. $m(ctrl)=1.27$ ($SD=3.71$), $p=.01$). This work extends existing findings of increased delay-discounting among substance-dependent individuals to homeless, substance-dependent, non-treatment seeking MSM. The authors conclude that a better understanding of the prevalence of delay-discounting type behaviors among homeless, substance-dependent MSM can be used to inform the development of tailored substance abuse interventions for this high-risk population. Dierst-Davies R, Reback CJ, Peck JA, Nuno M, Kamien JB, Amass L. Delay-discounting among homeless, out-of-treatment, substance-dependent men who have sex with men. *The American Journal of Drug And Alcohol Abuse.* 2011 Mar; 37(2): 93-97.

Costs and Cost-effectiveness of Three Types of Motivational Interviewing Training

The objective of this study was to evaluate the cost and cost-effectiveness of three strategies for teaching community program clinicians motivational

interviewing (MI): self-study (SS), expert-led (EX), and train-the-trainer (TT). This economic analysis was conducted as part of a three-arm clinician training trial comprising 12 community treatment programs randomly assigned to the three conditions (n=92 clinician participants). EX and TT conditions used skill-building workshops and three monthly supervision sessions. SS provided clinicians MI training materials only. The primary outcome measure was the number of clinicians meeting MI performance standards at 12-week follow-up. Unit costs were obtained via surveys administered at the 12 participating programs. Resource utilizations and clinician outcomes were obtained from the training trial. Costs and outcomes were normalized to account for differing numbers of clinicians across programs and conditions. Incremental cost-effectiveness ratios and cost-effectiveness acceptability curves were used to evaluate the relative cost-effectiveness of the three training strategies. Results indicated that SS is likely to be the most cost-effective training strategy if the threshold value to decision makers of an additional clinician meeting MI performance standards at 12-week follow-up is less than approximately \$2,870, and EX is likely to be the most cost-effective strategy when the threshold value is greater than approximately \$2,870. This study provides accurate estimates of the economic costs and relative cost-effectiveness of three different strategies for training community program clinicians in motivational interviewing and should be of interest to decision makers seeking to implement empirically supported addiction treatments with scarce resources. Olmstead T, Carroll KM, Canning-Ball M, Martino S. Cost and cost-effectiveness of three strategies for training clinicians in motivational interviewing. *Drug Alcohol Depend.* 2011 Jan. [Epub ahead of print].

Money Management Therapy Increases Value of Future Rewards

A positive association between delay discounting and substance use has been documented; substance users tend to discount future rewards more than non-users. However, studies detailing the responsiveness of delay discounting to interventions are lacking, and few have examined how any behavioral intervention affects delay discounting and whether these effects moderate changes in substance abuse. This study assesses the effectiveness of a money management intervention, Advisor-Teller Money Manager (ATM), in reducing delay discounting over time and the relationship of these effects to changes in cocaine use. Ninety psychiatric patients with histories of cocaine and/or alcohol use were randomly assigned to 36-weeks of ATM treatment or to a minimal-attention control condition. Delay discounting and cocaine use were measured throughout the intervention with a 52-week follow up measure of cocaine use. Analyses were conducted of (a) the effect of ATM on slopes of delay discounting and cocaine abstinence and (b) the relationship between change in delay discounting and change in cocaine abstinence. The ATM intervention was associated with significantly less delay discounting and less cocaine use over time relative to controls. Increases in delay discounting were associated with decreased abstinence from cocaine. ATM treatment decreased delay discounting rates and these effects extended to cocaine use. Concrete conceptualizations of future events, as occur in financial planning, with higher perceived probability may account for higher valuation of future rewards in counseled patients. Black AC, Rosen MI. A money management-based substance use treatment increases valuation of future rewards. *Addict Behav.* 2011 Jan-Feb; 36(1-2): 125-128.

Computer Treatments Promising but Not Used without Incentives

Computerized therapy approaches may expand the reach of evidence-based treatment; however, it is unclear how to integrate these therapies into community-based treatment. The authors conducted a two-phase pilot study to explore (a) whether clients' use of the Therapeutic Education System (TES), a Web-based community reinforcement approach (CRA) learning program, would

benefit them in the absence of counselor support and (b) whether counselors and clients would use the TES in the absence of tangible research-based reinforcement. In Phase 1, clients in the TES condition ($n = 14$) demonstrated large improvements in knowledge, $F(1, 20) = 8.90$, $p = .007$, $d = 1.05$, and were significantly more likely to select CRA style coping responses, $F(1, 20) = 11.95$, $p = .002$, $d = 1.16$, relative to the treatment-as-usual group ($n = 14$). The authors also detected small, nonsignificant, between-group effects indicating TES decreased cocaine use during treatment. In Phase 2, counselors referred only around 10% of their caseload to the TES, and the modal number of completed modules in the absence of tangible reinforcement was three. Computer-based therapy approaches are viable in community-based treatment but must be integrated with incentive systems to ensure engagement. Brooks AC, Ryder D, Carise D, Kirby KC. Feasibility and effectiveness of computer-based therapy in community treatment. *J Subst Abuse Treat.* 2010 Oct; 39(3): 227-235.

Longer Duration of Vouchers Promising as Possible Maintenance Intervention

The objective of this study was to determine whether longer durations of voucher-based reinforcement therapy (VBRT) increase long-term abstinence compared to standard durations. Cocaine-abusing or dependent methadone-maintenance patients ($N = 130$) were randomized to receive either Standard (12-week; $n = 62$) or Extended (36-week; $n = 68$) VBRT. Participants provided 3 urine samples weekly during VBRT, and each cocaine-negative sample produced a voucher exchangeable for goods and services. Extended VBRT produced longer durations of self-reported continuous abstinence during study Year 1 ($M = 74$ vs. 46 days; $F(1,128) = 5.23$, $P = 0.024$), but not during Year 2. However, each week of abstinence during Year 1 was associated with an increase of 9.19 days of abstinence during Year 2, regardless of study condition ($t(1) = 4.92$, $P < 0.001$). Longer-duration VBRT can increase abstinence during VBRT, but may not maintain it afterwards. However, longer during-treatment abstinence begets later abstinence suggesting that further research regarding this relationship is needed. Carpenedo CM, Kirby KC, Dugosh KL, Rosenwasser BJ, Thompson DL. Extended voucher-based reinforcement therapy for long-term drug abstinence. *Am J Health Behav.* 2010 Nov-Dec 34(6): 776-787.

Family and Individual Factors Associated with Substance Involvement and PTS Symptoms among Adolescents in Greater New Orleans after Hurricane Katrina

This study examined the influence of hurricane impact as well as family and individual risk factors on posttraumatic stress (PTS) symptoms and substance involvement among clinically referred adolescents affected by Hurricane Katrina. A total of 80 adolescents (87% male; 13-17 years old; mean age = 15.6 years; 38% minorities) and their parents were interviewed at the adolescent's intake into substance abuse treatment, 16 to 46 months post disaster. Independent measures included hurricane impact variables (initial loss/disruption and perceived life threat); demographic and predisaster variables (family income, gender, predisaster adolescent substance use, predisaster trauma exposure, and parental substance abuse); postdisaster family factors (parental psychopathology, family cohesion, and parental monitoring); and postdisaster adolescent delinquency. Hierarchical multivariate regression analyses showed that adolescent substance involvement was associated with higher family income, lower parental monitoring (adolescent report), and more adolescent delinquency. Adolescent-reported PTS symptoms were associated with greater hurricane-related initial loss/disruption, lower family cohesion (adolescent report), and more adolescent delinquency, whereas parent-reported adolescent PTS symptoms were associated with greater parental psychopathology, lower parental monitoring (adolescent

report), and lower family cohesion (parent report). The results suggest that hurricane impact was related only to adolescent-reported PTS. However, certain postdisaster family and individual risk factors (low family cohesion and parental monitoring, more adolescent delinquency) were associated both with adolescent substance involvement and with PTS symptoms. Identification of these factors suggests directions for future research as well as potential target areas for screening and intervention with substance-abusing adolescents after disasters. Rowe CL, La Greca AM, Alexandersson A. Family and individual factors associated with substance involvement and PTS symptoms among adolescents in greater New Orleans after Hurricane Katrina. *J Consult Clin Psychol*. 2010 Dec; 78(6): 806-817.

Lower Task Persistence in Smokers with Schizophrenia as Compared to Non-Psychiatric Control Smokers

One contributing factor to difficulty in quitting smoking may be task persistence, which can be viewed as a behavioral manifestation of distress tolerance, and describes the act of persisting in a difficult or effortful task. Task persistence was assessed in smokers with schizophrenia and schizoaffective disorder (SZ/SA; N = 71) and non-psychiatric controls (N = 78) before a quit attempt. These data support the hypothesis that smokers with SZ/SA display less task persistence than do non-psychiatric controls when persistence is measured via mirror tracing and a 2-item persistence measure. Lower persistence may partially explain the reduced smoking cessation successes of smokers with SZ/SA as compared to the general population. These data also replicate findings regarding relationships between histories of ability to quit smoking and task persistence and expand them to a new population of smokers. The absence of a diagnostic status by length of previous abstinence interaction suggests that the contribution of task persistence to smoking cessation is similar for smokers with and without schizophrenia. Future studies should evaluate the ability of task persistence to predict abstinence from cigarettes prospectively among smokers with schizophrenia. Steinberg ML, Williams JM, Gandhi KK, Foulds J, Brandon TH. Lower task persistence in smokers with schizophrenia as compared to non-psychiatric control smokers. *Psychol Addict Behav*. 2010 Dec; 24(4): 724-729.

A Review of Computer-Based Interventions Used in the Assessment, Treatment, and Research of Drug Addiction

Computer-based interventions are cost-efficient methods that may result in greater access to drug addiction treatment. The authors review recent findings from their laboratory where computer-based interventions have produced outcomes that are comparable to therapist-delivered interventions. They also examine how computer-based interventions targeting substance abuse disorders relate to cognitive functioning. This review will suggest that not only are computer-based interventions cost-efficient and accessible but that they are also effective methods for the motivation, engagement, and treatment of drug-dependent individuals. Moreover, computer-based interventions are compatible with a recently proposed biological mechanism implicated as the basis for drug addiction. Bickel WK, Christensen DR, Marsch LA. A review of computer-based interventions used in the assessment, treatment, and research of drug addiction. *Subst Use Misuse*. 2011; 46(1): 4-9.

Integrated Smoking Cessation and Binge Drinking Intervention for Young Adults: A Pilot Investigation

Alcohol consumption is strongly associated with cigarette smoking in young adults. The aim of this study was to evaluate the acceptability and estimate the magnitude of the effect of a novel-integrated smoking cessation and binge-

drinking intervention for young adults compared with standard treatment control. Participants were 41 young adult smokers (10 cigarettes per day) who regularly (2 times per month) binge drank who were randomly assigned to standard treatment (n = 19) involving eight individual treatment visits plus 8 weeks of nicotine patch therapy or the identical smoking cessation treatment integrated with a binge-drinking intervention (integrated intervention; n = 22). Participants rated integrated intervention as highly acceptable as indicated by 100% of participants rating helpfulness as 5 on 5-point scale. Using an intent-to-treat analysis for tobacco abstinence, at both week 12 end of treatment and week 24 follow-up, more participants who received integrated intervention were biochemically confirmed abstinent from tobacco than those who received standard treatment (36% vs. 21% at week 12; 23% vs. 11% at week 24). At week 24, change from baseline in binge-drinking episodes, drinks consumed, and drinking days between treatment groups were similar (intent-to-treat analysis was not used for alcohol data). Preliminary data support the intriguing possibility that integrated intervention may enhance smoking cessation and reduce binge drinking. Integrated smoking cessation and binge drinking intervention for young adults: a pilot investigation. Ames SC, Werch CE, Ames GE, Lange LJ, Schroeder DR, Hanson AC, Patten CA. *Ann Behav Med.* 2010 Dec; 40(3): 343-349.

Bupropion SR and Contingency Management for Adolescent Smoking Cessation

There is a significant need for evidence-based treatments for adolescent smoking cessation. Prior research, although limited, has suggested potential roles for bupropion sustained-release (SR) and contingency management (CM), but no previous studies have assessed their combined effect. In a double-blind, placebo-controlled design, 134 adolescent smokers were randomized to receive a 6-week course of bupropion SR + CM, bupropion SR + non-CM, placebo + CM, or placebo + non-CM, with final follow-up at 12 weeks. The primary outcome was 7-day cotinine-verified point prevalence abstinence, allowing for a 2-week grace period. Combined bupropion SR + CM treatment yielded significantly superior abstinence rates during active treatment when compared with placebo + non-CM treatment. In addition, combined treatment showed greater efficacy at multiple time points than did either bupropion SR + non-CM or placebo + CM treatment. Combined bupropion SR and CM appears efficacious, at least in the short-term, for adolescent smoking cessation and may be superior to either intervention alone. Gray KM, Carpenter MJ, Baker NL, Hartwell KJ, Lewis AL, Hiott DW, Deas D, Upadhyaya HP. Bupropion SR and contingency management for adolescent smoking cessation. *J Subst Abuse Treat.* 2011 Jan; 40(1): 77-86.

"Everyone Deserves Services No Matter What": Defining Success in Harm-Reduction-Based Substance User Treatment

This article reports qualitative interview data from a study of participant-generated outcomes of two harm reduction programs in the United States. The authors address the question: "What does success in harm-reduction-based substance user treatment look like?" Providers in this study understood harm reduction to adhere to notions of "any positive change," client centeredness, and low-threshold services. Participants reported changes in demarginalization, engagement in the program, quality of life, social functioning, changes in substance use, and changes in future goals and plans. The nature of these changes is difficult to articulate within traditional notions of success (i.e., abstinence, program completion, etc.). The authors conclude that participants in harm reduction programs experience tangible positive changes but that legitimization of these changes calls for a reconceptualization of "outcomes" and "success" in the current context of substance user treatment and research. Lee HS, Zerai A. Everyone deserves services no matter what: Defining success in

harm-reduction-based substance user treatment. *Subst Use Misuse*. 2010 Dec; 45(14): 2411-2427.

Weight Concerns, Mood, and Postpartum Smoking Relapse

The majority of women who quit smoking as a result of pregnancy will resume smoking during the first 6 months postpartum. Evidence suggests that changes in depressive symptoms, perceived stress, and concerns about weight may relate to postpartum smoking relapse. This study was designed to prospectively evaluate the relationship of mood and weight concerns to postpartum smoking among women who quit smoking during pregnancy. Pregnant women who had quit smoking (N=183) were recruited between February 2003 and November 2006. Women completed assessments of mood (depressive symptoms, perceived stress, positive and negative affect) and weight concerns during the third trimester of pregnancy and at 6, 12, and 24 weeks postpartum. Self-reported smoking status was verified by expired-air carbon monoxide and salivary cotinine at each assessment. Cox regression analyses in which mood and weight concerns were treated as time-dependent covariates were conducted in 2007 and 2009. By 24 weeks postpartum, 65% of women had resumed smoking. Smoking-related weight concerns increased risk of relapse, and positive affect and self-efficacy for weight management without smoking decreased risk of relapse postpartum. Moreover, after controlling for variables previously related to postpartum relapse, weight concerns remained significantly related to smoking relapse. Smoking-related weight concerns and positive affect increase the likelihood that a woman will resume smoking postpartum. Moreover, weight concerns appear to be salient even in the context of other factors shown to affect postpartum smoking. This study suggests that interventions may need to address women's weight concerns and mood to help sustain smoking abstinence after childbirth. Levine MD, Marcus MD, Kalarchian MA, Houck PR, Cheng Y. Weight concerns, mood, and postpartum smoking relapse. *Am J Prev Med*. 2010 Oct; 39(4): 345-351.

Intentions to Quit Smoking: Causal Attribution, Perceived Illness Severity, and Event-Related Fear During an Acute Health Event

Experiencing a serious consequence related to one's health behavior may motivate behavior change. This study sought to examine how causal attribution, perceived illness severity, and fear secondary to an acute health event relate to intentions to quit smoking. Using a cross-sectional survey design, adult emergency department patients who smoked provided demographic data and ratings of nicotine dependence, causal attribution, perceived illness severity, event-related fear, and intentions to quit smoking. A linear regression analysis was used to examine the relations between the independent variables and quit intentions. The authors enrolled 186 participants. After adjusting for nicotine dependence, smoking-related causal attribution and event-related fear were associated with intentions to quit ($B = 0.26$, $p < 0.01$ and $B = 0.21$, $p < 0.01$, respectively). Perceived illness severity was correlated with event-related fear ($r = 0.46$, $p < 0.001$) but was not associated with intentions to quit ($B = -0.08$, $p = 0.32$). While causal attribution and event-related fear were modestly associated with quit intentions, perceived illness severity was not. Longitudinal studies are needed to better explicate the relation between these variables and behavior change milestones. Intentions to quit smoking: causal attribution, perceived illness severity, and event-related fear during an acute health event. Boudreaux ED, Moon S, Baumann BM, Camargo CA Jr, O'Hea E, Ziedonis DM. *Ann Behav Med*. 2010 Dec; 40(3): 350-355.

A Population-Based Examination of Cigarette Smoking and Mental Illness in Black Americans

This study examines the relation between tobacco use and cessation with lifetime and past year mental illness in a nationally representative sample of Blacks. This cross-sectional study analyzed nationally representative data from 3,411 adult Blacks participating in the 2001-2003 National Survey of American Life. Smoking prevalence and quit rates according to lifetime and past year Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition mental disorders were assessed by a modified version of the Composite International Diagnostic Interview. Compared with those without mental illness, respondents with a lifetime, past year, or past month mental illness had a higher smoking prevalence (20.6%, 35.6%, 36.0%, and 45.4%, respectively) and lower quit rate (40.5%, 31.2%, and 26.2%, respectively). The odds of being a current smoker among Blacks with mental illness in their lifetime, past year, and past month, after adjusting for age, gender, education, poverty, and marital status were 1.76 (95% CI = 1.39-2.22), 1.57 (95% CI = 1.22-2.03), and 2.20 (95% CI = 1.56-3.12), respectively. Mental illness also was associated with heavier smoking. Blacks with past year mental illness represented 18.1% of the sample, yet consumed 23.9% of cigarettes smoked by Black smokers. Past year (odds ratio [OR] = 0.72, 95% CI = 0.53-0.97) and past month (OR = 0.54, 95% CI = 0.29-0.98) mental illness were associated with a lower odds of quitting for at least 1 year. Findings indicate that mental illness is significantly associated with tobacco use in Blacks. Tobacco cessation interventions that address mental illness as a barrier to cessation are needed. Hickman NJ 3rd, Delucchi KL, Prochaska JJ. A population-based examination of cigarette smoking and mental illness in Black Americans. *Nicotine Tob Res.* 2010 Nov; 12(11): 1125-1132.

Moderation of Gender on Smoking and Depression in Chinese Americans

This study examined the moderating role of gender in the association between smoking status and depression in a nationwide convenience sample of Chinese American current, former, and never smokers (N=1393). Participants were recruited in smoker-supporter dyads. Multilevel modeling was used to take into account the dyadic nature of the data. Depressive symptoms were measured by a 10-item CES-D (Center of Epidemiological Studies-Depression Scale). Results showed significant effects of smoking status by gender interaction and smoking status on depression after adjusting for acculturation and social support. Among Chinese females, current smokers reported elevated depression level than both former and never smokers. Among Chinese males, current smokers reported more depressive symptoms when compared to former smokers only. Chinese females reported higher depression level than males among current smokers; no gender difference in depression was observed among former or never smokers. The association between smoking and depression is moderated by gender among Chinese Americans where substantial gender difference in smoking prevalence exists. Findings highlight the importance of addressing depression in treating tobacco use among Chinese American smokers, especially among females. Luk JW, Tsoh JY. Moderation of gender on smoking and depression in Chinese Americans. *Addict Behav.* 2010 Nov; 35(11): 1040-1043.

Using Treatment Process Data to Predict Maintained Smoking Abstinence

The objective of this study was to identify distinct subgroups of treatment responders and nonresponders to aid in the development of tailored smoking-cessation interventions for long-term maintenance using signal detection analysis (SDA). The secondary analyses (n = 301) are based on data obtained in our randomized clinical trial designed to assess the efficacy of extended cognitive behavior therapy for cigarette smoking cessation. Model 1 included

only pretreatment factors, demographic characteristics, and treatment assignment. Model 2 included all Model 1 variables, as well as clinical data measured during treatment. SDA was successfully able to identify smokers with varying probabilities of maintaining abstinence from end-of-treatment to 52-week follow-up; however, the inclusion of clinical data obtained over the course of treatment in Model 2 yielded very different partitioning parameters. The findings from this study may enable researchers to target underlying factors that may interact to promote maintenance of long-term smoking behavior change. Bailey SR, Hammer SA, Bryson SW, Schatzberg AF, Killen JD. Using treatment process data to predict maintained smoking abstinence. *Am J Health Behav.* 2010 Nov-Dec; 34(6): 801-810.

Future Altruism: Social Discounting of Delayed Rewards

Social discounting assesses an individual's willingness to forgo an outcome for the self in lieu of a larger outcome for someone else. The purpose of the present research was to examine the effect of adding a common delay to outcomes in a binary choice, social discounting procedure. Based on the premise that both social and temporal distances are dimensions of psychological distance, the authors hypothesized that social discounting should decrease as a function of delay to the outcomes. Across two within-subject experiments, participants indicated preference between a hypothetical money reward for the self or for someone else. The outcomes were associated with no, short, and long delays. Both studies confirmed our hypothesis that adding any delay to the receipt of outcomes decreases social discounting, though no significant differences were observed between short and long delays. These results are discussed in the context of some existing literature on altruism. Yi R, Charlton S, Porter C, Carter AE, Bickel WK. Future altruism: Social discounting of delayed rewards. *Behav Processes.* 2011 Jan; 86(1): 160-163.

A Pilot Randomized Clinical Trial of Two Medication Adherence and Drug Use Interventions for HIV+ Crack Cocaine Users

Crack cocaine use undermines adherence to highly active antiretroviral therapy (HAART). This pilot randomized clinical trial tested the feasibility and efficacy of 2 interventions based on the Information-Motivation-Behavioral Skill model to improve HAART adherence and reduce crack cocaine problems. Participants were 54 adults with crack cocaine use and HIV with <90% HAART adherence. Most participants were African-American (82%) heterosexual (59%), and crack cocaine dependent (92%). Average adherence was 58% in the past 2 weeks. Average viral loads (VL) were detectable (logVL 2.97). The interventions included 6 sessions of Motivational Interviewing plus feedback and skills building (MI+), or Video information plus debriefing (Video+) over 8 weeks. Primary outcomes were adherence by 14-day timeline follow-back and Addiction Severity Index (ASI) Drug Composite Scores at 3 and 6 months. Repeated measure ANOVA assessed main effects of the interventions and interactions by condition. Significant increases in adherence and reductions in ASI Drug Composite Scores occurred in both conditions by 3 months and were maintained at 6 months, representing medium effect sizes. No between group differences were observed. No VL changes were observed in either group. Treatment credibility, retention, and satisfaction were high and not different by condition. A counseling and a video intervention both improved adherence and drug problems durably among people with crack cocaine use and poor adherence in this pilot study. The interventions should be tested further among drug users with poor adherence. Video interventions may be feasible and scalable for people with HIV and drug use. Ingersoll KS, Farrell-Carnahan L, Cohen-Filipic J, Heckman CJ, Ceperich SD, et al. A pilot randomized clinical trial of two medication adherence and drug use interventions for HIV+ crack cocaine users. *Drug Alcohol Depend.* 2011 Feb 7. [Epub ahead of print].

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. McDonnell MG, Angelo F, Sugar A, Rainey C, Srebniak 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. *Drug Alcohol Abuse*. 2011 Mar; 37(2): 137-140.

Examining the Effect of the Life Enhancement Treatment for Substance Use (LETS ACT) on Residential Substance Abuse Treatment Retention

Effective, parsimonious behavioral interventions that target reinforcement are needed for substance users with depression to improve mood as well as treatment retention. The Life Enhancement Treatment for Substance Use (LETS ACT; Daughters et al., 2008) is a behavioral activation-based approach tailored to increase levels of positive reinforcement among depressed substance users while in substance abuse treatment. The current study tested the efficacy of LETS ACT compared to a contact-time matched control condition, supportive counseling (SC), examining effects on depressed mood, substance abuse treatment retention, and behavioral activation outcomes. Fifty-eight adult substance users in residential substance abuse treatment presenting with depressive symptoms (BDI = 12) were randomly assigned to LETS ACT or SC. Assessments were administered at pre- and post-treatment and included assessment of DSM-IV psychiatric diagnoses, depression severity, treatment motivation, overall activation, environmental reward, and substance abuse treatment retention. Patients in LETS ACT had significantly higher rates of substance abuse treatment retention and significantly greater increases in activation on the Behavioral Activation for Depression Scale (BADS) compared to those in SC. Both groups had decreased depression severity at post-treatment, although the group by time interaction was not significant. This study was the first to compare LETS ACT to a contact-time matched control treatment to evaluate effects on substance abuse treatment retention and two distinct measures of behavioral activation: overall activation and environmental reward. Findings suggest preliminary support for the feasibility, tolerability, and efficacy of a brief behavioral activation-based protocol that may be particularly useful to improve substance abuse treatment retention. Magidson JF, Gorka SM, Macpherson L, Hopko DR, Blanco C, Lejuez CW, Daughters SB. Examining the effect of the Life Enhancement Treatment for Substance Use (LETS ACT) on residential substance abuse treatment retention. *Addict Behav*. 2011 Jan 21. [Epub ahead of print].

Computer-Assisted HIV Prevention for Youth with Substance Use Disorders

The authors developed an interactive, customizable, Web-based program focused on the prevention of HIV, sexually transmitted infections, and hepatitis among youth. Results from a randomized, controlled trial with youth in treatment for substance use demonstrated that this Web-based tool, when provided as an adjunct to an educator-delivered prevention intervention, increased accurate prevention knowledge, increased intentions to carefully choose partners, and was perceived as significantly more useful relative to the educator-delivered intervention when provided alone. Results suggest this Web-based program may be effective and engaging and may increase the adoption of effective HIV and disease prevention science for youth. Limitations are discussed. Marsch LA, Grabinski MJ, Bickel WK, Desrosiers A, Guarino H, Muehlbach B, Solhkhah R, Taufique S, Acosta M. Computer-assisted HIV Prevention for youth with substance use disorders. *Subst Use Misuse*. 2011; 46(1): 46-56.

Hypothetical Intertemporal Choice and Real Economic Behavior: Delay Discounting Predicts Voucher Redemptions during Contingency-Management Procedures

Delay discounting rates are predictive of drug use status, the likelihood of becoming abstinent, and a variety of health behaviors. Rates of delay discounting may also be related to other relevant behaviors associated with addiction, such as the frequency at which individuals redeem contingency management voucher earnings. This study examined the discounting rates of 152 participants in a buprenorphine treatment program for opioid abuse. Participants received up to 12 weeks of buprenorphine treatment combined with contingency management. Participant's drug use was measured via urine specimens submitted three times a week. Successive negative urine specimens were reinforced with increasing amounts of money. After each negative urine specimen, a participant could either redeem his or her earnings or accumulate it in an account. Analysis of the frequency of redemptions showed that participants with higher rates of delay discounting at study intake redeemed their earnings significantly more often than participants with lower rates of discounting. Age and income also predicted redemption rates. The authors suggest that delay discounting rates can be used to predict redemption behaviors in a contingency management treatment program and that these findings are consistent with the recent theory of the competing neurobehavioral decision systems. Bickel WK, Jones BA, Landes RD, Christensen DR, Jackson L, Mancino M. Hypothetical intertemporal choice and real economic behavior: Delay discounting predicts voucher redemptions during contingency-management procedures. *Exp Clin Psychopharmacol*. 2010 Dec; 18(6): 546-552.

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*. 2010 Dec 3. [Epub ahead of print].

Remember the Future: Working Memory Training Decreases Delay Discounting among Stimulant Addicts

Excessive discounting of future rewards has been observed in a variety of disorders and has been linked both to valuation of the past and to memory of past events. To explore the functionality of discounting and memory, the authors examined whether training of working memory would result in less discounting of future rewards. In this study, 27 adults in treatment for stimulant use were randomly assigned to receive either working memory training or control training according to a yoked experimental design. Measures of delay discounting and several other cognitive behaviors were assessed pre- and posttraining. Rates of discounting of delayed rewards were significantly reduced among those who received memory training but were unchanged among those who received control training; other cognitive assessments were not affected by memory training. Discount rates were positively correlated with memory training performance measures. To the authors' knowledge, this is the first study demonstrating that neurocognitive training on working memory decreases delay discounting. These results offer further evidence of a functional relationship between delay discounting and working memory. Bickel WK, Yi R, Landes RD, Hill PF, Baxter C. Remember the future: Working memory training decreases delay discounting among stimulant addicts. *Biol Psychiatry*. 2011 Feb 1; 69(3): 260-265.

Contingency Management for Behavior Change: Applications to Promote Brief Smoking Cessation among Opioid-Maintained Patients

Cigarette smoking is highly prevalent among patients who are being treated for opioid-dependence, yet there have been limited scientific efforts to promote smoking cessation in this population. Contingency management (CM) is a behavioral treatment that provides monetary incentives contingent upon biochemical evidence of drug abstinence. This paper discusses the results of two studies that utilized CM to promote brief smoking cessation among opioid-maintained patients. Participants in a pilot study were randomly assigned for a 2-week period to a Contingent group that earned monetary vouchers for providing biochemical samples that met criteria for smoking abstinence, or a Noncontingent group that earned monetary vouchers independent of smoking status (Dunn et al., 2008). Results showed Contingent participants provided significantly more smoking-negative samples than Noncontingent participants (55% vs. 5%, respectively). A second randomized trial that utilized the same 2-week intervention and provided access to the smoking cessation pharmacotherapy bupropion replicated the results of the pilot study (55% and 17% abstinence in Contingent and Noncontingent groups, respectively; Dunn et al, 2010). Relapse to illicit drug use was also evaluated prospectively and no association between smoking abstinence and relapse to illicit drug use was observed (Dunn et al., 2009). It will be important for future studies to evaluate participant characteristics that might predict better treatment outcome, to assess the contribution that pharmacotherapies might have alone or in

combination with a CM intervention on smoking cessation and to evaluate methods for maintaining the abstinence that is achieved during this brief intervention for longer periods of time. Dunn KE, Saulsgiver KA, Sigmon SC. Contingency Management for behavior change: Applications to promote brief smoking cessation among opioid-maintained patients. *Exp Clin Psychopharmacol.* 2011 Feb; 19(1): 20-30.

A Placebo-Controlled Trial of Memantine for Cocaine Dependence with High-Value Voucher Incentives during a Pre-Randomization Lead-in Period

Preclinical findings suggest that the inhibition of NMDA glutamatergic neurotransmission may have beneficial effects in the treatment of cocaine dependence. The authors hypothesized that memantine, a low potency, uncompetitive NMDA receptor antagonist, would be safe and effective in the treatment of cocaine dependence, particularly in preventing relapse to cocaine use in abstinent individuals. Cocaine dependent patients (N=112) were enrolled. The trial began with a 2-week placebo lead-in period during which patients received high-value voucher contingency management to induce abstinence. Participants were then randomized to receive either memantine 20mg bid (N=39) or placebo (N=42) for 12-weeks in combination with individual relapse-prevention therapy. The randomization was stratified by abstinence status during the lead-in period. The primary outcome was the weekly proportion of days of cocaine use. There were no significant differences in cocaine use outcome between the groups treated with memantine versus placebo. Thus, the efficacy of memantine 40 mg/d for the treatment of cocaine dependence was not supported. Urine-confirmed abstinence during the lead-in period was achieved by 44% of participants, and was a strong predictor of subsequent cocaine abstinence during the trial. This suggests that this clinical trial design, an intensive behavioral intervention during a lead-in period, resolves cocaine dependent patients into two subgroups, one that rapidly achieves sustained abstinence and may not need a medication, and another that displays persistent cocaine use and would most likely benefit from a medication to help induce abstinence. Targeting the latter subgroup may advance medication development efforts. Bisaga A, Aharonovich E, Cheng WY, Levin FR, Mariani JJ, Raby WN, Nunes EV. A placebo-controlled trial of memantine for cocaine dependence with high-value voucher incentives during a pre-randomization lead-in period. *Drug Alcohol Depend.* 2010 Sep 1; 111(1-2): 97-104.

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.* 2010 Oct 30. [Epub ahead of print].

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

Research Findings - Research on Pharmacotherapies for Drug Abuse

Cocaine Analog Coupled to Disrupted Adenovirus: A Vaccine Strategy to Evoke High-titer Immunity Against Addictive Drugs

Based on the concept that anticocaine antibodies could prevent inhaled cocaine from reaching its target receptors in the brain, an effective anticocaine vaccine could help reverse cocaine addiction. Leveraging the knowledge that E1(-)E3(-) adenovirus (Ad) gene transfer vectors are potent immunogens, the authors have developed a novel vaccine platform for addictive drugs by covalently linking a cocaine analog to the capsid proteins of noninfectious, disrupted Ad vector. The Ad-based anticocaine vaccine evokes high-titer anticocaine antibodies in mice sufficient to completely reverse, on a persistent basis, the hyperlocomotor activity induced by intravenous administration of cocaine. Hicks MJ, De BP, Rosenberg JB, Davidson JT, Moreno AY, Janda KD, Wee S, Koob GF, Hackett NR, Kaminsky SM, Worgall S, Toth M, Mezey JG, Crystal RG *Mol Ther.* 2011 Mar; 19(3): 612-619.

Synthesis and Characterization of [³H]-SN56, a Novel Radioligand for the δ_1 Receptor

The study of the binding characteristics of δ ligands in vivo and in vitro requires radiolabeled probes with high affinity and selectivity. The radioligand presently used for in vitro studies of the δ_1 receptor, [³H](+)-pentazocine, has significant limitations; it is difficult to synthesize, has limited chemical stability, and can be problematic to obtain. Evaluation of a series of novel 2(3H)-benzothiazolone compounds revealed SN56 to have sub-nanomolar and preferential affinity for the δ_1 subtype, relative to δ_2 and non-sigma, binding sites. The goal of this study was to characterize the binding of [³H]-SN56 to δ_1 receptors isolated from rat brain. Standard in vitro binding techniques were utilized to 1) determine the specificity and affinity of binding to δ_1 receptors, 2) confirm that [³H]-SN56 labels sites previously identified as δ_1 by comparing binding to sites labeled by [³H](+)-pentazocine, and 3) characterize the kinetics of binding. The results indicate that [³H]-SN56 exhibits 1) specific, saturable, and reversible binding to the δ_1 receptor, with B(max)=340±10 fmol/mg and K(d)=0.069±0.0074 nM, 2) competitive displacement by classical sigma compounds, yielding δ_1 K(i) values consistent with those reported in the literature, and 3) binding kinetics compatible with a 90 min incubation, and filtration for separation of free and bound radioligand. The results of these studies suggest that [(3)H]-SN56 may serve as a viable alternative to [³H](+)-pentazocine in radioligand binding assays. Fishback JA, Mesangeau C, Poupaert JH, McCurdy CR, Matsumoto RR. *Eur J Pharmacol.*2011; 653: 1-7.

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Repeated N-acetyl Cysteine Reduces Cocaine Seeking in Rodents and Craving in Cocaine-dependent Humans

Addiction is a chronic relapsing disorder hypothesized to be produced by drug-induced plasticity that renders individuals vulnerable to craving-inducing stimuli such as re-exposure to the drug of abuse. Drug-induced plasticity that may result in the addiction phenotype includes increased excitatory signaling within corticostriatal pathways that correlates with craving in humans and is necessary for reinstatement in rodents. Reduced cystine-glutamate exchange by system x(c)- appears to contribute to heightened excitatory signaling within the striatum, thereby posing this as a novel target in the treatment of addiction. In the present report, the authors examined the impact of repeated N-acetyl cysteine, which is commonly used to activate cystine-glutamate exchange, on reinstatement in rodents in a preclinical study and on craving in cocaine-dependent humans in a preliminary, proof-of-concept clinical experiment. Interestingly, repeated administration (7 days) of N-acetyl cysteine (60 mg/kg, IP) produced a significant reduction in cocaine (10 mg/kg, IP)-induced reinstatement, even though rats (N=10-12/group) were tested 24 h after the last administration of N-acetyl cysteine. The reduction in behavior despite the absence of the N-acetyl cysteine indicates that repeated N-acetyl cysteine may have altered drug-induced plasticity that underlies drug-seeking behavior. In parallel, the authors' preliminary clinical data indicate that repeated administration (4 days) of N-acetyl cysteine (1200-2400 mg/day) to cocaine-dependent human subjects (N=4 per group) produced a significant reduction in craving following an experimenter-delivered IV injection of cocaine (20 mg/70 kg/60 s). Collectively, these data demonstrate that N-acetyl cysteine diminishes the motivational qualities of a cocaine challenge injection possibly by altering pathogenic drug-induced plasticity. Amen SL, Piacentine LB, Ahmad ME, Li SJ, Mantsch JR, Risinger RC, Baker DA. *Neuropsychopharmacology*. 2011 Mar 36: 871-878.

Varenicline Blocks Nicotine Intake In Rats With Extended Access To Nicotine Self-Administration

Much evidence indicates that individuals use tobacco primarily to experience the psychopharmacological properties of nicotine. Varenicline, a partial $\alpha 4\text{B}2$ nicotinic acetylcholine receptor (nAChR) agonist, is effective in reducing nicotine craving and relapse in smokers, suggesting that $\alpha 4\text{B}2$ nAChRs may play a key role in nicotine dependence. In rats, the effect of varenicline on nicotine intake has only been studied with limited access to the drug, a model of the positive reinforcing effect of nicotine. Varenicline has not been tested on the increase in motivation to take nicotine in nicotine-dependent rats. The present study evaluated the effects of varenicline on nicotine intake in rats with extended access to nicotine self-administration (23 h/day), a condition leading to the development of nicotine dependence. The authors hypothesized that varenicline's effects on nicotine self-administration would be greater in rats with extended than limited access to the drug and after forced abstinence rather than during baseline self-administration. Varenicline dose-dependently decreased nicotine self-administration in rats with limited (1 h/day) and extended (23 h/day) access. Despite an increased sensitivity to the motivational effects of abstinence on nicotine intake compared with limited-access rats, varenicline was equally effective in decreasing nicotine intake in dependent rats with extended access to nicotine. These results suggest that $\alpha 4\text{B}2$ nAChRs are critical in mediating the positive reinforcing effects of nicotine but may not be a key element underlying the negative reinforcement process responsible for the increased nicotine intake after abstinence in dependent subjects. George O, Lloyd A, Carroll FI, Damaj MI, Koob GF. *Psychopharmacology (Berl)*. 2011 Feb 213: 715-722.

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SA 4503 Attenuates Cocaine-Induced Hyperactivity and Enhances Methamphetamine Substitution For A Cocaine Discriminative Stimulus

Cocaine exhibits preferential (~15-fold) affinity for $\delta 1$ over $\delta 2$ sigma receptors, and previous research has shown an interaction of $\delta 1$ receptor-selective ligands and cocaine's behavioral effects. The present study investigated the effect of the putative sigma receptor agonist SA 4503 (1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride) on cocaine's locomotor stimulatory and discriminative stimulus properties. At doses without intrinsic activity, SA 4503 dose-dependently attenuated cocaine-induced hyperactivity in mice. This inhibition was overcome by increasing the cocaine dose. In rats trained to use cocaine as a discriminative stimulus in a drug discrimination task, doses of SA 4503 that did not substitute for the cocaine stimulus did not alter the cocaine substitution curve. However, SA 4503 potentiated the effect of methamphetamine to substitute for the cocaine stimulus. These data support a role for sigma receptors in the locomotor-activating properties of cocaine and, importantly, indicate a role for these receptors in the discriminative stimulus effects of methamphetamine. The data also suggest sigma receptors mediate the activity of different dopamine pathways responsible for the behavioral effects of psychostimulants. Rodvelt KR, Lever SZ, Lever JR, Blount LR, Fan KH, Miller DK. *Pharmacol Biochem Behav.* 2011 Feb 97: 676-682.

Discovery of Novel Allosteric Modulators of Metabotropic Glutamate Receptor Subtype 5 Reveals Chemical and Functional Diversity and In Vivo Activity In Rat Behavioral Models of Anxiolytic and Antipsychotic Activity

Modulators of metabotropic glutamate receptor subtype 5 (mGluR5) may provide novel treatments for multiple central nervous system (CNS) disorders, including anxiety and schizophrenia. Although compounds have been developed to better understand the physiological roles of mGluR5 and potential usefulness for the treatment of these disorders, there are limitations in the tools available, including poor selectivity, low potency, and limited solubility. To address these issues, the authors developed an innovative assay that allows simultaneous screening for mGluR5 agonists, antagonists, and potentiators. They identified multiple scaffolds that possess diverse modes of activity at mGluR5, including both positive and negative allosteric modulators (PAMs and NAMs, respectively). 3-Fluoro-5-(3-(pyridine-2-yl)-1,2,4-oxadiazol-5-yl)benzotrile (VU0285683) was developed as a novel selective mGluR5 NAM with high affinity for the 2-methyl-6-(phenylethynyl)-pyridine (MPEP) binding site. VU0285683 had anxiolytic-like activity in two rodent models for anxiety but did not potentiate phencyclidine-induced hyperlocomotor activity. (4-Hydroxypiperidin-1-yl)(4-phenylethynyl) phenyl)methanone (VU0092273) was identified as a novel mGluR5 PAM that also binds to the MPEP site. VU0092273 was chemically optimized to an orally active analog, N-cyclobutyl-6-((3-fluorophenyl)ethynyl)nicotinamide hydrochloride (VU0360172), which is selective for mGluR5. This novel mGluR5 PAM produced a dose-dependent reversal of amphetamine-induced hyperlocomotion, a rodent model predictive of antipsychotic activity. Discovery of structurally and functionally diverse allosteric modulators of mGluR5 that demonstrate in vivo efficacy in rodent models of anxiety and antipsychotic activity provide further support for the tremendous diversity of chemical scaffolds and modes of efficacy of mGluR5 ligands. In addition, these studies provide strong support for the hypothesis that multiple structurally distinct mGluR5 modulators have robust activity in animal models that predict efficacy in the treatment of CNS disorders. Rodriguez AL, Grier MD, Jones CK, Herman EJ, Kane AS, Smith RL, Williams R, Zhou Y, Marlo JE, Days EL, Blatt TN, Jadhav S, Menon UN, Vinson PN, Rook JM, Stauffer SR, Niswender CM, Lindsley CW, Weaver CD, Conn PJ. *Mol Pharmacol.* 2010 Dec 78: 1105-1123.

Antagonism of Δ 9-THC Induced Behavioral Effects By Rimonabant: Time Course Studies In Rats

The objective was to examine the time course of the cannabinoid 1 receptor antagonist/inverse agonist rimonabant's ability to antagonize in vivo cannabinergic agonist effects. The authors used two behavioral procedures sensitive to the effects of Δ 9-tetrahydrocannabinol (Δ 9-THC): rat drug discrimination (EXP-1) and suppression of fixed-ratio responding (FR) for food reinforcement (EXP-2). Two training doses of Δ 9-THC (1.8 and 3 mg/kg) served as discriminative cues in two groups discriminating Δ 9-THC from vehicle; injections were i.p. 20 min before session onset. Tests assessed the dose-response functions of Δ 9-THC and the time course for rimonabant in its ability to block the discriminative stimulus effects of Δ 9-THC. For antagonism testing, the training doses of Δ 9-THC were used and the rimonabant dose was 1mg/kg. Tests were 20, 60, 120, and 240 min post rimonabant administration; Δ 9-THC was always administered 20 min prior to testing. For EXP-2, only one response lever was activated and every 10th (FR-10) press on that lever resulted in food delivery. Once the response rate stabilized, tests occurred with Δ 9-THC, rimonabant and combinations of the drugs. The ED(50) estimates for the dose-response functions were 0.38 (\pm 0.28-0.51) and 0.50 (\pm 0.40-0.63) mg/kg for the training doses of 1.8 and 3 mg/kg Δ 9-THC, respectively. The time course studies suggested functional half-life estimates of 128.4 (\pm 95.7-172.2) and 98.4 (\pm 64.2-150.7) min by rimonabant for the two groups in EXP-1, respectively. Similarly, the functional half-life of rimonabant was 118.9 (\pm 66.1-213.9) min in EXP-2. Thus, antagonism of Δ 9-THC by rimonabant is relatively short lasting. Järbe TU, Gifford RS, Makriyannis A. Eur J Pharmacol. 2010 Dec 648: 133-138.

Sigma (Σ) Receptor Ligand, AC927 (N-Phenethylpiperidine Oxalate), Attenuates Methamphetamine-Induced Hyperthermia and Serotonin Damage In Mice

Methamphetamine interacts with sigma (δ) receptors and AC927, a selective δ receptor ligand, protects against methamphetamine-induced dopaminergic neurotoxicity. In the present study, the effects of AC927 on methamphetamine-induced hyperthermia and striatal serotonergic neurotoxicity were evaluated. Male, Swiss Webster mice were injected (i.p.) every 2 h, for a total of four times, with one of the following treatments: Saline+Saline; Saline+Methamphetamine (5 mg/kg); AC927 (5, 10, 20 mg/kg)+Methamphetamine (5 mg/kg); or AC927 (5, 10, 20 mg/kg)+Saline. Pretreatment with AC927 (10 mg/kg) significantly attenuated methamphetamine-induced striatal serotonin depletions, striatal serotonin transporter reductions, and hyperthermia. At the doses tested, AC927 itself had no significant effects on serotonin levels, serotonin transporter expression, or body temperature. To evaluate the effects of higher ambient temperature on methamphetamine-induced neurotoxicity, groups of mice were treated at 37 $^{\circ}$ C. Overall, there was an inverse correlation between the body temperature of the animals and striatal serotonin levels. Together, the data suggest that AC927 (10 mg/kg) protects against methamphetamine-induced neurotoxicity. The reduction of methamphetamine-induced hyperthermia by AC927 may contribute to the observed neuroprotection in vivo. Seminerio MJ, Kaushal N, Shaikh J, Huber JD, Coop A, Matsumoto RR. Pharmacol Biochem Behav. 2011 Mar 98: 12-20.

Opioid Bifunctional Ligands from Morphine and the Opioid Pharmacophore Dmt-Tic

Bifunctional ligands containing an ester linkage between morphine and the δ -

selective pharmacophore Dmt-Tic were synthesized, and their binding affinity and functional bioactivity at the μ , δ and κ opioid receptors determined. Bifunctional ligands containing or not a spacer of B-alanine between the two pharmacophores lose the μ agonism deriving from morphine becoming partial μ agonists 4 or μ antagonists 5. Partial κ agonism is evidenced only for compound 4. Finally, both compounds showed potent δ antagonism. Balboni G, Salvadori S, Marczak ED, Knapp BI, Bidlack JM, Lazarus LH, Peng X, Si YG, Neumeyer JL. *Eur J Med Chem.* 2011 Feb 46: 799-803.

Reaction Pathway and Free Energy Profile for Butyrylcholinesterase-Catalyzed Hydrolysis of Acetylcholine

A catalytic mechanism for the butyrylcholinesterase (BChE)-catalyzed hydrolysis of acetylcholine (ACh) has been studied by performing pseudobond first-principles quantum mechanical/molecular mechanical-free energy calculations on both acylation and deacylation of BChE. It has been shown that the acylation with ACh includes two reaction steps, including nucleophilic attack on the carbonyl carbon of ACh and dissociation of choline ester. The deacylation stage includes nucleophilic attack of a water molecule on the carboxyl carbon of the substrate and dissociation between the carboxyl carbon of the substrate and the hydroxyl oxygen of the Ser198 side chain. Notably, despite the fact that acetylcholinesterase (AChE) and BChE are very similar enzymes, the acylation of BChE with ACh is rate-determining, which is remarkably different from the AChE-catalyzed hydrolysis of ACh, in which the deacylation is rate-determining. The computational prediction is consistent with available experimental kinetic data. The overall free energy barrier calculated for BChE-catalyzed hydrolysis of ACh is 13.8 kcal/mol, which is in good agreement with the experimentally derived activation free energy of 13.3 kcal/mol. Chen X, Fang L, Liu J, Zhan CG. *J Phys Chem B.* 2011 Feb 115: 1315-1322.

Design, Preparation, and Characterization of High-Activity Mutants of Human Butyrylcholinesterase Specific For Detoxification of Cocaine

Cocaine is a widely abused drug without a U.S. Food and Drug Administration-approved medication. There is a recognized, promising anticocaine medication to accelerate cocaine metabolism, producing biologically inactive metabolites via a route similar to the primary cocaine-metabolizing pathway [i.e., cocaine hydrolysis catalyzed by butyrylcholinesterase (BChE) in plasma]. An ideal, therapeutically valuable mutant of human BChE should have not only a significantly improved catalytic activity against (-)-cocaine but also certain selectivity for (-)-cocaine over neurotransmitter acetylcholine (ACh), such that one would not expect systemic administration of the BChE mutant to interrupt cholinergic transmission. The present study accounting for the mutation-caused changes of the catalytic activities of BChE against both (-)-cocaine and ACh by means of molecular modeling and site-directed mutagenesis has led to identification of three BChE mutants that have not only a considerably improved catalytic efficiency against (-)-cocaine but also the desirable selectivity for (-)-cocaine over ACh. Two representative BChE mutants have been confirmed to be potent in actual protection of mice from acute toxicity (convulsion and lethality) of a lethal dose of cocaine (180 mg/kg). Pretreatment with the BChE mutant (i.e., 1 min before cocaine administration) dose-dependently protected mice against cocaine-induced convulsions and lethality. In particular, all mice pretreated with the mutant (e.g., 0.02 mg or more of A199S/F227A/S287G/A328W/E441D BChE) survived. The *in vivo* data reveal the primary factor (i.e., the relative catalytic efficiency), determining the efficacy in practical protection of mice from the acute cocaine toxicity and future direction for further improving the efficacy of the enzyme in the cocaine overdose treatment. Xue L, Ko MC, Tong M, Yang W, Hou S, Fang L, Liu J,

Zheng F, Woods JH, Tai HH, Zhan CG. *Mol Pharmacol*. 2011 Feb 79: 290-297.

Increased Cocaine Self-Administration in M(4) Muscarinic Acetylcholine Receptor Knockout Mice

The reinforcing effects of cocaine are mediated by the mesolimbic dopamine system. Behavioral and neurochemical studies have shown that the cholinergic muscarinic M(4) receptor subtype plays an important role in regulation of dopaminergic neurotransmission. The authors investigated for the first time the involvement of M(4) receptors in the reinforcing effects of cocaine using chronic intravenous cocaine self-administration in extensively backcrossed M(4) receptor knockout (M(4) (-/-)) mice. The authors evaluated acquisition of cocaine self-administration in experimentally naïve mice. Both cocaine self-administration and food-maintained operant behavior were evaluated under fixed ratio 1 (FR 1) and progressive ratio (PR) schedules of reinforcement. In addition, cocaine-induced dopamine release and cocaine-induced hyperactivity were evaluated. M(4) (-/-) mice earned significantly more cocaine reinforcers and reached higher breaking points than their wild-type littermates (M(4) (+/+)) at intermediate doses of cocaine under both FR 1 and PR schedules of reinforcement. Under the PR schedule, M(4) (-/-) mice exhibited significantly higher response rates at the lowest liquid food concentration. In accordance with these results, cocaine-induced dopamine efflux in the nucleus accumbens and hyperlocomotion were increased in M(4) (-/-) mice compared to M(4) (+/+) mice. The authors concluded that the data suggest that M(4) receptors play an important role in regulation of the reward circuitry and may serve as a new target in the medical treatment of drug addiction. Schmidt LS, Thomsen M, Weikop P, Dencker D, Wess J, Woldbye DP, Wortwein G, Fink-Jensen A. Increased cocaine self-administration in M(4) muscarinic acetylcholine receptor knockout mice. *Psychopharmacology (Berl)*. 2011 Mar 5. [Epub ahead of print].

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(α)₂ histamine₁ serotonin (5-HT)₂(A/C), and 5-HT₃ receptors. This pharmacologic profile prompted the authors' 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. Mirtazapine alters cue-associated methamphetamine seeking in rats. *Biological Psychiatry*. 2011; 69(3): 275-281.

Immunogenicity and Smoking-Cessation Outcomes for a Novel Nicotine

Immuno-therapeutic NicVAX, a nicotine vaccine (3'AmNic-rEPA), has been clinically evaluated to determine whether higher antibody (Ab) concentrations are associated with higher smoking abstinence rates and whether dosages and frequency of administration are associated with increased Ab response. This randomized, double-blinded, placebo-controlled multicenter clinical trial (N = 301 smokers) tested the results of 200- and 400- μ g doses administered four or five times over a period of 6 months, as compared with placebo. 3'AmNic-rEPA recipients with the highest serum antinicotine Ab response (top 30% by area under the curve (AUC)) were significantly more likely than the placebo recipients (24.6% vs. 12.0%, $P = 0.024$, odds ratio (OR) = 2.69, 95% confidence interval (CI), 1.14-6.37) to attain 8 weeks of continuous abstinence from weeks 19 through 26. The five-injection, 400- μ g dose regimen elicited the greatest Ab response and resulted in significantly higher abstinence rates than placebo. This study demonstrates, as proof of concept, that 3'AmNic-rEPA elicits Abs to nicotine and is associated with higher continuous abstinence rates (CAR). Its further development as a treatment for nicotine dependence is therefore justified. Hatsukami DK, Jorenby DE, Gonzales D, Rigotti NA, Glover ED, Oncken CA, Tashkin DP, Reus VI, Akhavan RC, Fahim RE, Kessler PD, Niknian M, Kalnik MW, Rennard SI. Immunogenicity and smoking-cessation outcomes for a novel nicotine immunotherapeutic. *Clin. Pharmacol. Ther.* 2011 Mar 89(3).

Smoking Withdrawal Modulates Right Inferior Frontal Cortex But Not Pre-supplementary Motor Area Activation During Inhibitory Control

Smokers exhibit decrements in inhibitory control (IC) during withdrawal. The objective of this study was to investigate the neural basis of these effects in critical substrates of IC--right inferior frontal cortex (rIFC) and presupplementary motor area (pre-SMA). Smokers were scanned following smoking as usual and after 24-h smoking abstinence. During scanning they completed a Go/No-Go task that required inhibiting responses to infrequent STOP trials. Event-related brain activation in response to successfully inhibited STOP trials was evaluated in two regions of interest: rIFC (10 mm sphere, $x=40$, $y=30$, $z=26$) and pre-SMA (10 mm sphere, $x=2$, $y=18$, $z=40$). Smoking abstinence robustly increased errors of commission on STOP trials (37.1 vs 24.8% in the satiated condition, $p<0.001$) while having no effects on GO trial accuracy or reaction time (RT). In rIFC, smoking abstinence was associated with a significantly increased event-related BOLD signal ($p=0.026$). Pre-SMA was unaffected by smoking condition. The results of this preliminary study suggest that successful IC during withdrawal is associated with increased processing demands on a cortical center associated with attention to inhibitory signals. Kozink RV, Kollins SH, McClernon FJ. Smoking withdrawal modulates right inferior frontal cortex but not presupplementary motor area activation during inhibitory control. *Neuropsychopharmacology*. 2010 Dec; 35(13): 2600-2606.

Physician Barriers to Incorporating Pharmacogenetic Treatment Strategies for Nicotine Dependence Into Clinical Practice

Advances in genomics research may improve health outcomes by tailoring treatment according to patients' genetic profiles. The treatment of nicotine dependence, in particular, may soon encompass pharmacogenetic treatment models. Realizing the benefits of such treatment strategies may depend on physicians' preparedness to incorporate genetic testing into clinical practice. This article describes barriers to clinical integration of pharmacogenetic treatments that will need to be addressed to realize the benefits of individualized smoking-cessation treatment. Schnoll RA, Shields AE. Physician barriers to incorporating pharmacogenetic treatment strategies for nicotine

dependence into clinical practice. *Clin Pharmacol Ther.* 2011 Mar; 89(3): 345-347.

Nicotine Metabolite Ratio Predicts Smoking Topography and Carcinogen Biomarker Level

Variability in smoking behavior is partly attributable to heritable individual differences in nicotine clearance rates. This can be assessed as the ratio of the metabolites cotinine and 3'-hydroxycotinine (referred to as the nicotine metabolism ratio; NMR). The authors hypothesized that faster NMR would be associated with greater cigarette puff volume and higher levels of total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a carcinogen biomarker. Current smokers (n = 109) smoked one of their preferred brand cigarettes through a smoking topography device and provided specimens for NMR and total NNAL assays. Faster nicotine metabolizers (third and fourth quartiles versus first quartile) based on the NMR exhibited significantly greater total puff volume and total NNAL; the total puff volume by daily cigarette consumption interaction was a significant predictor of total NNAL level. A heritable biomarker of nicotine clearance predicts total cigarette puff volume and total NNAL. If validated, the NMR could contribute to smoking risk assessment in epidemiologic studies and potentially in clinical practice. Strasser AA, Benowitz NL, Pinto AG, Tang KZ, Hecht SS, Carmella SG, Tyndale RF, Lerman CE. Nicotine metabolite ratio predicts smoking topography and carcinogen biomarker level. *Cancer Epidemiol Biomarkers Prev.* 2011 Feb; 20(2): 234-238.

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. The authors 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 Mar 8. [Epub ahead of print].

Pharmacogenetics of Smoking Cessation in General Practice: Results From the Patch II and Patch in Practice Trials

Cigarette smoking remains the leading cause of preventable death worldwide. However, the efficacy of available first-line therapies remains low, particularly in primary care practice where most smokers seek and receive treatment. These observations reinforce the notion that 'one size fits all' smoking cessation therapies may not be optimal. Therefore, a translational research

effort was launched by the Imperial Cancer Research Fund (later Cancer Research UK) General Practice Research Group, who led a decade-long research enterprise that examined the influence of pharmacological hypothesis-driven research into genetic influences on drug response for smoking cessation with transdermal nicotine replacement therapy in general practice. New and previously published smoking cessation genetic association results of 30 candidate gene polymorphisms genotyped for participants in two transdermal nicotine replacement clinical trials based in UK general practices, which employed an intention to analyze approach. By this high bar, one of the polymorphisms (COMT rs4680) was robust to correction for multiple comparisons. Moreover, future research directions are outlined; and lessons learned as well as best-practice models for designing, analyzing, and translating results into clinical practice are proposed. The results and lessons learned from this general practice-based pharmacogenetic research programme provide transportable insights at the transition to the second generation of pharmacogenetic and genomic investigations of smoking cessation and its translation to primary care. David SP, Johnstone EC, Churchman M, Aveyard P, Murphy MF, Munaf MR. Pharmacogenetics of smoking cessation in general practice: Results From the Patch II and Patch in Practice Trials. *Nicotine Tob Res.* 2011 Mar; 13(3): 157-167.

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 Feb 4. [Epub ahead of print].

Cigarette Smoking Reduction and Changes in Nicotine Dependence

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

their reported lifetime peak. About 44% (n = 3,077) of the sample reported reducing their smoking from their lifetime peak, with a mean reduction of 14.4 CPD (SD = 8.9) or a 54.0% reduction compared with peak smoking.

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

D-Cycloserine Selectively Decreases Nicotine Self-Administration in Rats with Low Baseline Levels of Response

Expanding the variety of treatments available to aid smoking cessation will allow the treatments to be customized to particular types of smokers. The key is to understand which subpopulations of smokers respond best to which treatment. This study used adult female Sprague-Dawley rats to evaluate the efficacy of d-cycloserine, a partial NMDA glutamate receptor agonist, in reducing nicotine self-administration. Rats were trained to self-administer nicotine (0.03mg/kg/infusion, IV) via operant lever response (FR1) with a secondary visual reinforcer. Two studies of d-cycloserine effects on nicotine self-administration were conducted: an acute dose-effect study (0, 10, 20 and 40mg/kg, sc) and a chronic study with 40mg/kg given before each test session for two weeks. Effects on rats with low or high pretreatment baseline levels of nicotine self-administration were assessed. In the acute study there was a significant interaction of d-cycloserine x baseline level of nicotine self-administration. In the low baseline group, 10mg/kg d-cycloserine significantly decreased nicotine self-administration. In the high baseline group, 40mg/kg significantly increased nicotine self-administration. In the repeated injection study, there was also a significant interaction of d-cycloserine x baseline level of nicotine self-administration. Chronic d-cycloserine significantly reduced nicotine self-administration selectively in rats with low baseline nicotine use, but was ineffective with the rats with higher levels of baseline nicotine self-administration. NMDA glutamate treatments may be particularly useful in helping lighter smokers successfully quit smoking, highlighting the need for diverse treatments for different types of smokers. Levin ED, Slade S, Wells C, Petro A, Rose JE. D-cycloserine selectively decreases nicotine self-administration in rats with low baseline levels of response. *Pharmacol Biochem Behav.* 2011 Apr; 98(2): 210-214. [Epub 2010 Dec 28].

Relationship Between Attentional Bias to Cocaine-Related Stimuli and Impulsivity in Cocaine-Dependent Subjects

Cocaine-dependent subjects show attentional bias to cocaine-related stimuli, increased impulsivity on questionnaires, and impaired inhibitory control (one component of impulsivity on behavioral tasks). However, the relationship between attentional bias, impulsivity, and inhibitory control in cocaine-dependent subjects is unknown. To investigate the relationship between attentional bias to cocaine-related stimuli, impulsivity, and inhibitory control in cocaine dependence This study employed the cocaine Stroop task to measure attentional bias to cocaine-related stimuli, immediate memory task (IMT) to measure inhibitory control, and Barratt Impulsiveness Scale version 11 to measure impulsivity. Thirty-two controls and 37 cocaine-dependent subjects were recruited through newspaper advertisement. Cocaine-dependent subjects had higher attentional bias to cocaine-related words, higher scores for Barratt Impulsiveness Scale, and higher commission error rate on the IMT than controls. The attentional bias was positively correlated with the commission error rate on the IMT in the cocaine-dependent subjects but not in control

subjects. Cocaine-dependent subjects showed attentional bias to cocaine-related words, increased impulsivity, and poor inhibitory control compared with controls. The attentional bias was associated with inhibitory control in cocaine-dependent subjects but not in control subjects. The authors findings suggest that cocaine-dependent subjects with poor inhibitory control may show higher attentional bias to cocaine-related words compared with controls and those with better inhibitory control. Liu S, Lane SD, Schmitz JM, Waters AJ, Cunningham KA, Moeller FG. Relationship between attentional bias to cocaine-related stimuli and impulsivity in cocaine-dependent subjects. *Am J Drug Alcohol Abuse*. 2011 Mar; 37(2): 117-122. [Epub 2011 Jan 5].

A Randomized Controlled Trial of Fluoxetine in the Treatment of Cocaine Dependence Among Methadone-Maintained Patients

Cocaine abuse and dependence continue to be widespread. Currently, there are no pharmacotherapies shown to be effective in the treatment of cocaine dependence. A 33-week outpatient clinical trial of fluoxetine (60 mg/day, po) for cocaine dependence that incorporated abstinence-contingent voucher incentives was conducted. Participants (N = 145) were both cocaine and opioid dependent and treated with methadone. A stratified randomization procedure assigned subjects to one of four conditions: fluoxetine plus voucher incentives (FV), placebo plus voucher incentives (PV), fluoxetine without vouchers (F), and placebo without vouchers (P). Dosing of fluoxetine/placebo was double blind. Primary outcomes were treatment retention and cocaine use based on thrice-weekly urine testing. The PV group had the longest treatment retention (M = 165 days) and lowest probability of cocaine use. The adjusted predicted probabilities of cocaine use were 65% in the P group, 60% in the F group, 56% in the FV group, and 31% in the PV group. Fluoxetine was not efficacious in reducing cocaine use in patients dually dependent on cocaine and opioids. Winstanley EL, Bigelow GE, Silverman K, Johnson RE, Strain EC. A randomized controlled trial of fluoxetine in the treatment of cocaine dependence among methadone-maintained patients. *J Subst Abuse Treat* 2011 Jan 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 Mar 5. [Epub ahead of print].

Galantamine Improves Sustained Attention in Chronic Cocaine Users

Chronic cocaine users are known to have cognitive deficits that are predictive of poor treatment response. Whether these deficits improve with medications targeting specific cognitive functions has not been examined in previous studies. The goal of this study was to evaluate galantamine's efficacy on selected cognitive outcomes, including measures of sustained attention, response inhibition, and attentional bias in recently abstinent cocaine users. Galantamine, a reversible and competitive inhibitor of acetylcholinesterase, is used clinically in the treatment of Alzheimer's dementia. In a randomized, double-blind, parallel-group study, 34 participants were randomized to galantamine (8 mg/day) or placebo treatment for 10 days. Cognitive and self-report mood measures were obtained at baseline and on Days 5 and 10 after the initiation of treatment. Galantamine treatment, compared to placebo, improved the reaction time, $F(2, 50) = 8.6, p < .01$, detection sensitivity (A'), $F(2, 50) = 4.9, p < .03$, number of hits, $F(2, 50) = 4.2, p < .04$, and number of correct rejections, $F(2, 50) = 5.6, p < .02$, on the Rapid Visual Information Processing task. With the exception of speeding the reaction time on the Stroop, galantamine did not affect performance on other tasks, ($p > .05$). These results demonstrate that medications can enhance cognitive function (e.g., sustained attention) in abstinent cocaine users. The potential efficacy of galantamine as a treatment for cocaine abuse needs to be further evaluated in clinical trials. Sofuoglu M, Waters AJ, Poling J, Carroll KM. Galantamine improves sustained attention in chronic cocaine users. *Exp Clin Psychopharmacol*. 2011 Feb; 19(1): 11-19.

The Effects of Oral Micronized Progesterone on Smoked Cocaine Self-Administration in Women

There are currently no FDA-approved pharmacotherapies for cocaine abuse. Converging preclinical and clinical evidence indicates that progesterone may have potential as a treatment for cocaine-abusing women, who represent a growing portion of cocaine users. The authors have previously shown that oral progesterone reduced the positive subjective effects of cocaine in female cocaine users during the follicular phase of the menstrual cycle, when endogenous progesterone levels were low. To extend these findings, the present study assessed the effects of oral progesterone (150 mg BID) administered during the follicular phase on smoked cocaine self-administration in women relative to the normal follicular and luteal phases. Healthy, non-treatment seeking female cocaine smokers (N=10) underwent three 4-day inpatient stays, during: 1) a normal follicular phase; 2) a normal luteal phase; and 3) a follicular phase when oral progesterone was administered. During each stay, participants completed 4 self-administration sessions in which they first smoked a "sample" dose of cocaine (0, 12, 25 or 50 mg) and then had 5 opportunities at 14-minute intervals to self-administer that dose at a cost of \$5 per dose. Expected cocaine dose effects on self-administration, subjective effects, and cardiovascular effects were observed. However, there was no effect of oral progesterone administration or menstrual cycle phase on cocaine self-administration. Thus, oral progesterone was not effective in reducing cocaine use in women under the current conditions. However, based on previous literature, further research assessing the role of oral progesterone for the treatment of cocaine dependence in women is warranted. Reed SC, Evans SM, Bedi G, Rubin E, Foltin RW. The effects of oral micronized progesterone on smoked cocaine self-administration in women. *Horm Behav*. 2011 Feb; 59(2): 227-235.

Selective Cocaine-Related Difficulties in Emotional Intelligence: Relationship to Stress and Impulse Control

Emotional Intelligence (EI) comprises the ability to perceive, use, understand, and regulate emotions and may potentially contribute to variability in risk-related factors such as stress perception and impulse control in cocaine dependent individuals. The main objective of the current study is to better define EI in cocaine dependent individuals compared with healthy controls, using the Mayer, Salovey, and Caruso Emotional Intelligence Test (MSCEIT). Secondary analysis investigates the association between EI, IQ factors, perceived stress, and impulse control in both populations. Seventy-two abstinent treatment-seeking cocaine patients and 52 healthy controls were administered the MSCEIT as well as measures of IQ, perceived stress, and impulse control. Findings showed that cocaine dependent participants demonstrated highly selective EI difficulties compared with healthy controls, specifically with regard to higher-level emotional reasoning including the understanding, management, and regulation of emotion. These EI problems were associated with increased perceived stress and impulse control difficulties. IQ was significantly associated with all MSCEIT measures in the cocaine dependent participants, but not controls. Findings indicate that specific aspects of EI may be of clinical importance to cocaine dependent populations, impacting relapse-related factors such as stress dysregulation and impulse control. Fox HC, Bergquist KL, Casey J, Hong KA, Sinha R. Selective cocaine-related difficulties in emotional intelligence: relationship to stress and impulse control. *Am J Addict.* 2011 Mar-Apr; 20(2): 151-160.

Long-Term Opioid Blockade and Hedonic Response: Preliminary Data From Two Open-Label Extension Studies with Extended-Release Naltrexone

The emergence of extended-release naltrexone (XR-NTX) raises the opportunity to explore the role of endorphin blockade on hedonic response during long-term alcohol dependence treatment. A hedonic survey was administered to 74 alcohol dependent patients treated for an average of 3.5 years with nearly continuous month-long intramuscular XR-NTX. The paper-and-pencil, one-time survey asked patients about the degree of pleasure they experienced in the past 90 days with drinking alcohol, sex, exercise and other daily activities. The data revealed lower pleasure ratings for alcohol than for sex, exercise and 10 other common activities. Mean responses to drinking alcohol and gambling were significantly lower than to listening to music, sex, reading, being with friends, eating good food, eating spicy food, and playing video/card games. This effect was independent of XR-NTX dose or duration. Although this exploratory study lacked baseline data, a comparison group or control for the impact of patient discontinuation, the data indicate the feasibility of examining long-term hedonic response in recovery. The differential hedonic ratings suggest that, in patients who persist with long-term continuous therapy, XR-NTX may selectively inhibit the pleasure associated with drinking alcohol, compared to a variety of other activities. O'Brien CP, Gastfriend DR, Forman RF, Schweizer E, Pettinati HM. Long-term opioid blockade and hedonic response: preliminary data from two open-label extension studies with extended-release naltrexone. *Am J Addict.* 2011 Mar; 20(2): 106-112.

Induction of Opioid-Dependent Individuals onto Buprenorphine and Buprenorphine/ Naloxone Soluble-Films

A sublingual soluble-film formulation of buprenorphine/naloxone (B/N) has been approved by the US Food and Drug Administration for the treatment of opioid dependency. This preparation provides unit-dose, child-resistant

packaging amenable to tracking and accountability, offers more rapid dissolution, and has a potentially preferred taste vs. tablets. This study compared the ability of buprenorphine (B) and B/N films to suppress spontaneous withdrawal in opioid-dependent volunteers. Participants were maintained on morphine and underwent challenge sessions to confirm sensitivity to naloxone-induced opioid withdrawal. Subjects were randomized to receive either B (16 mg, n = 18) or B/N (16/4 mg, n = 16) soluble films for 5 days. The primary outcome measure was the Clinical Opiate Withdrawal Scale (COWS) score. Thirty-four subjects completed induction onto soluble films. There was a significant decrease in COWS scores but no significant differences between the groups. The results support the use of B and B/N soluble films as safe and effective delivery methods for opioid induction. Strain EC, Harrison JA, Bigelow GE. Induction of opioid-dependent individuals onto buprenorphine and buprenorphine/naloxone soluble-films. *Clin Pharmacol Ther.* 2011 Mar; 89(3): 443-449.

The Pharmacodynamic and Pharmacokinetic Profile of Intranasal Crushed Buprenorphine and Buprenorphine/Naloxone Tablets in Opioid Abusers

Sublingual buprenorphine and buprenorphine/naloxone are efficacious opioid dependence pharmacotherapies, but there are reports of their diversion and misuse by the intranasal route. The study objectives were to characterize and compare their intranasal pharmacodynamic and pharmacokinetic profiles. (A randomized, double-blind, placebo-controlled, crossover study, an inpatient research unit at the University of Kentucky, healthy adults (n = 10) abusing, but not physically dependent on, intranasal opioids participated, six sessions (72 hrs apart) tested five intranasal doses [0/0, crushed buprenorphine (2, 8 mg), crushed buprenorphine/naloxone (2/0.5, 8/2 mg)] and one intravenous dose (0.8 mg buprenorphine/0.2 mg naloxone for bioavailability assessment), plasma samples, physiologic, subject- and observer-rated measures were collected before and for up to 72 hrs after drug administration. Both formulations produced time- and dose-dependent increases on subjective and physiological mu-opioid agonist effects (e.g., "liking," miosis). Subjects reported higher subjective ratings and street values for 8 mg compared to 8/2 mg, but these differences were not statistically significant. No significant formulation differences in peak plasma buprenorphine concentration or time course were observed. Buprenorphine bioavailability was 38-44% and T(max) was 35-40 min after all intranasal doses. Naloxone bioavailability was 24% and 30% following 2/0.5 and 8/2 mg, respectively. It is difficult to determine if observed differences in abuse potential between intranasal buprenorphine and buprenorphine/naloxone are clinically relevant at the doses tested. Greater bioavailability and faster onset of pharmacodynamic effects compared to sublingual administration suggests a motivation for intranasal misuse in non-dependent opioid abusers. However, significant naloxone absorption from intranasal buprenorphine/naloxone administration may deter the likelihood of intranasal misuse of buprenorphine/naloxone, but not buprenorphine, in opioid dependent individuals. Middleton LS, Nuzzo PA, Lofwall MR, Moody DE, Walsh SL. The pharmacodynamic and pharmacokinetic profile of intranasal crushed buprenorphine and buprenorphine/naloxone tablets in opioid abusers. *Addiction.* 2011 Mar 11. [Epub ahead of print].

Acute, Low-Dose Methamphetamine Administration Improves Attention/Information Processing Speed and Working Memory in Methamphetamine-Dependent Individuals Displaying Poorer Cognitive Performance at Baseline

Abstinent methamphetamine (Meth) dependent individuals demonstrate poorer performance on tests sensitive to attention/information processing speed,

learning and memory, and working memory when compared to non-Meth dependent individuals. The poorer performance on these tests may contribute to the morbidity associated with Meth-dependence. In light of this, the authors sought to determine the effects of acute, low-dose Meth administration on attention, working memory, and verbal learning and memory in 19 non-treatment seeking, Meth-dependent individuals. Participants were predominantly male (89%), Caucasian (63%), and cigarette smokers (63%). Following a four day, drug-free washout period, participants were given a single-blind intravenous infusion of saline, followed the next day by 30mg of Meth. A battery of neurocognitive tasks was administered before and after each infusion, and performance on measures of accuracy and reaction time were compared between conditions. While acute Meth exposure did not affect test performance for the entire sample, participants who demonstrated relatively poor performance on these tests at baseline, identified using a median split on each test, showed significant improvement on measures of attention/information processing speed and working memory when administered Meth. Improved performance was seen on the following measures of working memory: choice reaction time task ($p = 0.04$), a 1-back task ($p = 0.01$), and a 2-back task ($p = 0.04$). In addition, those participants demonstrating high neurocognitive performance at baseline experienced similar or decreased performance following Meth exposure. These findings suggest that acute administration of Meth may temporarily improve Meth-associated neurocognitive performance in those individuals experiencing lower cognitive performance at baseline. As a result, stimulants may serve as a successful treatment for improving cognitive functioning in those Meth-dependent individuals experiencing neurocognitive impairment. Mahoney JJ 3rd, Jackson BJ, Kalechstein AD, De La Garza R 2nd, Newton TF. Acute, low-dose methamphetamine administration improves attention/information processing speed and working memory in methamphetamine-dependent individuals displaying poorer cognitive performance at baseline. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010 Nov 29. [Epub ahead of print].

A Double-Blind, Placebo-Controlled Study of N-Acetyl Cysteine Plus Naltrexone for Methamphetamine Dependence

Reducing both glutamatergic and dopaminergic drive in the nucleus accumbens may offer complementary mechanisms by which to reduce drug cravings. This 8-week study sought to examine the efficacy of a combination of a glutamate modulator, N-acetyl cysteine (NAC), plus the opioid antagonist, naltrexone, compared to placebo in the treatment of methamphetamine dependence. Thirty-one subjects with methamphetamine dependence (mean age 36.8 ± 7.12 years; 29% female) were randomly assigned in a 1:1 fashion to NAC plus naltrexone or placebo and returned for one post-baseline visit. The Penn Craving Scale was the primary outcome measure. Self-report methamphetamine use frequency and urine toxicology were secondary measures. NAC plus naltrexone failed to demonstrate statistically significant differences from placebo on primary and secondary outcomes. The current study failed to demonstrate greater efficacy for NAC plus naltrexone compared to placebo. Given the small sample size, the statistical power to detect significant effects of active treatment versus placebo was limited. The question of whether a larger, well-powered sample would have detected differences between NAC plus naltrexone and placebo deserves further examination. Grant JE, Odlaug BL, Kim SW. A double-blind, placebo-controlled study of N-acetyl cysteine plus naltrexone for methamphetamine dependence. *Eur Neuropsychopharmacol*. 2010 Nov; 20(11):823-828.

Characterizing Methamphetamine Withdrawal in Recently Abstinent Methamphetamine Users: A Pilot Field Study

Methamphetamine dependence has become a significant problem, but

methamphetamine withdrawal symptoms have not been well studied. This prospective observational pilot study was designed to examine withdrawal symptoms, mood, anxiety, cognitive function, and subjective measures of sleep over a 4-week period in six patients entering residential treatment for methamphetamine dependence. Methamphetamine withdrawal symptoms, mood, and anxiety symptoms all resolve fairly quickly within 2 weeks of cessation of methamphetamine. Sleep was disrupted over the course of the 4-week study. No clinically significant alterations in blood pressure or heart rate were identified. This study did not demonstrate any alterations in cognitive function over the 4 weeks of the residential stay. This pilot study points toward the need for a double-blind, placebo-controlled amphetamine withdrawal paradigm in humans where changes in sleep, cognitive function, and withdrawal measures can be explored more fully. This study extends the literature by pointing toward a methamphetamine withdrawal syndrome that includes alterations in measures of sleep quality and refreshed sleep, early improvement in depression and anxiety symptoms, most striking during the first week, but persisting into the second week. Mancino MJ, Gentry BW, Feldman Z, Mendelson J, Oliveto A. Characterizing methamphetamine withdrawal in recently abstinent methamphetamine users: a pilot field study. *Am J Drug Alcohol Abuse*. 2011 Mar; 37(2): 131-136.

Dronabinol for the Treatment of Cannabis Dependence: A Randomized, Double-Blind, Placebo-Controlled Trial

Cannabis dependence is a substantial public health problem. Behavioral treatments have shown promise, but there are no effective medications for cannabis dependence. The purpose of this study was to evaluate the safety and efficacy of dronabinol, a synthetic form of delta-9-tetrahydrocannabinol, a naturally occurring pharmacologically active component of marijuana, in treating cannabis dependence. 156 cannabis-dependent adults were enrolled in a randomized, double-blind, placebo-controlled, 12-week trial. After a 1-week placebo lead-in phase, participants were randomized to receive dronabinol 20mg twice a day or placebo. Doses were maintained until the end of week 8 and then tapered off over 2 weeks. All participants received weekly motivational enhancement and relapse prevention therapy. Marijuana use was assessed using the timeline followback method. There was no significant difference between treatment groups in the proportion of participants who achieved 2 weeks of abstinence at the end of the maintenance phase (dronabinol: 17.7%; placebo: 15.6%). Although both groups showed a reduction in marijuana use over time, there were no differences between the groups. Treatment retention was significantly higher at the end of the maintenance phase on dronabinol (77%), compared to placebo (61%) ($P=.02$), and withdrawal symptoms were significantly lower on dronabinol than placebo ($P=.02$). This is the first trial using an agonist substitution strategy for treatment of cannabis dependence. Dronabinol showed promise, it was well-tolerated, and improved treatment retention and withdrawal symptoms. Future trials might test higher doses, combinations of dronabinol with other medications with complementary mechanisms, or with more potent behavioral interventions. Levin FR, Mariani JJ, Brooks DJ, Pavlicova M, Cheng W, Nunes EV. Dronabinol for the treatment of cannabis dependence: A randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend*. 2011 Feb 8. [Epub ahead of print].

Efficacy and Tolerability of High-Dose Dronabinol Maintenance in HIV-Positive Marijuana Smokers: A Controlled Laboratory Study

Dronabinol

(Δ 9)tetrahydrocannabinol) is approved for HIV-related anorexia, yet, little is known about its effects in HIV-positive marijuana smokers. HIV-negative marijuana smokers require higher than recommended dronabinol doses to

experience expected effects. Employing a within-subjects, double-blind, placebo-controlled design, the authors assessed the effects of repeated high-dose dronabinol in HIV-positive marijuana smokers taking antiretroviral medication. Participants (N = 7), who smoked marijuana 4.2 ± 2.3 days/week, resided in a residential laboratory for two 16-day stays, receiving dronabinol (10 mg QID) in one stay and placebo in the other. Efficacy was assessed with objectively verified food intake and body weight. Tolerability was measured with sleep, subjective, and cognitive assessments. For analyses, each inpatient stay was divided into two phases, days 1-8 and 9-16; the authors compared dronabinol's effects with placebo in each 8-day phase to investigate tolerance. Despite sustained increases in self-reported food cravings, dronabinol only increased caloric intake in the initial 8 days of dosing. Similarly, sleep quality was improved only in the first 8 days of dosing. Dronabinol's mood-enhancing effects were sustained across the 16-day inpatient stay. Dronabinol was well tolerated, causing few negative subjective or cognitive effects. In HIV-positive marijuana smokers, high dronabinol doses safely and effectively increased caloric intake. However, repeated high-dose dronabinol appeared to result in selective tolerance to these effects. These findings indicate that HIV-positive individuals who smoke marijuana may require higher dronabinol doses than are recommended by the FDA. Future research to establish optimal dosing regimens, and reduce the development of tolerance, is required. Bedi G, Foltin RW, Gunderson EW, Rabkin J, Hart CL, Comer SD, Vosburg SK, Haney M. Efficacy and tolerability of high-dose dronabinol maintenance in HIV-positive marijuana smokers: a controlled laboratory study. *Psychopharmacology (Berl)*. 2010 Dec; 212(4): 675-686.

Quantification and Comparison of Marijuana Smoking Practices: Blunts, Joints, and Pipes

The quantification method for collecting self-reported marijuana use data is not standardized as it is for alcohol or cigarettes, which presents a methodologic challenge for marijuana use disorder treatment studies. Serum and urine markers of marijuana use have a long half-life, limiting their utility as a clinical trial outcome measure. Structured calendar-based interview procedures can accurately measure the frequency of self-reported marijuana use, but are unable to reliably address issues such as quantity of use or potency. This study compared the quantity and assigned-dollar value among users of blunts, joints, and pipes enrolled in two clinical trials testing pharmacotherapies for marijuana dependence. The timeline follow-back method was modified to incorporate using a surrogate substance to represent marijuana to enable participants to estimate the amount and value used. Blunt users were mostly black and Hispanic, while users of joints and pipes were primarily white. Participants reported that they placed 50% more marijuana in blunts than in joints and placed more than twice the amount of marijuana in blunts than in pipes. These findings demonstrate the feasibility of using a surrogate weight estimation procedure to augment calendar-based methods of measuring self-reported marijuana use. Individual variability in use practices limits the utility of this method to estimating within-subject comparisons, rather than between subject comparisons. Mariani JJ, Brooks D, Haney M, Levin FR. Quantification and comparison of marijuana smoking practices: blunts, joints, and pipes. *Drug Alcohol Depend*. 2011 Jan 15; 113(2-3): 249-251.

An Evidence Based Review of Acute and Long-Term Effects of Cannabis Use on Executive Cognitive Functions

Cannabis use has been shown to impair cognitive functions on a number of levels—from basic motor coordination to more complex executive function tasks, such as the ability to plan, organize, solve problems, make decisions, remember, and control emotions and behavior. These deficits differ in severity depending on the quantity, recency, age of onset and duration of marijuana

use. Understanding how cannabis use impairs executive function is important. Individuals with cannabis-related impairment in executive functions have been found to have trouble learning and applying the skills required for successful recovery, putting them at increased risk for relapse to cannabis use. Here the authors review the research on the acute, residual, and long-term effects of cannabis use on executive functions, and discuss the implications for treatment. Crean RD, Crane NA, Mason BJ. An Evidence Based Review of Acute and Long-Term Effects of Cannabis Use on Executive Cognitive Functions. *J Addict Med.* 2011 Mar 1; 5(1):1-8.

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 Feb 4. [Epub ahead of print]

Increased Blood Pressure Following Abrupt Cessation of Daily Cannabis Use

Cannabis is the most widely used illicit drug. Acute cannabis administration increases blood pressure and heart rate and tolerance develops to these effects with heavy use. A valid and reliable withdrawal syndrome occurs in most daily users, but few studies have assessed the cardiovascular effects of withdrawal. The objective of this report is to describe unexpected changes in cardiovascular function during brief periods of supervised cannabis use and abstinence in daily cannabis users. A within-subjects ABAC crossover study in which inpatient volunteers smoked cannabis ad-libitum (A), and abstained from cannabis (B/C). Vital signs were obtained three times daily during eleven inpatient days for thirteen daily cannabis users (11 Male, 8 African American). Blood pressure increased significantly during periods of cannabis abstinence compared with periods of cannabis use. The magnitude of increase was substantial in a subset (N=6) of participants, with mean increases of up to 22.8mmHg systolic and 12.3mmHg diastolic blood pressure observed. Heart rate also increased during abstinence when measures collected during periods of acute intoxication were excluded, but the magnitude of effect was not clinically significant. Abrupt cessation of heavy cannabis use may cause clinically significant increases in blood pressure in a subset of users. Blood pressure should be monitored

among those attempting to reduce or quit frequent cannabis use, particularly those with preexisting hypertension. The time course of this effect is currently unknown and requires further study. Vandrey R, Umbricht A, Strain EC. Increased Blood pressure following abrupt cessation of daily cannabis use. *J Addict Med.* 2011 Mar; 5(1): 16-20.

The Safety of Modafinil in Combination with Oral Δ 9-Tetrahydrocannabinol in Humans

Marijuana (cannabis) is the most widely used illicit substance globally, and cannabis use is associated with a range of adverse consequences. Currently, no medications have been proven to be effective for the treatment of cannabis addiction. The goals of this study were to examine the safety and efficacy of a potential treatment medication, modafinil, in combination with oral Δ 9-tetrahydrocannabinol (THC). Twelve male and female occasional cannabis users participated in an outpatient double-blind, placebo-controlled, crossover study. Across four sessions, participants were randomly assigned to a sequence of four oral treatments: (1) 400 mg modafinil+placebo, (2) 15 mg THC+placebo, (3) 400 mg modafinil+15 mg THC, or (4) placebo+placebo. Outcome measures included heart rate, blood pressure, performance on the Rapid Visual Information Processing (RVIP), and the Hopkins Verbal Learning Test (HVLT), and subjective measures. Oral THC increased heart rate, and produced increased subjective ratings of feeling "high" and "sedated," as well as increased ratings of euphoria. Modafinil alone increased the Profiles of Mood States (POMS) subscales of vigor and tension. These findings support the safety of modafinil in combination with THC. The effects of modafinil in combination with a range of doses of THC need to be determined in future studies. Sugarman DE, Poling J, Sofuoglu M. The safety of modafinil in combination with oral Δ 9-tetrahydro- cannabinol in humans. *Pharmacol Biochem Behav.* 2011 Mar; 98(1): 94-100.

Drug Treatment as HIV Prevention: A Research Update

Drug use continues to be a major factor fueling the global epidemic of HIV infection. This article reviews the current literature on the ability of drug treatment programs to reduce HIV transmission among injection and noninjection drug users. Most data come from research on the treatment of opiate dependence and provide strong evidence on the effectiveness of medication-assisted treatment for reducing the frequency of drug use, risk behaviors, and HIV infections. This has been a consistent finding since the epidemic began among diverse populations and cultural settings. Use of medications other than methadone (such as buprenorphine/naloxone and naltrexone) has increased in recent years with promising data on their effectiveness as HIV prevention and as new treatment options for communities heavily affected by opiate use and HIV infection. However, few treatment interventions for stimulant abuse and dependence have shown efficacy in reducing HIV risk. The cumulative literature provides strong support of drug treatment programs for improving access and adherence to antiretroviral treatment. Drug users in substance abuse treatment are significantly more likely to achieve sustained viral suppression, making viral transmission less likely. Although there are challenges to implementing drug treatment programs for maximum impact, the scientific literature leaves no doubt about the effectiveness of drug treatment as an HIV prevention strategy. Metzger DS, Woody GE, O'Brien CP. Drug treatment as HIV prevention: a research update. *J Acquir Immune Defic Syndr.* 2010 Dec 1; 55 Suppl 1: S32-36.



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

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

Evidence for the Innate Immune Response as a Correlate of Protection in Human Immunodeficiency Virus (HIV)-1 Highly Exposed Seronegative Subjects (HESN)

The description of highly exposed individuals who remain seronegative (HESN) despite repeated exposure to human immunodeficiency virus (HIV)-1 has heightened interest in identifying potential mechanisms of HIV-1 resistance. HIV-specific humoral and T cell-mediated responses have been identified routinely in HESN subjects, although it remains unknown if these responses are a definitive cause of protection or merely a marker for exposure. Approximately half of HESN lack any detectable HIV-specific adaptive immune responses, suggesting that other mechanisms of protection from HIV-1 infection also probably exist. In support of the innate immune response as a mechanism of resistance, increased natural killer (NK) cell activity has been correlated with protection from infection in several high-risk cohorts of HESN subjects, including intravenous drug users, HIV-1 discordant couples and perinatally exposed infants. Inheritance of protective NK KIR3DL1high and KIR3DS1 receptor alleles have also been observed to be over-represented in a high-risk cohort of HESN intravenous drug users and HESN partners of HIV-1-infected subjects. Other intrinsic mechanisms of innate immune protection correlated with resistance in HESN subjects include heightened dendritic cell responses and increased secretion of anti-viral factors such as B-chemokines, small anti-viral factors and defensins. This review will highlight the most current evidence in HESN subjects supporting the role of epithelial microenvironment and the innate immune system in sustaining resistance against HIV-1 infection. The authors argue that as a front-line defence the innate immune response determines the threshold of infectivity that HIV-1 must overcome to establish a productive infection. Tomescu C, Abdulhaqq S, Montaner LJ. Evidence for the innate immune response as a correlate of protection in human immunodeficiency virus (HIV)-1 highly exposed seronegative subjects (HESN). Clin Exp Immunol. 2011 Mar 17. 1365-2249 [Epub ahead of print].

Vitamin D Deficiency is Associated with Significant Coronary Stenoses in Asymptomatic African American Chronic Cocaine Users

Chronic cocaine use may lead to premature atherosclerosis, however, the prevalence of and risk factors for coronary artery disease in asymptomatic cocaine users have not been reported. Between August 2007 and June 2010, 385 African American chronic cocaine users aged 25 to 54 years were consecutively enrolled in a study to investigate the prevalence of CT angiographically-defined significant (≥ 50%) coronary stenosis and related risk

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factors. Sociodemographic, drug-use behavior, medical history and medication data were obtained by interview and confirmed by medical chart review. Clinical examinations were performed as well as extensive laboratory tests including those for fasting lipid profiles, HIV, high sensitivity C-reactive protein, and vitamin D. Contrast-enhanced coronary CT angiography was performed. Significant coronary stenosis was detected in 52 of 385 participants (13.5%). The prevalences were 12% and 30% in those with low risk and with middle-high risk Framingham score, respectively. In those with low risk scores, the prevalences of significant stenosis were 10% and 18% in those without and with vitamin D deficiency, defined as serum 25-(OH) vitamin D < 10 ng/mL ($p = 0.08$). Multiple logistic regression analysis revealed that vitamin D deficiency (adjusted OR = 2.18, 95% CI: 1.07-4.43) is independently associated with the presence of significant coronary stenosis after controlling for traditional risk factors. The study indicates that the prevalence of significant coronary stenoses is high in asymptomatic young and middle-aged African American chronic cocaine users. These findings emphasize the importance of aggressive reduction of risk factors, including vitamin D deficiency in this population. Lai H, Fishman EK, Gerstenblith G, Brinker JA, Tong W, Bhatia S, Detrick B, Lai S. Vitamin D deficiency is associated with significant coronary stenoses in asymptomatic African American chronic cocaine users. *Int J Cardiol.* 2011 Feb 2. [Epub ahead of print].

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HIV-1 Tat Upregulates Expression of Histone Deacetylase-2 (HDAC2) in Human Neurons: Implication for HIV-Associated Neurocognitive Disorder (HAND)

Histone deacetylases (HDACs) play a pivotal role in epigenetic regulation of transcription and homeostasis of protein acetylation in histones and other proteins involved in chromatin remodeling. Histone hypoacetylation and transcriptional dysfunction have been shown to be associated with a variety of neurodegenerative diseases. More recently, neuron specific overexpression of HDAC2 has been shown to modulate synaptic plasticity and learning behavior in mice. However, the role of HDAC2 in development of HIV-associated neurocognitive disorders (HAND) is not reported. Herein the authors report that HIV-1 Tat protein upregulate HDAC2 expression in neuronal cells leading to transcriptional repression of genes involved in synaptic plasticity and neuronal function thereby contributing to the progression of HAND. The authors' results indicate upregulation of HDAC2 by Tat treatment in dose and time dependant manner by human neuroblastoma SK-N-MC cells and primary human neurons. Further, HDAC2 overexpression was associated with concomitant downregulation in CREB and CaMKIIa genes that are known to regulate neuronal activity. These observed effects were completely blocked by HDAC2 inhibition. These results for the first time suggest the possible role of HDAC2 in development of HAND. Therefore, use of HDAC2 specific inhibitor in combination with HAART may be of therapeutic value in treatment of neurocognitive disorders observed in HIV-1 infected individuals. Saiyed ZM, Gandhi N, Agudelo M, Napuri J, Samikkannu T, Reddy PV, Khatavkar P, Yndart A, Saxena SK, Nair MP. *Neurochem Int.* 2011 Feb 17. [Epub ahead of print].

HIV Treatment Outcomes among HIV-Infected, Opioid-Dependent Patients Receiving Buprenorphine/Naloxone Treatment within HIV Clinical Care Settings: Results From a Multisite Study

Having opioid dependence and HIV infection are associated with poor HIV-related treatment outcomes. HIV-infected, opioid-dependent subjects (N = 295) recruited from 10 clinical sites initiated buprenorphine/naloxone (BUP/NX) and were assessed at baseline and quarterly for 12 months. Primary outcomes included receiving antiretroviral therapy (ART), HIV-1 RNA suppression, and mean changes in CD4 lymphocyte count. Analyses were stratified for the 119

subjects not on ART at baseline. Generalized estimating equations were deployed to examine time-dependent correlates for each outcome. At baseline, subjects on ART (N = 176) were more likely than those not on ART (N = 119) to be older, heterosexual, have lower alcohol addiction severity scores, and lower HIV-1 RNA levels; they were less likely to be homeless and report sexual risk behaviors. Subjects initiating BUP/NX (N = 295) were significantly more likely to initiate or remain on ART and improve CD4 counts over time compared with baseline; however, these improvements were not significantly improved by longer retention on BUP/NX. Retention on BUP/NX for three or more quarters was, however, significantly associated with increased likelihood of initiating ART (B = 1.34 [1.18, 1.53]) and achieve viral suppression (B = 1.25 [1.10, 1.42]) for the 64 of 119 (54%) subjects not on ART at baseline compared with the 55 subjects not retained on BUP/NX. In longitudinal analyses, being on ART was positively associated with increasing time of observation from baseline and higher mental health quality of life scores (B = 1.25 [1.06, 1.46]) and negatively associated with being homo- or bisexual (B = 0.55 [0.35, 0.97]), homeless (B = 0.58 [0.34, 0.98]), and increasing levels of alcohol addiction severity (B = 0.17 [0.03, 0.88]). The strongest correlate of achieving viral suppression was being on ART (B = 10.27 [5.79, 18.23]). Female gender (B = 1.91 [1.07, 3.41]), Hispanic ethnicity (B = 2.82 [1.44, 5.49]), and increased general health quality of life (B = 1.02 [1.00, 1.04]) were also independently correlated with viral suppression. Improvements in CD4 lymphocyte count were significantly associated with being on ART and increased over time. Initiating BUP/NX in HIV clinical care settings is feasible and correlated with initiation of ART and improved CD4 lymphocyte counts. Longer retention on BPN/NX was not associated with improved prescription of ART, viral suppression, or CD4 lymphocyte counts for the overall sample in which the majority was already prescribed ART at baseline. Among those retained on BUP/NX, HIV treatment outcomes did not worsen and were sustained. Increasing time on BUP/NX, however, was especially important for improving HIV treatment outcomes for those not on ART at baseline, the group at highest risk for clinical deterioration. Retaining subjects on BUP/NX is an important goal for sustaining HIV treatment outcomes for those on ART and improving them for those who are not. Comorbid substance use disorders (especially alcohol), mental health problems, and quality-of-life indicators independently contributed to HIV treatment outcomes among HIV-infected persons with opioid dependence, suggesting the need for multidisciplinary treatment strategies for this population. Altice FL, Bruce RD, Lucas GM, Lum PJ, Korthuis PT, Flanigan TP, Cunningham CO, Sullivan LE, Vergara-Rodriguez P, Fiellin DA, Cajina A, Botsko M, Nandi V. HIV treatment outcomes among HIV-infected, opioid-dependent patients receiving buprenorphine/naloxone treatment within HIV clinical care settings: Results from a multisite study. *J Acquir Immune Defic Syndr*. 2011 Mar 1; 56 Suppl 1: S22-32.

Testing an Optimized Community-Based Human Immunodeficiency Virus (HIV) Risk Reduction and Antiretroviral Adherence Intervention for HIV-Infected Injection Drug Users

The authors conducted a preliminary study of the 4-session Holistic Health for HIV (3H+), which was adapted from a 12-session evidence-based risk reduction and antiretroviral adherence intervention. Improvements were found in the behavioral skills required to properly adhere to HIV medication regimens. Enhancements were found in all measured aspects of sex-risk reduction outcomes, including HIV knowledge, motivation to reduce sex-risk behavior, behavioral skills related to engaging in reduced sexual risk, and reduced risk behavior. Improvements in drug use outcomes included enhancements in risk reduction skills as well as reduced heroin and cocaine use. Intervention effects also showed durability from post-intervention to the follow-up assessment point. Females responded particularly well in terms of improvements in risk reduction skills and risk behavior. This study suggests that an evidence-based

behavioral intervention may be successfully adapted for use in community-based clinical settings where HIV-infected drug users can be more efficiently reached. Copenhaver MM, Lee IC, Margolin A, Bruce RD, Altice FL. Testing an optimized community-based human immunodeficiency virus (HIV) risk reduction and antiretroviral adherence intervention for HIV-infected injection drug users. *Subst Abus.* 2011 Jan; 32(1): 16-26.

Cocaine Reduces Thymic Endocrine Function: Another Mechanism for Accelerated HIV Disease Progression

Thymulin is a thymic peptide important for the maturation and differentiation of immature thymocytes, which have been found to be depressed in patients with low-level CD4(+) cell recovery despite viral control. Substance use is associated with faster progression of HIV disease, which has been ascribed to poor adherence to antiretroviral medication. Recent findings of an association between cocaine use and decline in CD4(+) cell counts independent of antiretroviral adherence indicate alternative mechanisms for disease progression. The authors evaluated the relationship between thymulin activity, CD4(+) and CD8(+) cell counts and the CD4(+)/CD8(+) ratio, and the covariate effects of substance use cross-sectionally in 80 HIV(+) active substance users and over 12 months in 40 participants. Thymulin activity was analyzed in plasma using a modification of the sheep rosette bioassay. Thymulin activity was negatively associated with cocaine use ($B = -0.908$, 95% CI: -1.704, -0.112; $p = 0.026$). Compared to those who do not use cocaine, cocaine users were 37% less likely to have detectable thymulin activity (RR = 0.634, 95% CI: 0.406, 0.989 $p = 0.045$) and were 75 times more likely to show a decrease in thymulin activity (OR = 74.7, 95% CI: 1.59, 3519.74; $p = 0.028$) over time. CD4(+) cell count was positively associated with thymulin activity ($B = 0.127$, 95% CI: 0.048, 0.205; $p = 0.002$), detectable thymulin activity was 2.32 times more likely in those with a CD4 cell count ≥ 200 cells/ μ l (RR = 2.324, 95% CI: 1.196, 4.513, $p = 0.013$), and those with an increase in CD4 cell counts were more likely to show an increase in thymulin activity (OR = 1.02, 95% CI: 1.00, 1.034; $p = 0.041$) over time. Thymulin activity is predictive of HIV disease progression and is depressed in cocaine users independent of antiretroviral treatment (ART) and HIV viral load. Understanding the mechanisms for accelerated HIV disease progression provides opportunities to find alternative strategies to counteract immunosuppression. Rafie C, Campa A, Smith S, Huffman F, Newman F, Baum MK. Cocaine reduces thymic endocrine function: another mechanism for accelerated HIV disease progression. *AIDS Res Hum Retroviruses.* 2011 Jan 15. [Epub ahead of print].

Molecular Epidemiology of HIV Type 1 in Singapore and Identification of Novel CRF01_AE/B Recombinant Forms

To investigate HIV-1 molecular epidemiology in Singapore, the authors sequenced portions of three regions of the HIV-1 genome (protease HXB2: 2163 to 2620, gp120 HXB2: 6904 to 7628, and gp41 HXB2: 7817 to 8264) from 212 plasma samples collected between February 2008 and August 2009. From these samples, 109 (51.4%) generated interpretable data in all regions. Sixty-one (56.0%) were identified as CRF01_AE, 26 (23.9%) as subtype B and 14 (12.8%) as possible novel recombinant forms. The main novel recombinant pattern, detected in 13 sequences, had subtype B in protease and gp41 and CRF01_AE in gp120. There was intermixing of subtypes within transmission risk groups. However, 85% of subjects infected with the novel recombinant forms self-identified as men who have sex with men or bisexuals compared with only 41% of individuals infected with CRF01_AE and 62% infected with subtype B ($p = 0.001$). Ng OT, Munshaw S, Lamers SL, Chew KK, Lin L, Redd AD, Manucci J, Quinn TC, Ray SC, Chua A, Leo YS, Laeyendecker O. *AIDS Res Hum Retroviruses.* 2011 Feb 14. [Epub ahead of print].

Evolution of the HIV-1 Nef Gene in HLA-B*57 Positive Elite Suppressors

Elite controllers or suppressors (ES) are HIV-1 infected patients who maintain viral loads of < 50 copies/ml without antiretroviral therapy. CD8+ T cells are thought to play a key role in the control of viral replication and exert selective pressure on gag and nef in HLA-B*57 positive ES. The authors previously showed evolution in the gag gene of ES which surprisingly was mostly due to synonymous mutations rather than non-synonymous mutation in targeted CTL epitopes. This finding could be the result of structural constraints on Gag, and the authors therefore examined the less conserved nef gene. The authors found slow evolution of nef in plasma virus in some ES. This evolution is mostly due to synonymous mutations and occurs at a rate similar to that seen in the gag gene in the same patients. The results provide further evidence of ongoing viral replication in ES and suggest that the nef and gag genes in these patients respond similarly to selective pressure from the host. Salgado M, Brennan TP, O'Connell KA, Bailey JR, Ray SC, Siliciano RF, Blankson JN. *Retrovirology*. 2010 Nov 8; 7: 94.

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 14 day treatment with the PI in either staggered (MDZ ~12 hrs after PI) or simultaneous (MDZ and PI co-administered) manner. Oral and intravenous MDZ plasma AUCs 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 (SCHHs) rather than human liver microsomes (HLMs). Kirby BJ, Collier AC, Kharasch ED, Whittington D, Thummel KE, Unadkat JD. *Drug Metab Dispos*. 2011 Mar 15. [Epub ahead of print].

HIV Vaccine Trial Willingness Among Injection and Non-Injection Drug Users in Two Urban Centres, Barcelona and San Francisco

Being able to recruit high-risk volunteers who are also willing to consider future participation in vaccine trials are critical features of vaccine preparedness studies. The authors described data from two cohorts of injection- and non-injection drug users in Barcelona, Spain [Red Cross centre] and in San Francisco, USA, [UFO-VAX study] at high risk of HIV/HCV infection to assess behaviour risk exposure and willingness to participate in future preventive HIV vaccine trials. The authors successfully identified drug-using populations that would be eligible for future HIV vaccine efficacy trials, based on reported levels of risk during screening and high levels of willingness to participate. In both groups, Red Cross and UFO-VAX respectively, HCV infection was highly prevalent at baseline (41% and 34%), HIV baseline seroprevalence was 4.2% and 1.5%, and high levels of willingness were seen (83% and 78%). Etcheverry MF, Lum PJ, Evans JL, Sanchez E, de Lazzari E, Mendez-Arancibia E, Sierra E, Gatell JM, Page K, Joseph J. *Vaccine*. HIV vaccine trial willingness among injection and non-injection drug users in two urban centers. 2011 Feb

24; 29(10): 1991-1996. Epub 2011 Jan 15.

Pre-Exposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Antiretroviral chemoprophylaxis before exposure is a promising approach for the prevention of human immunodeficiency virus (HIV) acquisition. The authors randomly assigned 2,499 HIV-seronegative men or transgender women who have sex with men to receive a combination of two oral antiretroviral drugs, emtricitabine and tenofovir disoproxil fumarate (FTC-TDF), or placebo once daily. All subjects received HIV testing, risk-reduction counseling, condoms, and management of sexually transmitted infections. The study subjects were followed for 3,324 person-years (median, 1.2 years; maximum, 2.8 years). Of these subjects, 10 were found to have been infected with HIV at enrollment, and 100 became infected during follow-up (36 in the FTC-TDF group and 64 in the placebo group), indicating a 44% reduction in the incidence of HIV (95% confidence interval, 15 to 63; $P=0.005$). In the FTC-TDF group, the study drug was detected in 22 of 43 of seronegative subjects (51%) and in 3 of 34 HIV-infected subjects (9%) ($P<0.001$). Nausea was reported more frequently during the first 4 weeks in the FTC-TDF group than in the placebo group ($P<0.001$). The two groups had similar rates of serious adverse events ($P=0.57$). Oral FTC-TDF provided protection against the acquisition of HIV infection among the subjects. Detectable blood levels strongly correlated with the prophylactic effect. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, Goicochea P, Casap'a M, Guanira-Carranza JV, Ramirez-Cardich ME, Montoya-Herrera O, Fernández T, Veloso VG, Buchbinder SP, Charialertsak S, Schechter M, Bekker LG, Mayer KH, Kallás EG, Amico KR, Mulligan K, Bushman LR, Hance RJ, Ganoza C, Defechereux P, Postle B, Wang F, McConnell JJ, Zheng JH, Lee J, Rooney JF, Jaffe HS, Martinez AI, Burns DN, Glidden DV; iPrEx Study Team. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010 Dec 30; 363(27): 2587-2599.

Proposing a Tentative Cut Point for the Compulsive Sexual Behavior Inventory

Bivariate analyses were utilized in order to identify the relations between scores on the Compulsive Sexual Behavior Inventory (CSBI) and self-report of risky sexual behavior and drug abuse among 482 racially and ethnically diverse men and women. CSBI scores were associated with both risky sexual behavior and drug abuse among a diverse non-clinical sample, thereby providing evidence of criterion-related validity. The variables that demonstrated a high association with the CSBI were subsequently entered into a multiple regression model. Four variables (number of sexual partners in the last 30 days, self-report of trading drugs for sex, having paid for sex, and perceived chance of acquiring HIV) were retained as variables with a good model fit. Receiver operating characteristic (ROC) curve analyses were conducted in order to determine the optimal tentative cut point for the CSBI. The four variables retained in the multiple regression model were utilized as exploratory gold standards in order to construct ROC curves. The ROC curves were then compared to one another in order to determine the point that maximized both sensitivity and specificity in the identification of compulsive sexual behavior with the CSBI scale. The current findings suggest that a tentative cut point of 40 may prove clinically useful in discriminating between persons who exhibit compulsive sexual behavior and those who do not. Because of the association between compulsive sexual behavior and HIV, STIs, and drug abuse, it is paramount that a psychometrically sound measure of compulsive sexual behavior is made available to all healthcare professionals working in disease prevention and other areas. Storholm ED, Fisher DG, Napper LE, Reynolds GL, Halkitis PN. *Arch. Sex Behav*. Proposing a Tentative Cut Point for the Compulsive Sexual Behavior Inventory. 2011 Jan 4. [Epub ahead of print].

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 \times 100) were calculated. The authors compared change in QIs and summary quality scores in patients receiving bup/nx versus other participants. 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 (B 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 PT, Fiellin DA, Fu R, Lum PJ, Altice FL, Sohler N, Tozzi MJ, Asch SM, Botsko M, Fishl M, Flanigan TP, Boverman J, McCarty D; BHIVES Collaborative. Improving adherence to HIV quality of care indicators in persons with opioid dependence: the role of buprenorphine. *J Acquir Immune Defic Syndr*. 2011 Mar 1; 56 Suppl 1: S83-90.

Sex, Race, and Geographic Region Influence Clinical Outcomes Following Primary HIV-1 Infection

It is unknown whether sex and race influence clinical outcomes following primary human immunodeficiency virus type 1 (HIV-1) infection. Data were evaluated from an observational, multicenter, primarily North American cohort of HIV-1 seroconverters. Of 2,277 seroconverters, 5.4% were women. At enrollment, women averaged .40 \log_{10} fewer copies/mL of HIV-1 RNA ($P < .001$) and 66 more CD4(+) T cells/ μ L ($P = .006$) than men, controlling for age and race. Antiretroviral therapy (ART) was less likely to be initiated at any time point by nonwhite women and men compared to white men ($P < .005$), and by individuals from the southern United States compared to others ($P = .047$). Sex and race did not affect responses to ART after 6 months ($P > .73$). Women were 2.17-fold more likely than men to experience >1 HIV/AIDS-related event ($P < .001$). Nonwhite women were most likely to experience an HIV/AIDS-related event compared to all others ($P = .035$), after adjusting for intravenous drug use and ART. Eight years after diagnosis, >1 HIV/AIDS-related event had occurred in 78% of nonwhites and 37% of whites from the southern United States, and 24% of whites and 17% of nonwhites from other regions ($P < .001$). Despite more favorable clinical parameters initially, female HIV-1-seroconverters had worse outcomes than did male seroconverters. Elevated morbidity was associated with being nonwhite and residing in the southern United States. Meditz AL, MaWhinney S, Allshouse A, Feser W, Markowitz M, Little S, Hecht R, Daar ES, Collier AC, Margolick J, Kilby JM, Routy JP, Conway B, Kaldor J, Levy J, Schooley R, Cooper DA, Altfeld M, Richman D, Connick E. Sex, race, and geographic region influence clinical outcomes following primary HIV-1 infection. *J Infect Dis*. 2011 Feb 15; 203(4): 442-451. Epub 2011 Jan 18.

Strategies to Improve Access to and Utilization of Health Care Services and Adherence to Antiretroviral Therapy Among HIV-Infected Drug Users

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

High Rates of Transitions to Injecting Drug Use Among Mexican American Non-Injecting Heroin Users in San Antonio, Texas (Never and Former Injectors)

The purpose of this study was to assess the incidence and rate of transition to injecting among Mexican American noninjecting heroin users. In a prospective cohort study of street-recruited MA-NIU in San Antonio, Texas, 2002-2005, participants were administered structured interviews and tested for Human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). The analysis sample comprised former injection drug users (last injected >6 months ago, n=47) and those who had never injected drugs and tested HCV negative (n=219). A transition to injecting was defined as the first injection of illicit drugs since baseline interview. Transition rates were based on person-years at-risk (PYAR). Proportional hazards regression was used to estimate crude and adjusted (for significant differences between former and never injectors) hazard ratios and 95% confidence intervals of injecting history on transitioning to injecting. Sixty-three (24%) participants transitioned to injecting at a rate of 22.3/100 PYAR (95% CI: 17.2-28.2). Former-injectors were significantly more likely to transition than never injectors (43% or 20/47 vs. 20% or 43/219; $p < 0.001$), and did so at a faster rate (40.4/100 PYAR, 95% CI: 24.6-60.0 vs. 18.5/100 PYAR, 95% CI: 13.4-24.4), with the crude HR=1.931 (95% CI: 1.116, 3.341) and adjusted HR=2.263 (95% CI: 1.192-4.294). The rate of transitioning to injecting was high and greater among former injectors. Of particular concern is the high rate of injecting initiation among never injectors. Future analyses will examine factors associated with injecting initiation, including individual susceptibility and behaviors, social networks, and the cultural and drug market context. Valdez A, Neaigus A, Kaplan C, Cepeda A. High rates of transitions to injecting drug use among Mexican American non-injecting heroin users in San Antonio, Texas (never and former injectors). *Drug Alcohol Depend*. 2010 Nov 12. [Epub ahead of print].

Controlled HIV Viral Replication, Not Liver Disease Severity Associated with Low Bone Mineral Density in HIV/HCV Co-Infection

The purpose of this study was to evaluate the prevalence and risk factors for low bone mineral density (BMD) in persons co-infected with HIV and Hepatitis C. HIV/HCV co-infected study participants (n=179) were recruited into a prospective cohort and underwent dual-energy X-ray absorptiometry (DXA)

within 1 year of a liver biopsy. Fibrosis staging was evaluated according to the METAVIR system. Osteoporosis was defined as a T-score < -2.5. Z-scores at the total hip, femoral neck, and lumbar spine were used as the primary outcome variables to assess the association between degree of liver disease, HIV-related variables, and BMD. The population was 65% male, 85% Black with mean age 50.3 years. The prevalence of osteoporosis at either the total hip, femoral neck, or lumbar spine was 28%, with 5% having osteoporosis of the total hip, 6% at the femoral neck, 25% at the spine. The mean Z-scores (standard deviation) were -0.42 (1.01) at the total hip, -0.16 (1.05) at the femoral neck, and -0.82 (1.55) at the lumbar spine. In multivariable models, controlled HIV replication (HIV RNA < 400 copies/mL vs ≥ 400 copies/mL) was associated with lower Z-scores (mean ± standard error) at the total hip (-0.44±0.17, p=0.01), femoral neck (-0.59±0.18, p=0.001), and the spine (-0.98±0.27, p=0.0005). There was no association between degree of liver fibrosis and Z-score. Osteoporosis was very common in this population of predominately African-American HIV/HCV co-infected patients, particularly at the spine. Lower BMD was associated with controlled HIV replication, but not liver disease severity. El-Maouche D, Mehta SH, Sutcliffe C, Higgins Y, Torbenson MS, Moore RD, Thomas DL, Sulkowski MS, Brown TT. Controlled HIV viral replication, not liver disease severity associated with low bone mineral density in HIV/HCV co-infection. *J Hepatol.* 2011 Feb 18. [Epub ahead of print].

Concurrent Assessment of Hepatic and Intestinal Cytochrome P450 3A Activities Using Deuterated Alfentanil

Alfentanil (ALF) is a validated probe for hepatic, first-pass, and intestinal cytochrome P450 (CYP) 3A activity, using plasma clearances, single-point concentrations, and noninvasive pupil diameter change (miosis). Assessing intravenous (i.v.) and oral drug disposition typically requires separate dosing. This investigation evaluated concurrent administration of oral deuterated and i.v. unlabeled ALF to assess both intestinal and hepatic CYP3A, and compare sequential and simultaneous dosing. ALF disposition was evaluated after strong hepatic and/or intestinal CYP3A induction and inhibition by rifampin, ketoconazole, and grapefruit juice. Using plasma ALF concentrations and area under the curve (AUC), clearance, or single-point concentrations, both simultaneous and sequential dosing provided equivalent results and detected hepatic and intestinal CYP3A induction and inhibition. Miosis better detected CYP3A modulation with sequential vs. simultaneous dosing. These results show that concurrent administration of oral deuterated and i.v. ALF, either sequentially or simultaneously, is an efficient and effective approach to assessing hepatic and intestinal CYP3A activity. Kharasch ED, Vangveravong S, Buck N, London A, Kim T, Blood J, Mach RH. Concurrent assessment of hepatic and intestinal cytochrome P450 3A activities using deuterated alfentanil. *Clin Pharmacol Ther.* 2011 Feb 23. [Epub ahead of print].

Changes in Blood-Borne Infection Risk Among Injection Drug Users

Population-level hepatitis C virus (HCV) infection incidence is a surrogate for community drug-related risk. The authors characterized trends in human immunodeficiency virus (HIV) and HCV infection incidence and HCV infection prevalence among injection drug users (IDUs) recruited over 4 periods: 1988-1989, 1994-1995, 1998, and 2005-2008. The authors calculated HIV and HCV infection incidence within the first year of follow-up among IDUs whose test results were negative for these viruses at baseline (n = 2061 and n = 373, respectively). The authors used Poisson regression to compare trends across groups. HIV infection incidence declined significantly from 5.5 cases/100 person-years (py) in the 1988-1989 group to 2.0 cases/100 py in the 1994-1995 group to 0 cases/100 py in the 1998 and 2005-2008 groups. Concurrently, HCV infection incidence declined but remained robust (22.0

cases/100 py in the 1988-1989 cohort to 17.2 cases/100 py in the 1994-1995 cohort, 17.9 cases/100 py in the 1998 cohort, and 7.8 cases/100 py in the 2005-2008 cohort; $P = .07$). Likewise, HCV infection prevalence declined, but chiefly in younger IDUs. For persons aged <39 years, relative to the 1988-1989 cohort, all groups exhibited significant declines (adjusted prevalence ratio [PR] for the 2005-08 cohort, .73; 95% confidence interval [CI], .65-.81). However, for persons aged ≥ 39 years, only the 2005-2008 cohort exhibited declining prevalence compared with the 1988-1989 cohort (adjusted PR, .87; 95% CI, .77-.99). Although efforts to reduce blood-borne infection incidence have had impact, this work will need to be intensified for the most transmissible viruses, such as HCV. Mehta SH, Astemborski J, Kirk GD, Strathdee SA, Nelson KE, Vlahov D, Thomas DL. Changes in blood-borne infection risk among injection drug users. *J Infect Dis*. 2011 Mar; 203(5): 587-594. Epub 2011 Jan 31.

Patterns and Characteristics of Hepatitis C Transmission Clusters among HIV-Positive and HIV-Negative Individuals in the Australian Trial in Acute Hepatitis C

Injecting drug users remain the population at greatest risk of acquiring hepatitis C virus (HCV) infection, although a recent increase in cases of sexually transmitted HCV infection has been observed among human immunodeficiency virus (HIV)-infected individuals. The extent to which these separate epidemics overlap is unknown. The Australian Trial in Acute Hepatitis C (ATAHC) enrolled 163 individuals (29% of whom were HIV infected) with recent HCV infection. E1/HVR1 sequences were used to construct phylogenetic trees demonstrating monophyletic clusters or pairs, and viral epidemic history and phylogeography were assessed using molecular clock analysis. Individual clusters were characterized by clinical and demographic characteristics. Transmission through injection drug use occurred for 73% of subjects, with sexual transmission occurring for 18% (92% of whom were HIV infected). Among 112 individuals with available E1/HVR1 sequences, 23 (20%) were infected with a strain of HCV identical to that of another subject, comprising 4 homologous clusters and 3 monophyletic pairs, the majority of which (78%) were HIV infected. Clusters contained individuals with both injection drug use-related and sex-related acquisition, and in all clusters (except for 1 female HIV-uninfected pair), individuals identified as men who have sex with men, irrespective of HIV status. This large unique study of HIV-infected and HIV-uninfected individuals with recently acquired HCV infection demonstrates that clustering is common in the HIV-infected population and that it occurred almost invariably among men who have sex with men, irrespective of the actual mode of acquisition. These findings suggest the coexistence of both injection drug use and sexual risk behaviors for individuals in the same social networks and have implications for the development of public health messages. Matthews GV, Pham ST, Hellard M, Grebely J, Zhang L, Oon A, Marks P, van Beek I, Rawlinson W, Kaldor JM, Lloyd A, Dore GJ, White PA. Patterns and characteristics of hepatitis c transmission clusters among HIV-positive and HIV-negative individuals in the Australian Trial in Acute Hepatitis C. *Clin Infect Dis*. 2011 Mar; 52(6):803-811. Epub 2011 Jan 3.

Cross-Genotypic Polyclonal Anti-HCV Antibodies from Human Ascitic Fluid

Many anti-HCV antibodies are available, but more are needed for research and clinical applications. This study examines whether ascitic fluid from cirrhotic patients could be a source of reagent-grade antibodies. Ascitic fluid from 29 HCV patients was screened by ELISA for anti-HCV antibodies against three viral proteins: core, NS4B, and NS5A. Significant patient-to-patient variability in anti-HCV antibody titers was observed. Total ascitic fluid IgG purified by Protein-A chromatography reacted with HCV proteins in immunoblots, cell

extracts, and replicon-expressing cells. Affinity-purification using synthetic peptides as bait allowed the preparation of cross-genotypic antibodies directed against pre-selected regions of HCV core, NS4B, and NS5A proteins. The performance of the polyclonal antibodies was comparable to that of monoclonal antibodies. Anti-NS4B antibody preparations reacted with genotype 1a, 1b, and 2a NS4B proteins in immunoblots and allowed NS4B to be localized in replicon-expressing cells. Ascitic fluid is an abundant source of human polyclonal cross-genotypic antibodies that can be used as an alternative to blood. This study shows the utility of selectively purifying human polyclonal antibodies from ascitic fluid. Affinity purification allows antibodies to be selected that are comparable to monoclonal antibodies in their ability to react with targeted regions of viral proteins. Gutierrez JA, Klepper AL, Garber J, Walewski JL, Bateman K, Khaitova V, Syder A, Tscherne DM, Gauthier A, Jefferson D, Rice CM, Schiano TD, Branch AD. Cross-genotypic polyclonal anti-HCV antibodies from human ascitic fluid. *J Virol Methods*. 2011 Jan; 171(1):169-75. Epub 2010 Oct 27.

Incidence and Risk Factors for Steatosis Progression in Adults Coinfected With HIV and Hepatitis C Virus

Hepatic steatosis is a common histologic finding in patients coinfecting with human immunodeficiency virus (HIV) and hepatitis C virus (HCV), although little is known about its natural history. The authors prospectively examined the natural history of steatosis in patients coinfecting with HIV and HCV who attended an urban HIV clinic. The study cohort consisted of 222 coinfecting patients (87% black, 94% with HCV genotype 1 infection) who had at least 2 liver biopsies performed between 1993 and 2008. Biopsy specimens were scored by a single pathologist; samples were classified as having trivial (<5% of hepatocytes affected) or significant (>5%) levels of fat (steatosis). The authors characterized progression to significant levels of fat among patients whose first biopsy samples had no or trivial levels of fat, and regression among those with significant fat, using logistic regression. The authors' initial biopsy specimens from most patients (88%) had no or trivial amounts of fat. Among second biopsy samples, 74% had no or trivial fat and 13% had significant amounts of fat. The strongest risk factors for progression of steatosis were alcohol abuse and overweight/obesity; cumulative exposure to antiretroviral therapy between biopsies and high counts of CD4 (+) T cells were associated with reduced progression of steatosis. Among the 28 patients whose initial biopsy specimen had significant fat levels, most (75%) regressed. Antiretroviral therapy and high counts of CD4 (+) T cells are associated with reduced progression of steatosis in patients coinfecting with HIV and HCV. Efforts to diagnose and prevent steatosis should focus on persons with a high body mass index and excessive alcohol intake. Woreta TA, Sutcliffe CG, Mehta SH, Brown TT, Higgins Y, Thomas DL, Torbenson MS, Moore RD, Sulkowski MS. *Gastroenterology*. 2011 Mar; 140(3): 809-817. Epub 2010 Dec 4.

Incidence and Predictors of Acute Kidney Injury in an Urban Cohort of Subjects with HIV and Hepatitis C Virus Coinfection

Coinfection with hepatitis C (HCV) significantly increases the risk of acute and chronic renal disease in HIV-infected individuals. However, the burden of acute kidney injury (AKI) directly attributable to HIV among HCV-infected individuals and associated risk factors are not well understood. Within a prospective cohort, AKI episodes were identified by a rise in creatinine of 0.5 mg/dL. Incidence of first AKI events was calculated for HIV/HCV coinfecting versus HCV mono-infected subjects, and multivariable analyses using Cox proportional hazards were performed to identify predictors of AKI. Throughout the study period, 35% HIV/HCV coinfecting and 17% HCV mono-infected subjects developed AKI, with incidence of 8.74/100 person-years and 3.53/100 person-years, respectively (hazard ratio (HR) 2.48; [95% confidence interval (CI)

1.50, 3.74]). In multivariable analysis, HIV coinfection (HR 2.19 [1.33, 3.62]), decompensated cirrhosis (HR 6.64 [3.81, 11.6]), and cocaine use (HR 2.06 [1.15, 3.71]) were independently associated with AKI. HCV genotype, HCV viral load, hazardous drinking, and heroin use were not associated with AKI. Study limitations included potential misclassification bias of HCV-infected individuals as serial HIV antibody testing was not routinely performed after study entry, and inability to adjust for tenofovir use in multivariable analysis. In conclusion, among subjects with HCV infection, decompensated cirrhosis, HIV coinfection, and cocaine use are associated with increased risk of AKI. These findings highlight the importance of preventing and treating cirrhosis, controlling HIV coinfection, and reducing cocaine use in HIV/HCV coinfecting persons. Garg S, Hoenig M, Edwards EM, Bliss C, Heeren T, Tumilty S, Walley AY, Koziel MJ, Skolnik PR, Horsburgh CR, Cotton D. Incidence and predictors of acute kidney injury in an urban cohort of subjects with HIV and Hepatitis C virus coinfection. *AIDS Patient Care STDS*. 2011 Mar; 25(3): 135-141. Epub 2011 Feb 10.

Incident Hepatitis C Virus Infection among US HIV-Infected Men Enrolled in Clinical Trials

Outbreaks of sexually transmitted hepatitis C virus (HCV) infection have been reported among human immunodeficiency virus (HIV)-infected men who have sex with men in Europe, Australia, and New York. Whether this is occurring across the United States is unknown. The authors determined incidence of HCV infection during 1996-2008 among male participants of the AIDS Clinical Trial Group Longitudinal Linked Randomized Trials cohort, a long-term study of HIV-infected persons randomized into selected US-based clinical trials. The authors evaluated associations with self-reported injection drug use (IDU), time-varying CD4+ cell count, and HIV RNA level with use of multivariate Poisson regression. No sexual or non-IDU risk factor data was available. A total of 1,830 men had an initial negative HCV antibody test result and at least 1 subsequent HCV antibody test result, contributing >7000 person-years. At the time of the initial negative HCV antibody test result, 94% of men were receiving highly active antiretroviral therapy (HAART) and 6% reported current or prior IDU. Thirty-six seroconverted, with overall incidence of .51 cases per 100 person-years (95% confidence interval, .36-.70). Mean age at seroconversion was 46 years. Seroconversion was associated with IDU (25% of seroconverters reported IDU history vs 5% of nonseroconverters; $P < .001$), whereas 75% ($n = 27$) of seroconverters reported no IDU (incidence, 2.67 cases per 100 person-years among IDUs, .40 cases per 100 person-years among non-IDUs). Seroconversion was associated with HIV RNA level >400 copies/mL (44% at time of antibody positivity vs 21% at time of last negative antibody test result; $P = .02$) but not with CD4+ cell count. Incident HCV infection occurs in HIV-infected men involved in US HIV therapeutic trials, primarily through nonparenteral means, despite engagement in care and HAART. HCV antibody development was not related to immune status but was associated with inadequate HIV suppression. At-risk HIV-infected persons should have access to HCV surveillance. Taylor LE, Holubar M, Wu K, Bosch RJ, Wyles DL, Davis JA, Mayer KH, Sherman KE, Tashima KT. Incident Hepatitis C Virus Infection among US HIV-Infected Men Enrolled in Clinical Trials. *Clin Infect Dis*. 2011 Mar; 52(6): 812-818. Epub 2011 Jan 31.

Hepatitis C Pharmacogenetics: State of The Art in 2010

In 2009, a correlated set of polymorphisms in the region of the interleukin-28B (IL28B) gene were associated with clearance of genotype 1 hepatitis C virus (HCV) in patients treated with pegylated interferon-alfa and ribavirin. The same polymorphisms were subsequently associated with spontaneous clearance of HCV in untreated patients. The link between IL28B genotype and HCV clearance may impact decisions regarding initiation of current therapy, the

design and interpretation of clinical studies, the economics of treatment, and the process of regulatory approval for new anti-HCV therapeutic agents. Afdhal NH, McHutchison JG, Zeuzem S, Mangia A, Pawlotsky JM, Murray JS, Shianna KV, Tanaka Y, Thomas DL, Booth DR, Goldstein DB. Pharmacogenetics and Hepatitis C Meeting Participants. Collaborators: Aerssens J, Afdhal NH, Anderson SM, Amur SG, Birnkrant D, Murray JS, Robertson SM, Struble KA, Whitaker K, Apelian D, Appleman J, Arbeit RD, Berrey MM, Booth DR, Botfield M, George S, Brass C, Brews J, Clark P, McHutchison JG, Naggie S, Patel K, Thompson AJ, Brun SC, Carrington M, Chao S, Rossi SJ, Cloherty G, Coakley EP, Fellay J, Goldstein DB, Shianna KV, Urban TJ, Faruki H, Hopkins S, Hughes N, Kish C, Kreter B, Lee WA, Liang TJ, Thomas E, Lopatin U, Manda V, Scherer R, Van Antwerp W, Mangia A, Mizokami M, Oldach D, Pawlotsky JM, Picchio G, Schulman KA, Subramanian GM, Sulkowski MS, Tanaka Y, Thommes JA, Zeuzem S, Zhu Y. *Hepatology*. 2011 Jan; 53(1): 336-345.

Predictors and Effects of Alcohol Use on Liver Function Among Young HCV-Infected Injection Drug Users in a Behavioral Intervention

Hepatitis C virus (HCV) screening can provide opportunities to reduce disease progression through counseling against alcohol use, but empirical data on this issue are sparse. The authors determined the efficacy of a behavioral intervention in reducing alcohol use among young, HCV-infected injection drug users (IDUs) (n=355) and assessed whether changes in liver enzymes were associated with changes in alcohol consumption. Both the intervention and attention-control groups were counseled to avoid alcohol use, but the intervention group received enhanced counseling. Logistic regression, ANOVA, and continuous time Markov models were used to identify factors associated with alcohol use, changes in mean ALT and AST levels, and change in alcohol use post-intervention. Six months post-intervention, alcohol abstinence increased 22.7% in both groups, with no difference by intervention arm. Transition from alcohol use to abstinence was associated with a decrease in liver enzymes, with a marginally greater decrease in the intervention group (p=0.05 for ALT; p=0.06 for AST). In multivariate Markov models, those who used marijuana transitioned from alcohol abstinence to consumption more rapidly than non-users (RR=3.11); those who were homeless transitioned more slowly to alcohol abstinence (RR=0.47); and those who had ever received a clinical diagnosis of liver disease transitioned more rapidly to abstinence (RR=1.88). Although, behavioral counseling to reduce alcohol consumption among HCV-infected IDUs had a modest effect, reductions in alcohol consumption were associated with marked improvements in liver function. Interventions to reduce alcohol use among HCV-infected IDUs may benefit from being integrated into clinical care and monitoring of HCV infection. Drumright LN, Hagan H, Thomas DL, Latka MH, Golub ET, Garfein RS, Clapp JD, Campbell JV, Bonner S, Kapadia F, Thiel TK, Strathdee SA. *J Hepatol*. 2010 Nov 24.

IL28B and the Control of Hepatitis C Virus Infection

Treatment-induced control and spontaneous clearance of hepatitis C virus (HCV) infection are affected by various host factors. Polymorphisms in the region of the gene IL28B are associated with HCV clearance, implicating the gene product, interferon (IFN)- γ 3, in the immune response to HCV. Although it is not clear how the IL28B haplotype affects HCV clearance, IFN- γ 3 up-regulates interferon-stimulated genes, similar to IFN- α and IFN- β but via a different receptor. There is also evidence that IFN- γ 3 affects the adaptive immune response. The IL28B genotype can be considered, along with other factors, in predicting patient responses to therapy with pegylated IFN- α and ribavirin. The authors review the genetic studies that uncovered the association between IL28B and HCV clearance, the biology of IFN- γ 3, the clinical

implications of the genetic association, and areas of future research. Balagopal A, Thomas DL, Thio CL. *Gastroenterology*. 2010 Dec; 139(6): 1865-76. Epub 2010 Oct 13.

Clinical Experience with the Treatment of Hepatitis C Infection in Patients on Opioid Pharmacotherapy

The purpose of this study was to evaluate the efficacy, safety and adherence to hepatitis C (HCV) therapy in patients attending tertiary hepatitis clinics who are receiving opioid replacement therapy. The study was a non-randomized, open-label study. Participants were treated with pegylated interferon alfa-2a and weight-based ribavirin for 24 weeks (genotype non-1, n=31) or 48 weeks (genotype 1, n=22). The study setting was four tertiary hospital hepatitis clinics in Australia. Fifty-three patients with chronic HCV who were receiving opioid replacement therapy served as subjects. Patients were monitored for virological response, adverse events and adherence. They were also screened for psychiatric illness prior to and throughout the study utilizing 2 validated instruments: the MINI and BDI-II. The overall sustained virological response (SVR) rate was 57% (71% genotype non-1 vs. 36% genotype 1), and was similar in active injectors (63%) and non-injectors (53%). The psychological profile of patients based on validated instruments did not change on therapy. The pattern and frequency of AEs were comparable to non-opioid replacement patients. Eighty-five percent of patients were adherent to therapy by 80/80/80 criteria and only 2 patients who had an end of treatment response relapsed, one of whom was not an active injector. Patients on opioid replacement therapy, even if they continue to actively inject, can achieve comparable SVR rates to other populations with pegylated interferon alfa-2a and ribavirin therapy, suffer no excess rates of AEs or psychological complications and have good adherence to therapy. Sasadeusz JJ, Dore G, Kronborg I, Barton D, Yoshihara M, Weltman M. *Addiction*. 2010 Dec 16.

Management of Adverse Effects of Peg-IFN and Ribavirin Therapy for Hepatitis C

HCV infects approximately 2-3% of the global population and is a leading cause of end-stage liver disease and hepatocellular carcinoma. Treatment of HCV infection with Peg-IFN in combination with ribavirin can eradicate HCV infection in 40-90% of patients; however, a major barrier to treatment uptake and delivery is the association of this therapy with frequent and, at times, serious adverse effects. Recognition and effective management of these adverse effects are critical components of the successful treatment of chronic HCV infection. In clinical trials, approximately 10-15% of patients discontinue Peg-IFN and ribavirin therapy due to adverse effects; however, in clinical practice, the rate of treatment discontinuation has been reported to be substantially higher. The off-target effect of Peg-IFN and ribavirin impacts most, if not all, organ systems; the most common adverse effects are hematologic, dermatologic, neurologic, immunologic, gastrointestinal, pulmonary, cardiovascular, and ocular. Regional and global variability exists in the nature of these adverse effects and the strategies employed to ameliorate their impact. This article provides a comprehensive literature review that systematically describes the adverse effects of Peg-IFN- α and ribavirin on various organ systems and, more importantly, recommends consensus approaches to managing those effects. Sulkowski MS, Cooper C, Hunyady B, Jia J, Ogurtsov P, Peck-Radosavljevic M, Shiffman ML, Yurdaydin C, Dalgard O. Management of adverse effects of Peg-IFN and ribavirin therapy for hepatitis C. *Nat Rev Gastroenterol Hepatol*. 2011 Mar 8. [Epub ahead of print].

Acute Effects of Waterpipe Tobacco Smoking: A Double-Blind, Placebo-Control Study

Waterpipe tobacco smoking usually involves heating flavored tobacco with charcoal and inhaling the resulting smoke after it has passed through water. Waterpipe tobacco smoking increases heart rate and produces subjective effects similar to those reported by cigarette smokers. These responses are thought to be nicotine-mediated, though no placebo-control studies exist. Accordingly, this double-blind, placebo-control study compared the acute physiological and subjective effects of waterpipe tobacco smoking to those produced when participants used a waterpipe to smoke a flavor-matched, tobacco-free preparation. Occasional waterpipe tobacco smokers (n=37; 2-5 monthly smoking episodes for 6 months) completed two double-blind, counterbalanced sessions that differed by product: preferred brand/flavor of waterpipe tobacco or flavor-matched, tobacco-free preparation. For each 45-min, ad lib smoking episode blood and expired air CO were sampled, cardiovascular and respiratory response were measured, and subjective response was assessed. Waterpipe tobacco smoking significantly increased mean (\pm SEM) plasma nicotine concentration (3.6 ± 0.7 ng/ml) and heart rate (8.6 ± 1.4 bpm) while placebo did not (0.1 ± 0.0 ng/ml; 1.3 ± 0.9 bpm). For carboxyhemoglobin (COHb) and expired air CO, significant increases were observed for tobacco ($3.8\pm 0.4\%$; 27.9 ± 2.6 ppm) and for placebo ($3.9\pm 0.4\%$; 27.7 ± 3.3 ppm) with no differences across condition. Independent of condition, symptoms of nicotine/tobacco abstinence (e.g., "urges to smoke", "anxious") were reduced and direct effects (e.g., "dizzy", "satisfy") increased. These results from the first placebo-control study of waterpipe tobacco smoking demonstrate that waterpipe-induced heart rate increases are almost certainly mediated by nicotine though the subjective effects observed in these occasional smokers were not. Blank MD, Cobb CO, Kilgalen B, Austin J, Weaver MF, Shihadeh A, Eissenberg T. Acute effects of waterpipe tobacco smoking: A double-blind, placebo-control study. *Drug Alcohol Depend.* 2011 Jan 28. [Epub ahead of print].

Intraoperative Methadone: Rediscovery, Reappraisal, and Reinvigoration?

Adequate relief of perioperative pain has been deemed a fundamental right of patients and an obligation of practitioners. Inadequately relieved postoperative pain has numerous physiologic complications, attendant risk of increased morbidity, and causes needless suffering. More than 40% of postoperative patients report inadequate pain relief, or pain of moderate or greater intensity, despite treatment. Unrelieved acute postoperative pain is a risk factor for the development of chronic postsurgical pain. It seems axiomatic that the duration of analgesia should match the duration of pain. Kharasch ED. Intraoperative methadone: rediscovery, reappraisal, and reinvigoration? *Anesth Analg.* 2011 Jan; 112(1): 13-16.

Pharmacokinetic Drug Interactions and Adverse Consequences Between Psychotropic Medications and Pharmacotherapy for the Treatment of Opioid Dependence

Psychiatric comorbidities among opioid-dependent patients are common. Many medications used to treat both conditions are metabolized through complimentary cytochrome P450 isoenzymes. When medication-assisted treatment for opioid dependence is concurrently used with psychotropic medications, problematic pharmacokinetic drug interactions may occur. The authors reviewed relevant English language articles identified through the MedLine, Scopus, and Embase databases from 1950 to December 2009 using the specific generic names of medications and keywords such as pharmacokinetics and drug interactions with buprenorphine, methadone, and naltrexone. Selected references from these articles were reviewed. Additionally, a review was conducted of abstracts and conference proceedings

from national and international meetings from 1990 to 2009. A total of 60 studies were identified and reviewed. Clinical case series and carefully controlled pharmacokinetic interaction studies have been conducted between methadone, buprenorphine, or naltrexone and some psychoactive medications. Important pharmacokinetic drug interactions have been demonstrated within each class of medications affecting either methadone and buprenorphine or psychoactive drugs. Few studies, however, have been conducted with naltrexone. Several interactions between methadone, buprenorphine, or naltrexone and psychoactive medications are described and may have important clinical consequences. To optimize care, clinicians must be alerted to these interactions. Saber-Tehrani AS, Bruce RD, Altice FL. *Am J Drug Alcohol Abuse*. 2011 Jan; 37(1): 1-11.

Waterpipe Tobacco Smoking and Cigarette Smoking: A Direct Comparison of Toxicant Exposure and Subjective Effects

Waterpipe tobacco smoking is increasing worldwide and is believed by many users to be less harmful and addictive than cigarette smoking. In fact, waterpipe tobacco and cigarette smoke contain many of the same chemicals, and users are exposed to the dependence-producing drug nicotine as well as other smoke toxicants. The subjective effect profile of these 2 tobacco use methods has not been compared directly, though this information is relevant to understanding the risk of dependence development. Fifty-four participants who reported waterpipe and cigarette smoking completed 2, 45-min, counter-balanced sessions in which they completed a waterpipe use episode (mean smoking time = 43.3 min) or a cigarette (mean = 6.1 min). Outcome measures included plasma nicotine, carboxyhemoglobin (COHb), and subjective effects, including those relevant to predicting dependence potential. Mean (\pm SEM) peak plasma nicotine concentration did not differ by session (waterpipe = 9.8 ± 1.0 ng/ml; cigarette = 9.4 ± 1.0 ng/ml). Mean peak COHb concentration differed significantly (waterpipe = $4.5\% \pm 0.3\%$; cigarette = $1.2\% \pm 0.1\%$). Subjective effect changes for waterpipe and cigarette were comparable in magnitude but often longer lived for waterpipe. Relative to a cigarette, waterpipe tobacco smoking was associated with similar peak nicotine exposure, 3.75-fold greater COHb, and 56-fold greater inhaled smoke volume. Waterpipe and cigarette influenced many of the same subjective effect measures. These findings are consistent with the conclusion that waterpipe tobacco smoking presents substantial risk of dependence, disease, and death, and they can be incorporated into prevention interventions that might help deter more adolescents and young adults from experimenting with an almost certainly lethal method of tobacco use. Cobb CO, Shihadeh A, Weaver MF, Eissenberg T. *Waterpipe tobacco smoking and cigarette smoking: a direct comparison of toxicant exposure and subjective effects*. *Nicotine Tob Res*. 2011 Feb; 13(2): 78-87. Epub 2010 Dec 2.

Estimated Infant Exposure to Enantiomer-Specific Methadone Levels in Breastmilk

Breastfeeding, a public health priority, improves outcomes for infants. Methadone is dispensed as a racemic mixture; R-methadone is the active enantiomer. Pharmacologic data for R-methadone in breastmilk could improve risk-benefit decision-making for treatment of lactating women. This study estimated infant exposure to R- and S-methadone via breastmilk by theoretic infant dose (TID) and relative infant dose (RID) and reported the milk-to-maternal plasma (M/P) ratio. Women treated with methadone doses of 40-200 mg/day (mean, 102 mg/day) provided concomitantly collected plasma and breastmilk samples 1-6 days after delivery. Most (16 of 20) samples were taken at the time of peak maternal plasma levels; thus infant exposure estimates are for maximum possible exposure. Concentrations of R- and S-methadone were measured in maternal plasma and breastmilk; M/P ratio, TID,

and RID were calculated for each enantiomer and total methadone. The 20 participants were 18-38 years old and publicly insured; a quarter did not complete high school, and only one was not white. R-Methadone concentration was 1.3-3.0 times that of S-methadone in all breastmilk samples. The mean (SD) R-, S-, and total methadone M/P ratios were 0.52 (0.28), 0.28 (0.15), and 0.40 (0.21), respectively. Mean (range) R-, S-, and total methadone TID were 0.02 mg/kg/day (0.004-0.099), 0.013 mg/kg/day (0.002-0.071), and 0.033 mg/kg/day (0.006-0.170), respectively. Mean (range) RID of R-, S-, and total methadone were 2.7% (0.7-10.1%), 1.6% (0.3-7.2%), and 2.1% (0.52-8.8%), respectively. R-Methadone is found in higher concentrations than S-methadone in breastmilk. Even at high methadone doses, breastmilk methadone concentrations were relatively low and support American Academy of Pediatrics recommendations that dose should not be a factor in determining whether women on methadone breastfeed. Bogen DL, Perel JM, Helsel JC, Hanusa BH, Thompson M, Wisner KL. Estimated Infant Exposure to Enantiomer-Specific Methadone Levels in Breastmilk. *Breastfeed Med.* 2011 Feb 24. [Epub ahead of print].

Potential Latent Effects of Prenatal Cocaine Exposure on Growth and the Risk of Cardiovascular and Metabolic Disease in Childhood

The literature strongly suggests that prenatal exposure to certain medications and substances does not cause major malformations in early childhood. However, these exposures may have far-reaching latent health effects, such as restricted growth, hypertension, and cardiovascular events in adulthood. The authors reviewed the literature to identify the effects of prenatal cocaine exposure on growth and the risk of cardiovascular and metabolic disease in late adolescence and early adulthood by examining studies that were published in peer-reviewed English-language journals from 1990 through 2009 and indexed in MEDLINE. The authors found that animal and clinical studies of the influence of prenatal cocaine exposure on child and adolescent growth and the subsequent development of myocardial and cardiometabolic disease risk factors are few and inconclusive. Studies support the hypothesis that vascular and hemodynamic functions are partially programmed in early life and thus substantially influence vascular aging and arterial stiffening in later life. Sub-optimal fetal nutrition and growth may increase blood pressure and the development of cardiovascular and metabolic disease in late life. How prenatal cocaine and other drug exposure effects this relationship is currently unknown. Despite high rates of cocaine and other drug use during pregnancy (up to 18% in some studies), little is known about the health effects of prenatal cocaine exposure in adolescence and early adulthood. The few studies of early growth deficits persisting into adolescence are inconclusive. The literature provides little information on how exposed children grow into adulthood and about their subsequent risk of cardiometabolic and vascular disease. Messiah SE, Miller TL, Lipshultz SE, Bandstra ES. Potential latent effects of prenatal cocaine exposure on growth and the risk of cardiovascular and metabolic disease in childhood. *Prog Pediatr Cardiol.* 2011 Jan 1; 31(1): 59-65.

The Feasibility of Ambulatory Biosensor Measurement of Salivary Alpha Amylase: Relationships with Self-Reported and Naturalistic Psychological Stress

Recent developments in biosensor technology allow point-of-use reporting of salivary alpha amylase (sAA) levels while approaching the precision and accuracy of conventional laboratory-based testing. The authors deployed a portable prototype sAA biosensor in 54 healthy, male dental students during a low stress baseline and during final exams. At baseline, participants completed the Brief Symptom Inventory (BSI). At baseline and the exam week, participants provided saliva samples at 10 AM, 1 PM, and 5 PM, and rated concurrent subjective distress. Although subjective distress was higher during

exams compared to baseline, sAA levels did not differ between baseline and exams. Higher sAA levels were related to higher concurrent subjective distress, and higher depressive and social isolation symptoms on the BSI were related to lower sAA during exams. Results from this study, in combination with previous validation data, suggest that the sAA biosensor is a promising tool for point-of-use measures of exposure to stress. The feasibility of ambulatory biosensor measurement of salivary alpha amylase: Relationships with self-reported and naturalistic psychological stress. Robles TF, Shetty V, Zigler CM, Glover DA, Elashoff D, Murphy D, Yamaguchi M. Biol Psychol. 2011 Jan; 86(1): 50-56. Epub 2010 Oct 16.

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

Research Findings - Services Research

Enrollment in Outpatient Care Among Newly Released HIV+ Prison Inmates

Although many prisoners infected with human immunodeficiency virus (HIV) initiate and adhere to treatment regimens while incarcerated, the benefits of in-prison therapy are frequently lost after community reentry. Little information is available on the percentage of released inmates who establish community-based HIV outpatient treatment in a timely fashion. The authors sought to determine the proportion of HIV-infected Texas prison inmates who enrolled in an HIV clinic within 90 days after release and to identify variables associated with timely linkage to clinical care. This was a retrospective cohort study of 1,750 HIV-infected inmates who were released from the Texas Department of Criminal Justice (TDCJ) and returned to Harris County between January 2004 and December 2007. Demographic and clinical data were obtained from centralized databases maintained by TDCJ and the Harris County Health District, and used logistic regression analysis to identify factors associated with linkage to post-release outpatient care. Only 20% of released inmates enrolled in an HIV clinic within 30 days of release, and only 28% did so within 90 days. Released inmates 30 years of age were more likely than their younger counterparts to have enrolled in care at the 30- and 90-day time points. Inmates diagnosed with schizophrenia were more likely to have initiated care within 30 days. Inmates who received antiretroviral therapy while incarcerated and those who received enhanced discharge planning were more likely to begin care at both time points. A large proportion of HIV-infected inmates fail to establish outpatient care after their release from the Texas prison system. Implementation of intensive discharge planning programs may be necessary to ensure continuity of HIV care among newly released inmates. Baillargeon JG, Giordano TP, Harzke AJ, Baillargeon G, Rich JD, Paar DP. Enrollment in outpatient care among newly released prison inmates with HIV infection. Public Health Rep. 2010; 125 (Supp 1): 64-71.

Clinic-based Treatment for Opioid-dependent HIV-infected Patients versus Referral to an Opioid Treatment Program

Opioid dependence is common in HIV clinics. Buprenorphine/ naloxone (BUP) is an effective treatment for opioid dependence that may be used in routine medical settings. This study compared clinic-based treatment with BUP (clinic-based BUP) with case management and referral to an opioid treatment program (referred-treatment). The design was a single-center, 12-month randomized trial. Participants and investigators were aware of treatment assignments. The setting was an HIV clinic in Baltimore, Maryland. Participants were 93 HIV-infected, opioid-dependent subjects who were not receiving opioid agonist therapy and were not dependent on alcohol or benzodiazepines. The

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clinic-based BUP strategy included BUP induction and dose titration, urine drug test monitoring, and individual counseling; the referred-treatment arm included case management and referral to an opioid treatment program. Measures were: Initiation and long-term receipt of opioid agonist therapy, urine drug test results, visit attendance with primary HIV providers, use of antiretroviral therapy, and changes in HIV RNA levels and CD4 cell counts. Results showed the average estimated participation in opioid agonist therapy was 74% (95% CI 61%-84%) in clinic-based BUP and 41% (29%-53%) in referred-treatment ($p < 0.001$). Opioid and cocaine positive urine drug tests were significantly less frequent in clinic-based BUP than in referred treatment, and study subjects in clinic-based BUP attended significantly more HIV primary care visits than study subjects in referred-treatment. Use of antiretroviral therapy and changes in HIV RNA levels and CD4 cell counts did not differ in the 2 arms of the study. This study suggests that management of HIV-infected, opioid-dependent patients with a clinic-based BUP strategy facilitates access to opioid agonist therapy and improves substance abuse treatment outcomes. Lucas GM, Chaudhry A, Hsu J, Woodson T, Lau B, Olsen Y, Keruly JC, Fiellin DA, Fiellin DARF, Barditch-Crovo P, Cook K, Moore RD. Clinic-based treatment for opioid-dependent HIV-infected patients versus referral to an opioid treatment program: A randomized controlled trial. *Ann Intern Med.* 2010; 152 (11): 704-711.

The Implementation of Tobacco-Related Brief Interventions in Substance Abuse Treatment Depend on Management Support and Counselor Knowledge and Personal Smoking

Most individuals receiving substance abuse treatment also use tobacco, which suggests that smoking cessation is an important clinical target for most clients. Few studies have measured the extent to which addiction treatment counselors address clients' tobacco use. This study examined counselors' implementation of brief interventions that are consistent with the U.S. Public Health Service's (PHS) clinical practice guideline, *Treating Tobacco Use and Dependence*, when counselors are engaging new clients in treatment. Specifically, the study examined to the extent to which implementation was associated with organizational and counselor-level factors. Data were collected from 2,067 counselors via mailed surveys with a 55% response rate. Relationships based upon least squares regression (Adjusted $R^2 = .26$, $p < .001$) are as follows. Implementation of recommended brief interventions during intake was significantly lower among counselors reporting greater barriers to smoking cessation services within their organizational context (Beta = $-.125$, $p < .001$). Perceived managerial support for smoking cessation services was positively associated with implementation (Beta = $.171$, $p < .001$). Counselors with greater knowledge of the PHS guideline and who believed in the positive impact of smoking cessation interventions on sobriety reported greater implementation (Beta = $.260$, $p < .001$). Relative to counselors who have never been tobacco users, current tobacco users reported significantly lower implementation of these brief interventions (Beta = $-.132$, $p < .001$). These findings suggest that attempts to increase the implementation of best practices in substance abuse treatment may require attention to organizational contexts and the individuals responsible for implementation. Knudsen H, Studts J. The implementation of tobacco-related brief interventions in substance abuse treatment: A national study of counselors. *J Subst Abuse Treat.* 2010; 38 (3): 212-219.

Use of Total Quality Management Principles Enhances Adoption of Evidence-Based Practices

This study investigates whether and how the delivery of evidence-based practices (EBPs) in addiction treatment programs is supported by the use of evidence-based program management practices, thus linking managerial and clinical performance. Face-to-face interviews were conducted with

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administrators and clinical directors of a nationally representative sample of 738 private and public sector drug treatment programs in 2002-2004. Data were collected on a number of key organizational characteristics, the use of Total Quality Management (TQM) practices (collection and use of data for clinical decisions; staff training; and quality planning); and the delivery of comprehensive care and EBPs as defined in NIDA's Principles of Drug Abuse Treatment. In multivariate models, several organizational variables (size, accreditation, staff credentials, caseload) predicted the use of TQM practices, which in turn was positively related to provision of comprehensive care and the use of EBPs. Thus, substance abuse treatment program's implementation of effective management practices appears to increase the likelihood of adopting clinical practices that ensure quality patient care. Fields D, Roman PM. Total quality management and performance in substance abuse treatment centers. *Health Serv Res.* 2010; 45 1630-1650.

Initiation and Engagement in Chronic Disease Management Care for Substance Dependence

Substance dependence treatment is often episodic and not well coordinated with healthcare for common co-morbidities. Chronic disease/care management (CDM), longitudinal, patient-centered care delivered by multidisciplinary health professionals, may be well suited to treat substance dependence (SD). The purpose of this study is to examine initiation and engagement with CDM care for SD located in a primary medical setting. The authors prospectively studied substance dependent participants enrolled in a trial of CDM addiction care. Primary study outcomes, based upon Washington Circle performance measures, were 14-day initiation of CDM care and 30-day engagement with CDM care. Factors associated with these outcomes were determined using multivariable logistic regression models. Authors also estimated the proportion of participants who eventually attended at least two visits and four visits by the end of the study (Kaplan-Meier method). It was found that of 282 participants, approximately half of the cohort (45%, 95% Confidence Interval [CI] 39-51%) met criteria for 14-day initiation and 23% (95% CI 18-28%) for 30-day engagement with CDM care. Most participants attended two or more (81%, 95% CI 76-85%) and four or more CDM visits (62%, 95% CI 56-68%). Major depressive episode (AOR 2.60, 95% CI 1.39, 4.87) was associated with higher odds of 14-day initiation; younger age, female sex, and higher alcohol addiction severity were associated with lower odds of 30-day engagement with CDM care. It was concluded that people with SD appear to be willing to initiate and engage with CDM care in a primary medical care setting. CDM care has the potential to improve the quality of care for people with addictions. Kim TW, Saitz R, Chang DM, Winter MR, Witas J, Samet JH. Initiation and engagement in chronic disease management care for substance dependence. *Drug Alcohol Depend.* 2010; N/Adoi:10.1016/j.drugalcdep.2010.10.013 (N/A): 1-7.

Effective HIV Risk Reduction Protocol for Drug-Using Women Sex Workers

HIV prevention is an especially salient issue for women, given the ongoing feminization of the epidemic. Female sex workers are especially vulnerable to HIV infection, particularly those who are drug-using and engage in street-based sex exchange. This paper examines risk behaviors and HIV sero-status of 806 drug-using women sex workers in Miami, Florida, and assesses the relative impact of two HIV and hepatitis prevention interventions on changes in risk behavior. Drug-using sex workers were recruited using targeted sampling strategies and were randomly assigned to one of two intervention conditions - the NIDA Standard, or an innovative Sex-Worker Focused (SWF) intervention. Interview data were collected pre-intervention and 3 and 6 months post-intervention, and blood samples were collected for HIV and hepatitis B and C testing. Overall, 21% of the sample tested HIV positive. Outcome analyses

indicate that both groups benefited from participation in the intervention trial. However, the SWF intervention was found to be more efficacious with reductions in unprotected oral sex, and sexual violence. These data support the importance of HIV testing and intervention programs for drug-using women sex workers. Surratt HL, Inciardi JA. An effective HIV risk reduction protocol for drug-using women sex workers. *J Prev Interv Community*. 2010; 38 (2): 118-131.

Training and Exposure Enhance Counselor Acceptance of Motivational Incentives

Counselor attitudes toward evidence-based practices, such as motivational incentives/ contingency management (MI/CM), are important in bridging the gap between research and practice. This study surveyed 1,959 substance abuse treatment counselors to measure attitudes and experience with MI/CM and barriers to its adoption. Counselors worked in 214 treatment programs affiliated with NIDA's Clinical Trials Network, or in any of 368 randomly-sampled public sector programs not affiliated with the CTN. On balance, counselors showed ambivalence toward MI/CM and strong disagreement with using monetary rewards for achievement of treatment goals. Greater resistance to the use of MI/CM was found among counselors with lower levels of educational attainment ($p < .001$) and stronger 12-step treatment ideology ($p < .001$); greater support for MI/CM was found among counselors working in opioid treatment programs ($p < .01$) and in programs affiliated with the CTN ($p < .05$). While exposure to MI/CM via training was more strongly associated with attitudes when counselors worked in programs that had adopted MI/CM. Receipt of training on MI/CM improved counselors' attitudes toward the use of tangible rewards ($p < .001$), but training had its greatest impact among counselors who also had hands-on experience using MI/CM in their treatment program ($p < .01$ for interaction term). Thus, while there remains substantial philosophical resistance to MI/CM among counselors, effective and targeted dissemination and training about the essential elements of MI/CM may enhance counselors' receptivity toward this intervention. Ducharme L, Knudsen H, Abraham A, Roman P. Training and exposure enhance counselor acceptance of motivational incentives *Am J Addict*. 2010; 19: 496-503.

Parity in the Federal Employees Health Benefit (FEHB) Plan Did Not Increase Total Expenditures on Substance Abuse Services among Those Continuously Enrolled in Preferred Provider Organizations (PPO)

The insurance claims experience of 45,000 beneficiaries age 18 to 64 continuously enrolled in one of six FEHB PPOs was examined to determine the impact of the presidential order requiring the 2001 implementation of comprehensive parity of addiction benefits in FEHB plans. Difference-in-difference (diff-in-diff) methods were used to analyze changes in utilization, expenditures, and quality measures from the two years prior (1999-2000) and post-implementation (2001-2002), using data from a matched sample of 45,000 beneficiaries enrolled in private health plans not subject to parity, from the MarketScan[®] database, to control for secular trends. Addiction diagnoses and services were identified using ICD-9-CM codes, and a two-part model was used to estimate average costs conditional on receiving any service. Minimum quality levels were assessed using the Washington Circle Performance measures for identification (the proportion of enrollees who received an addiction diagnosis or service), initiation (the proportion of adults with a new service who had a minimum of two additional services within 14 days), and engagement (the proportion of adults who met initiation who had a least two more services within the next 30 days). Results revealed that spending on and utilization of addiction services increased in both the FEHB and MarketScan[®] plans, but there was no significant difference in the increases across the two

groups. Out-of-pocket costs, however, were reduced over the time period for those in the FEHP plans compared with those in the MarketScan[®] plans (mean difference = -\$101.09, 95% CI = -\$198 to -\$4.12), and there was an increase in identification in the FEHB plans relative to the MarketScan[®] plans (diff-in-diff risk = 0.10, 95% CI 0.02-0.19). There were no statistically significant differences in the changes in the other quality measures. Azzone V, Frank R, Normand S, Burnam M. Effect of insurance parity on substance abuse treatment. *Psychiatr Serv.* 2011; 62 (2): 129-134.

NIDA Clinical Trials Network Participation Influences Innovations Outside CTN Protocols

Organizational participation in clinical research may lead to adoption of the intervention by treatment agencies, but it is not known whether research involvement enhances innovativeness beyond the specific interventions that are tested. The National Institute on Drug Abuse's Clinical Trials Network (CTN) is a platform for considering this research question. To date, the CTN has not conducted research on medications for alcohol use disorders (AUDs), so greater adoption of innovative AUD pharmacotherapies by CTN-affiliated programs would suggest an added value of research network participation. Using longitudinal data from a pooled sample of 147 publically-funded CTN clinics (86% response rate) and 327 publically-funded non-CTN (75% follow-up rate) the adoption of tablet naltrexone and acamprosate was examined over a 2-year period. At 24-month follow-up, CTN-affiliated programs were 3.5 times more likely to have adopted acamprosate and 3.18 times more likely to use tablet naltrexone. Research network participation thus appears to enhance organizational innovativeness to include interventions beyond the scope of the network. Abraham A, Knudsen H, Rothrauff T, Roman P. The adoption of alcohol pharmacotherapies in the Clinical Trials Network: The influence of research network participation. *J Subst Abuse Treat.* 2010; 38 (3): 275-283.

A Longitudinal Study Finds Modest Levels of Innovation and Dissemination Activities within NIDA Clinical Trials Network

The National Drug Abuse Treatment Clinical Trials Network (CTN) was instituted to conduct trials of promising substance abuse treatment interventions in diverse clinical settings and to disseminate results of these trials. This study focused on three dimensions of CTN's organizational functioning in a sample of 241 provider organizations (92% response rate). First, a longitudinal dataset is used to examine CTN's formation as a network of inter-organizational interaction among treatment practitioners and researchers. Data indicate strong relationships of interaction and trust, but a decline in problem-centered inter-organizational interaction over time. Second, adoption of buprenorphine, and motivational incentives among CTN's affiliated community treatment programs (CTPs) was examined over three waves of data over 48 months. Although adoption was found to increase with CTPs' participation in the CTN, there is only modest evidence of widespread penetration and implementation. Despite strong evidence of superior treatment effects, ideological beliefs of both organizations and incumbent staff often stymie post-trial implementation. Third, CTPs' pursuit of the CTN's dissemination goals indicated that organizational outreach activities are increasing. Evidence shows growing efforts to influence funding agencies to adopt innovations. Roman P, Abraham A, Rothrauff T, Knudsen H. A longitudinal study of organizational formation, innovation adoption, and dissemination activities within the National Drug Abuse Treatment Clinical Trials Network. *J Subst Abuse Treat.* 2010; 38 Suppl 1: S44-S52.

Testing an Optimized Community-Based HIV Risk Reduction and Antiretroviral Adherence Intervention

The authors conducted a preliminary study of the 4-session Holistic Health for HIV (3H+), which was adapted from a 12-session evidence-based risk reduction and antiretroviral adherence intervention. Participants ($n = 39$) were recruited in New Haven, CT, from community-based, non-research-oriented programs and health services centers (e.g., homeless shelters, addiction treatment centers, medical clinics). Invitation to participate required meeting the following criteria: (1) HIV-infected; (2) meeting Diagnostic and Statistical Manual of Mental Disorder Fourth Edition (DSM-IV) criteria for opioid dependence; (3) confirmation of current prescription of antiretroviral medications; and (4) self-reported HIV risk behavior within the past month. Improvements were found in the behavioral skills required to properly adhere to HIV medication from pre-intervention (mean=5.22, SD = 2.45) to post-intervention (mean = 6.64, SD=2.06). Improvements were found in all measured aspects of sex-risk reduction outcomes, including HIV knowledge, motivation to reduce sex-risk behavior, behavioral skills related to engaging in reduced sexual risk, and reduced risk behavior. Improvements in drug use outcomes included enhancements in risk reduction skills as well as reduced heroin use from pre-intervention (mean = 7.02 days in the past month, SD = 10.2) to post-intervention (mean = 0.87 days in the past month, SD = 2.1), $F(1, 19) = 8.19, P = .010$. Participants also reported significant reductions in cocaine use from pre-intervention (mean = 7.96 days in the past month, SD = 8.56) to post intervention (mean = 3.90 days in the past 30 month, SD=5.59), $F(1, 19)=4.55, P=.046$, to follow-up (mean = 4.81 days in the past month), $F(2, 30) = 4.48, P = .02$ (Figure 5). Intervention effects also showed durability from post-intervention to the follow-up assessment point. Females responded particularly well in terms of improvements in risk reduction skills and risk behavior. This study suggests that an evidence-based behavioral intervention may be successfully adapted for use in community-based clinical settings where HIV-infected drug users can be more efficiently reached. Copenhagen M, Lee I, Margolin A, Bruce R, Altice F. Testing an optimized community-based Human Immunodeficiency Virus (HIV) risk reduction and antiretroviral adherence intervention for HIV-infected injection drug users. *Subst Abus.* 2011; 32 (1): 16-26.

Predicting Non-response to Juvenile Drug Court Interventions

Using data from a recent randomized clinical trial involving juvenile drug court (JDC), youth marijuana use trajectories and the predictors of treatment non-response (intervention failure) were examined. Participants were 118 juvenile offenders meeting diagnostic criteria for substance use disorders assigned to JDC and their families. Youth were ages 12-17 years and resided with at least one parent: 83% were male, 67% were African American and 97.5% met diagnostic criteria for marijuana use or dependence at time of enrollment. To enhance generalizability, no youth was excluded due to mental health, physical health, or intellectual difficulties. Urine drug screen results were gathered from weekly court visits for 6 months, and youth reported their marijuana use over 12 months. Semi-parametric mixture modeling jointly estimated and classified trajectories of both marijuana use indices. Youth were classified into responder ($n=60$) versus non-responder ($n=58$) trajectory groups based on both outcomes. Regression analyses examined pretreatment individual, family, and extra-familial predictors of non-response. Results indicated that youth whose caregivers reported illegal drug use pretreatment were almost 10 times as likely to be classified into the non-responder trajectory group. No other variable significantly distinguished drug use trajectory groups. Findings have implications for the design of interventions to improve JDC outcomes. Halliday-Boykins C, Schaeffer C, Henggeler S, Chapman J, Cunningham P, Randall J, Shapiro S. Predicting nonresponse to juvenile drug court interventions. *J Subst Abuse Treat.* 2010; 39 (4): 318-328.

Psychiatric Distress, Risk Behavior, and Treatment Enrollment

Among NEPs

The present study evaluated psychiatric distress as a predictor of treatment enrollment in out-of-treatment injection opioid users newly registered at the Baltimore Needle Exchange Program (BNEP). Study participants (n=281) completed the Addiction Severity Index (ASI), the Risk Assessment Battery (RAB), and the Symptom Checklist-90 (SCL-90-R), and were randomly assigned to one of three different conditions for 4 months that evaluated referral strategies designed to promote treatment interest and enrollment. The Global Severity Index (GSI) of the SCL-90 was used as a measure of psychiatric distress. A logistic regression showed that higher GSI scores predicted more treatment enrollment (Adjusted OR=2.15, CI=1.10-4.23, p<0.05), after controlling for study condition, demographic variables, syringe exchange site, and severity of drug use. The results suggest that the data from the assessment of psychiatric distress in syringe exchange settings can be used to support motivational strategies for encouraging syringe exchangers to seek substance abuse treatment. Kidord M, King VL, Peirce J, Burke C, Kolodner K, Brooner RK. Psychiatric distress, risk behavior, and treatment enrollment among syringe exchange participants. *Addict Behav.* 2010; 35 499-503.

Outpatient Non-Methadone Programs Seen Adding Referrals to Medical Services

Data from a sample of 69 outpatient non-methadone programs from 4 US regions were used to examine changes in services provided between two time periods, and 2004-2005 and 2006-2007. Although services offered on-site did not change much between the two time periods, referral to services offsite did. The percentage of programs offering referral to detox increased from 17% of programs to 39%. The percentage offering referrals to diagnosis, testing, and treatment of medical conditions increased from 23% to 42%, and the percentage offering referrals to psychiatric services increased from 32% to 48%. At the same time, the proportion offering referrals for assistance obtaining social services and for employee and job training both declined (17% to 6%, and 41% to 28%, respectively). Knight D, Edwards J, Flynn P. Predictors of change in the provision of services within outpatient substance abuse treatment programs. *J Public Health Manag Pract.* 2010; 16 (6): 553-563.

Workplace Smoking Bans and Staff Tobacco Use

Counselors who smoke cigarettes are less likely to promote smoking cessation among their patients through screening, assessment, counseling, or the use of nicotine replacement therapies. One potential avenue to increasing the delivery of smoking cessation in drug treatment settings is to first reduce smoking among counselors. While indoor smoking bans reduce employee tobacco use, less is known about whether comprehensive bans, which prohibit smoking in both indoor and outdoor areas, are associated with lower rates of tobacco use than indoor-only bans. This study collected surveys from 1,910 substance abuse treatment counselors and telephone interviews with 417 administrators of substance abuse treatment organizations. Multinomial logistic regression was used to estimate the associations between counselors' self-reported tobacco use and administrators' reports about organizational smoking bans while controlling for counselors' professional and demographic characteristics. In this sample, 20.3% of counselors were current tobacco users, 47.7% identified as former users, and 32.0% reported never using tobacco products. Only 19.5% of counselors worked in a treatment organization that had a comprehensive smoking ban. Current smokers were significantly less likely to work in treatment programs with comprehensive smoking bans, even after controlling for professional and demographic characteristics. Smoking bans

may represent a promising direction for tobacco control in addiction treatment settings. Knudsen HK, Boyd SE, Studts JL. Substance abuse treatment counselors and tobacco use: A comparison of comprehensive and indoor-only workplace smoking bans. *Nicotine Tob Res.* 2010; 12 (11): 1151-1155.

Parent Organization Affiliation, Staff Job Satisfaction Statistically Associated with Supervisor Turnover in Outpatient Non-Methadone Addiction Treatment Programs

Data on a naturalistic quota sample of 86 US outpatient non-methadone addiction treatment programs were used to determine the statistical association between program-level factors and supervisor turnover. Data were collected using two survey instruments. First, the Survey of Structure and Operations (SSO), a survey of general program characteristics, organizational relationships, clinical assessment and practices, services provided, staff and client characteristics, and recent changes in staff, was completed by the program director or clinical manager upon entry into the study (reflecting on the past 6 months) and 12 months later (reflecting on the past year). Second, the Survey of Organizational Functioning was completed by clinical staff who answered questions on program needs, resources, staff attributes, organizational climate, job attitudes, and workplace practices. Five-hundred and thirty-two staff members, including 467 counselors and 65 clinical and program directors, responded to these surveys, and their responses were averaged to obtain mean scores for each program. Turnover was measured as a dichotomous variable where 0 = no supervisory turnover and 1 = one or more supervisor turnovers. Variables including program structure (regular outpatient, intensive outpatient or mixed), affiliation with a parent organization (yes or no), client characteristics (proportion referred from the criminal justice system, proportion dually diagnosed), treatment characteristics (number of hours a typical client spends in counseling per week, average counselor caseload), and program averages for staff member job satisfaction and burnout rates, and director leadership quality were examined as explanatory variables. Chi-square tests and ANOVA were used first to examine bivariate relationships between supervisor turnover and the explanatory variables. Logistic regression models including variables with p-values of .10 or less in the bivariate analyses assessed multivariate relationships. The results revealed that 30% of programs reported a change of supervisors in response to the first SSO, 33% in response to the second, 11% reported changes in both rounds of the survey. The multivariate model revealed that supervisory turnover was higher among programs that were affiliated with a parent organization (OR = 1.53, $p < 0.05$) and lower among programs with higher average staff job satisfaction scores (OR=0.80, $p < 0.05$). Knight DK, Broome KM, Edwards JR, Flynn PM. Supervisory turnover in outpatient substance abuse treatment. *J Behav Health Serv Res.* 2011; 38 (1): 80-90.

Gender Differences in Substance Use and Age of First Use Among Rural Appalachian Drug Users

Previous research suggests gender differences exist in types of substances used and age of first use. Recent studies exploring contextual differences in substance use between rural Appalachian and urban environments show different patterns of substance use in rural environments. This study explores whether previously established differences in gender and age of first use exist within a rural Appalachian environment. Data are from a community-based study of drug users in rural Appalachia (N=400). Self-reported substance use was recorded using an interviewer-administered questionnaire with questions from the Addiction Severity Index (ASI). On average, participants were 32 years old mean=32.33; median=31.00; interquartile range (IQR)=12) and the majority were male (59%). Examining the past 30-day substance use, more males reported alcohol (adjusted odds ratio (AOR): 2.11, 95% CI: 1.36, 3.23;

$p=.001$) and any illegal drug use (AOR: 1.85, 95% CI: 1.16, 2.95; $p=.010$), which included heroin, cocaine, crack cocaine, methamphetamine, marijuana, and hallucinogens, after controlling for socio-demographic characteristics. ANCOVA analyses showed that males reported the use of alcohol ($p=.000$), marijuana ($p=.007$), and hallucinogens ($p=.009$) at a significantly younger age than females. Findings suggest more men report the use of alcohol and "street" drugs, including heroin, crack cocaine, methamphetamine, marijuana, and hallucinogens. Furthermore, males report the use of alcohol, marijuana, and hallucinogens at a significantly younger age. Understanding gender differences in substance use as well as other differences among individuals living in rural Appalachia presents important opportunities to incorporate this knowledge into substance abuse early intervention, prevention, and treatment efforts. Shannon L, Havens J, Oser C, Crosby R, Leukefeld C. Examining gender differences in substance use and age of first use among rural appalachian drug users in Kentucky. *Am J Drug Alcohol Abuse*. 2011; 37 (2): 98-104.

Important Gender Differences in Prescription Opioid Non-medical Use and Access to Treatment

Significant gender differences in drug and alcohol use have been reported; however, little is known about gender differences in prescription opioid misuse and dependence. This study compared correlates, sources and predictors of prescription opioid non-medical use, as well as abuse or dependence among men and women in a nationally-representative sample. Participants were 55,279 (26,746 men, 28,533 women) non-institutionalized civilians aged 12 years and older who participated in the National Survey on Drug Use and Health. The survey sample employed a 50-state design with an independent, multistage area probability sample for each of the 50 states and the District of Columbia. The majorities of the participants were over 35 years of age, Caucasian, employed, and married. In the NSDUH survey, prescription opioid non-medical use was assessed with the following question: "Have you ever, even once, used (name of prescription opioid) that was not prescribed for you or that you took only for the experience or feeling it caused?" Examination of the specific types of prescription opioids used revealed that the most commonly reported were 1) hydrocodone products such as Vicodin, Lortab and Lorcet; 2) codeine products such as Darvocet, Darvon or Tylenol with codeine; and 3) oxycodone products such as Percocet, Percodan and Oxycontin. Overall rates of lifetime and past-year non-medical use of prescription opiates were 13.6% and 5.1%, respectively. Significantly more men than women endorsed lifetime (15.9% vs. 11.2%) and past-year use (5.9% vs. 4.2%; $p = 0.0001$). Among past-year users, 13.2% met criteria for current prescription opiate abuse or dependence, and this did not differ significantly by gender. The authors highlight that among past-year users, significantly more men than women reported receiving treatment for alcohol or drug use problems at any point in their lifetime (10.9% vs. 5.7%, $p=0.001$) and in the past year (5.0% vs. 2.7%, $p=0.02$). Gender-specific predictors of use as compared to abuse/dependence were observed. The findings suggest important differences between men and women using prescription opiates. The observed differences may help enhance the design of gender-sensitive surveillance, identification, and prevention and treatment interventions. In addition, treatment utilization was exceedingly low for both men and women and more aggressive screening and preventative efforts are clearly needed to help slow what has been a continued rise in rates of use, abuse and dependence in the United States over the past decade. Back S, Payne R, Simpson A, Brady K. Gender and prescription opioids: Findings from the National Survey on Drug Use and Health. *Addict Behav*. 2010; 35 (11): 1001-1007.

Substance Use Expectancies Associated with Marijuana Use Among Young Females

This study examined associations between the endorsement of drug use expectancies and the frequency and severity of marijuana use in a community sample of 332 women aged 18-24 years who were not explicitly seeking treatment for their marijuana use. Participants were enrolled in a larger intervention study of motivational interviewing for various health behaviors and provided self-reports of their current and past marijuana use, marijuana abuse/dependence symptoms, and marijuana use expectancies. Participants averaged 20.5 years of age, 225 were Caucasian, 10.5% were African-American, 11.4% were Hispanic, and 10.2% were of other ethnic or racial origins. A majority (69.9%) had at least some college education, and 96.4% had never been married. According to social learning theory, substance use expectancies are defined as beliefs regarding the anticipated effects from using substances that affect when and how much an individual engages in drug use. In this study, marijuana use expectancies were measured using the six subscales of the Marijuana Effects Expectancy Questionnaire (MEEQ). Use frequency was defined as the number of use days in the past month, severity as the total number of DSM-IV marijuana abuse or dependence symptom criteria met. Replicating and extending prior research, expectations regarding Relaxation and Tension Reduction emerged as a robust belief in this cohort, predicting not only frequency ($p < .01$) but also severity ($p < .01$) of marijuana use in multivariate analyses. Severity of marijuana use was further predicted by expectations regarding loss of control, affective changes following marijuana use, and other aspects of emotion dysregulation (Global Negative Effects, $p < .01$). These findings document meaningful associations between substance-related cognitions and use behavior and suggest that marijuana users who hold certain beliefs regarding marijuana use may be particularly susceptible to clinically significant problems associated with their substance use. As such, marijuana use expectancies may represent a clinical target that could be incorporated into future interventions. Hayaki J, Hagerty C, Herman D, de Dios M, Anderson B, Stein M. Expectancies and marijuana use frequency and severity among young females. *Addict Behav.* 2010; 35 (11): 995-1000.

Nicotine Exposure in Daily Waterpipe Smokers and its Relation to Puff Topography

Waterpipe tobacco smoking is increasing in popularity worldwide and available evidence point to its addictive and harmful potential. This study was conducted to assess nicotine exposure in daily waterpipe smokers, and its correlation with puff topography parameters. Sixty-one waterpipe tobacco smokers (56 males; mean age \pm SD, 30.9 \pm 9.5 years; mean number of weekly waterpipe smoking episodes 7.8 \pm 5.7) abstained from smoking for at least 24h, and then smoked tobacco from a waterpipe ad libitum in a laboratory setting. During the session puff topography parameters were monitored continuously, and pre- and post-smoking expired-air CO was measured. Before and after smoking, venous blood was sampled for the assessment of plasma nicotine using Gas Chromatography-Mass Spectrometry. The average pre- and post-smoking expired-air CO was 4 \pm 1.7 and 35.5 \pm 32.7 ppm, respectively (i.e., a CO boost of 31.5 ppm, $p < .001$). Mean plasma nicotine concentration increased from 3.07 \pm 3.05 ng/ml pre-smoking to 15.7 \pm 8.7 ng/ml post-smoking ($p < .001$). Plasma nicotine boost was correlated with total session time (Pearson correlation coefficient $r = .31$, $p = .04$), cumulative puff duration ($r = .37$, $p = .01$), mean puff duration ($r = .34$, $p = .02$), and total smoke inhaled in the session ($r = .34$, $p = .02$). These data show considerable nicotine exposure in daily waterpipe smokers, and that nicotine exposure is a function of waterpipe smoking patterns. Maziak W, Rastam S, Shihadeh A, Bazzi A, Ibrahim I, Zaatari G, Ward K, Eissenberg T. Nicotine exposure in daily waterpipe smokers and its relation to puff topography. *Addict Behav.* 2011; 36 (44): 397-399.

Completion and Subject Loss Within an Intensive Hepatitis Vaccination Intervention Among Homeless Adults

Unprotected sexual behavior, needle sharing, and a prison history are major correlates of hepatitis B Virus (HBV). These risk factors are common among homeless people who also have elevated rates of HBV. The authors examine whether these behaviors were associated with completion or loss to follow-up of the most intensive and successful condition of a 3-arm HBV vaccination intervention. Significant results would imply that those most in need are the least compliant. Contributions of baseline demographics, physical health, psychosocial variables, and health beliefs were also assessed. Three hundred thirty- one adults from Los Angeles' Skid Row were assigned to nurse-case-managed sessions with hepatitis education, incentives, and tracking. Successive predictive structural equation models assessed the amount of variance accounted for by the risk variables, demographics, and the health-related variables. The main outcome measures were: (1) Completion of 3 injections by 6 months; and (2) loss to a 6-month follow-up questionnaire. The 3 risk factors explained 2% of the variance in completion and 1% of the variance in loss. Adding the other variables increased the variance explained to 14% for completion and 13% for loss. African American ethnicity, positive coping, social support, poorer health, no prison history, and greater efficacy significantly predicted completion. White ethnicity, less social support, better health, and less intention to complete predicted participant loss. The program was not strongly rejected differentially as a function of preexisting hepatitis B risk behaviors. Programs designed for homeless people should include malleable psychosocial and health belief model variables. These aspects of the lives of homeless people provide leverage points for future interventions. Stein JA, Nyamathi AM. Completion and subject loss within an intensive hepatitis vaccination intervention among homeless adults: The role of risk factors, demographics, and psychosocial variables. *Health Psychol.* 2010; 29 (3): 317-323.

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

Research Findings - CTN-Related Research

Community Program Therapist Adherence and Competence in a Motivational Interviewing Assessment Intake Session

Teaching community program therapists to use motivational interviewing (MI) strategies for addictions treatment with sufficient frequency (i.e., adherence) and skill (i.e., competence) is a priority and challenge for the field. The development of psychometrically valid MI integrity measures that can be used for supervision and evaluation and be both sensitive and robust across clinical situations is needed. This article examines the performance of the Independent Tape Rating Scale (ITRS) when used to evaluate the delivery of MI within a one-session assessment intake. Audiotapes of 315 sessions of therapists in MI and counseling-as-usual conditions were rated according to the ITRS by raters blind to treatment condition. Results indicate that community therapists were successfully trained and supervised to use MI within an assessment intake session, with MI adherence and competence that was discriminable from counseling-as-usual practices. Increased therapist MI adherence and competence was associated with increases in an index of client motivation for change, though unrelated to treatment outcome. The ITRS appears to be a valid instrument for measuring therapist MI adherence and competence within an assessment intake. Gibbons CJ, Carroll KM, Ball SA, Nich C, Frankforter TL, Martino S. *Am J Drug Alcohol Abuse*. 2010 Nov; 36(6): 342-349. Epub 2010 Oct 14.

Substance Abuse Treatment as HIV Prevention: More Questions Than Answers

This report examines associations between the availability of human immunodeficiency virus (HIV)-related health services in substance abuse treatment programs and characteristics of the programs and the patients they serve. In a cross-sectional, descriptive design and via a validated survey, program administrators within the National Drug Abuse Treatment Clinical Trials Network provided information on program characteristics, patient characteristics (rates of risky sexual and drug behaviors and HIV infection), and the availability of 31 different HIV-related health services. Of 319 programs, 84% submitted surveys. Service availability rates ranged from: 10% (pneumococcal vaccination) to 86% (drug testing) for the 6 HIV-related services offered to all patients, 13% (Pap smear for women) to 54% (tuberculin skin testing) for the 6 services offered to new patients, 2% (sterile injection equipment) to 64% (male condoms) for the 4 risk-reduction services, 37% (Pap smear for women) to 61% (tuberculin skin testing) for the 11 biological assessments offered to HIV-positive patients, and 33% (medical treatments) to 52% (counseling) for the 4 other services offered to HIV-positive patients. The availability of these HIV-related services was associated

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with clinical settings, the types of addiction treatment services, the rates of risky drug and sexual behaviors, and HIV infection rates among patients. Availability of such services was below published guidelines. While the results provide another basis for the infection-related prevention benefits of substance abuse treatment, the variability in the availability of HIV-related health care deserves further study and has health policy implications in determining how to utilize substance abuse treatment in reducing drug-related HIV transmission. Brown LS Jr, Kritz S, Bini EJ, Louie B, Robinson J, Alderson D, Rotrosen J. Substance Abuse Treatment as HIV Prevention: More Questions Than Answers. *J Natl Med Assoc.* 2010; 102: 1183-1191.

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Transporting Clinical Research to Community Settings: Designing and Conducting a Multisite Trial of Brief Strategic Family Therapy

This paper describes the development and implementation of a trial of Brief Strategic Family Therapy (BSFT), an evidence-based drug intervention for adolescents, in eight community substance abuse treatment programs. Researchers and treatment programs collaborated closely to identify and overcome challenges, many of them related to achieving results that were both scientifically rigorous and applicable to the widest possible variety of adolescent substance abuse treatment programs. To meet these challenges, the collaborative team drew on lessons and practices from efficacy, effectiveness, and implementation research. Robbins MS, Alonso E, Horigian VE, Bachrach K, Burlaw AK, Carrion IS, Hodgkins C, Miller M, Schindler E, VanDeMark N, Henderson C, Szapocznik J. *Transporting Clinical Research to Community Settings: Designing and Conducting a multisite trial of Brief Strategic Family Therapy.* *Addiction Science & Clinical Practice* 2010; 5(2): 54-61.

Informal Discussions in Substance Abuse Treatment Sessions with Spanish-Speaking Clients

This study investigated the extent to which bilingual counselors initiated informal discussions about topics that were unrelated to the treatment of their monolingual Spanish-speaking Hispanic clients in a National Institute on Drug Abuse Clinical Trial Network protocol examining the effectiveness of motivational enhancement therapy (MET). Session audiotapes were independently rated to assess counselor treatment fidelity and the incidence of informal discussions. Eighty-three percent of the 23 counselors participating in the trial initiated informal discussions at least once in one or more of their sessions. Counselors delivering MET in the trial initiated informal discussion significantly less often than the counselors delivering standard treatment. Counselors delivering standard treatment were likely to talk informally the most when they were ethnically non-Latin. In addition, informal discussion was found to have significant inverse correlations with client motivation to reduce substance use and client retention in treatment. These results suggest that informal discussion may have adverse consequences on Hispanic clients' motivation for change and substance abuse treatment outcomes and that maintaining a more formal relationship in early treatment sessions may work best with Hispanic clients. Careful counselor training and supervision in MET may suppress the tendency of counselors to talk informally in sessions. Bamatter W, Carroll KM, Añez LM, Paris M Jr, Ball SA, Nich C, Frankforter TL, Suarez-Morales L, Szapocznik J, Martino S. *J Subst Abuse Treat.* 2010 Dec; 39(4): 353-363.

Mutual Influence in Therapist Competence and Adherence to Motivational Enhancement Therapy

Although psychotherapy involves the interaction of client and therapist, mutual influence is not typically considered as a source of variability in therapist

adherence and competence in providing treatments assessed in clinical trials. The authors examined variability in therapist adherence and competence in Motivational Enhancement Therapy (MET) both within and between caseloads in a large multi-site clinical trial. Three-level multilevel models (repeated measures, nested within clients, nested with therapists) indicated significant variability both within and between therapists. There was as much and sometimes more variability in MET adherence and competence within therapist caseloads than between therapists. Variability in MET adherence and competence within caseloads was not consistently associated with client severity of addiction at baseline. However, client motivation at the beginning of the session and days of use during treatment were consistent predictors of therapist adherence and competence. Results raise questions about the nature of therapist adherence and competence in treatment protocols. Accordingly, future analysis of clinical trials should consider the role of mutual influence in measures of therapist performance. Imel ZE, Baer JS, Martino S, Ball SA, Carroll KM. *Drug Alcohol Depend.* 2011 Jan 10. [Epub ahead of print].

Therapist Adherence in Brief Strategic Family Therapy for Adolescent Drug Abusers

Therapist adherence has been shown to predict clinical outcomes in family therapy. In prior studies, adherence has been represented broadly by core principles and a consistent family (vs. individual) focus. To date, these studies have not captured the range of clinical skills that are represented in complex family-based approaches or examined how variations in these skills predict different clinically relevant outcomes over the course of treatment. In this study, the authors examined the reliability and validity of an observational adherence measure and the relationship between adherence and outcome in a sample of drug-using adolescents who received brief strategic family therapy within a multisite effectiveness study. Participants were 480 adolescents (age 12-17) and their family members, who were randomized to the Brief Strategic Family Therapist treatment condition (J. Szapocznik, U. Hervis, & S. Schwartz, 2003) or treatment as usual. The adolescents were mostly male (377 vs. 103 female) and Hispanic (213), whereas 148 were White, and 110 were Black. Therapists were also randomly assigned to treatment condition within agencies. Results supported the proposed factor structure of the adherence measure, providing evidence that it is possible to capture and discriminate between distinct dimensions of family therapy. Analyses demonstrated that the mean levels of the factors varied over time in theoretically and clinically relevant ways and that therapist adherence was associated with engagement and retention in treatment, improvements in family functioning, and reductions in adolescent drug use. Clinical implications and future research directions are discussed, including the relevance of these findings on training therapists and studies focusing on mechanisms of action in family therapy. (PsycINFO Database Record (c) 2010 APA, all rights reserved). Robbins MS, Feaster DJ, Horigian VE, Puccinelli MJ, Henderson C, Szapocznik J. Therapist adherence in brief strategic family therapy for adolescent drug abusers. *J Consult Clin Psychol.* 2011 Feb; 79(1): 43-53.

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

Research Findings - International Research

INVEST Fellow: Anton Bernalov, Russia, 1994-1995

Bernalov AY, van Gaalen MM, Gross, G. Antidepressant treatment in anxiety disorders *Curr Top Behav Neurosci.* 2010; 2: 361-390.

Antidepressant drug treatment is the clinical standard of care for all types of anxiety disorders. Broad efficacy of selective serotonin reuptake inhibitors suggests the importance of enhanced serotonergic function of the anxiolytic properties of current antidepressants. However, analysis of the preclinical evidence indicates that most conventional "anxiolytic" drug tests are not sensitive to antidepressants. Such dissociation is not surprising because of the traditional approach to validation of preclinical tests that is to a large extent based on establishing face validity as well as sensitivity to benzodiazepine anxiolytics. The present review argues for extending the cognitive model of antidepressant drug action to cover their anxiolytic properties as well. Such an approach is based on ambiguity or uncertainty in a broad sense as the hallmark of human stress that has different expressions ready for experimental modeling. These possibilities include schedule-induced behaviors that are directly based on intermittent reinforcement, conditioning to ambiguous stimuli, social stress where agonistic confrontations are possible but not predictable or controlled by the subject, and an even larger class of behaviors that are critically dependent on the inhibition of the prepotent responses in exchange for the ambiguous possibility of a later gain in reinforcement. Interestingly, in all these cases, antidepressant drug treatment is clearly effective in preclinical laboratory settings. One of the cognitive functions that appears to be affected by antidepressant drugs is inhibitory control. Inhibition of prepotent responding has beneficial effects in the "uncertainty" stress situations discussed above and therefore it is this cognitive function that may be critical for anxiolytic effects of antidepressants and novel anxiolytic drug development.

INVEST Fellow: Guilherme Borges, Mexico, 1997-1998

Miller M, Borges G, Orozco R, Mukamal K, Rimm EB, Benjet C, Medina-Mora ME. Exposure to alcohol, drugs and tobacco and the risk of subsequent suicidality: Findings from the Mexican Adolescent Mental Health Survey *Drug Alcohol Depend.* 2011 Jan 15; 113(2-3): 110-117.

The aims of this study were to examine whether the association between prevalence measures of suicidality and substance abuse/dependence among adolescents (1) is attenuated when temporal priority of exposure and outcome are taken into account, (2) extends to substance use (i.e. without disorder), (3) applies to tobacco use and dependence independent of illicit drugs and alcohol use/disorder, and (4) is confounded by comorbid mental illness. Discrete-time survival models were applied to retrospectively reported age of onset of first suicidal ideation, plan and attempt and age of onset of first substance use and disorder. Participants were 3,005 adolescents aged 12-17 residing in the Mexico City Metropolitan Area in 2005. The World Mental Health

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computer-assisted adolescent version of the Composite International Diagnostic Interview was used to assess suicidal outcomes and psychiatric disorders including substance dependence/ abuse. Findings showed that use of and dependence on tobacco is as strong a predictor of subsequent suicidality as is use of and dependence with abuse of alcohol and drugs. The association between substance use and subsequent suicidality is not fully accounted for by comorbid mental illness. Efforts to reduce the use as well as the abuse of alcohol, drugs and tobacco may help reduce the risk of subsequent suicidal behaviors among adolescents in Mexico.

INVEST Fellow: Huaihui Zhang, China, 2009-2010

Zhang H, Li D, Su Y, Jiang S, Xu Y, Jiang K, Cui D. Identification of the N-acylsphingosine amidohydrolase 1 gene (ASAH1) for susceptibility to schizophrenia in a Han Chinese population. *The World Journal of Biological Psychiatry*, 2011; Early Online, 1-8.

The objective of this research was to study the involvement of the N-acylsphingosine amidohydrolase 1 gene (ASAH1) in the susceptibility to schizophrenia in the Han Chinese population. The authors performed cDNA microarray analysis to examine the gene expression profile in six schizophrenic patients and six healthy controls. They evaluated the ASAH1 expression levels in 30 subjects with chronic schizophrenia and 30 healthy controls by using real-time polymerase chain reaction (PCR). A total of 254 unrelated probands with schizophrenia and their biological parents were also genotyped at three single nucleotide polymorphisms (SNPs: rs3753118, rs3753116, and rs7830490) of the ASAH1 gene for association analysis. In the microarray analysis, the ASAH1 gene was down-regulated in all schizophrenic patients compared with healthy controls. In real-time PCR, the ASAH1 expression levels for schizophrenic patients with positive family history were significantly decreased ($P = 0.020$). In the association analyses, two SNPs (rs7830490 and rs3753118) and one haplotype (rs7830490 [A]-rs3753116 [G]) of ASAH1 showed significant evidence of nominal associations with schizophrenia ($P = 0.026$; $P = 0.046$; $P = 0.007$, respectively). The haplotype remained statistically significant (empirical $P = 0.045$) after correction for multiple testing. This study supports that the ASAH1 gene may be a potential candidate gene for schizophrenia in Han Chinese subjects.

HHH Fellow: Flavio Pechansky, Brazil, 1993-1994

Breitenbach TC, Pechansky F, Benzano D, De Boni R. High rates of injured motorcycle drivers in emergency rooms and the association with substance use in Porto Alegre, Brazil. *Emerg Med J*. 2011 Mar 1. [Epub ahead of print]

Although the fleet of motorcycles and the number of traffic accidents (TA) is increasing in the world, few studies have evaluated intoxication by alcohol and/or drugs in this group of drivers. This study aims to evaluate the prevalence of motorcycle riders among drivers who are victims of TA, and ascertain factors associated with drug and alcohol use. All TA victims admitted on a 24/7 routine between October and November 2008 to two trauma hospitals of Porto Alegre, Brazil were invited to participate, then submitted to an interview, breathalyzed and had their saliva collected for drugs. Among the overall sample of drivers, 78.4% were motorcycle riders. Toxicological analysis yielded a 15.3% prevalence of marijuana use, 9.2% of cocaine use, 3.2% benzodiazepine use and 7% of alcohol use. Factors associated with alcohol or drug intoxication were the diagnosis of alcohol abuse or dependence and history of previous TA. The prevalence of motorcycle riders among drivers who are victims of TA was alarming. The association of alcohol abuse or dependency and intoxication justifies the need for therapeutic interventions specifically targeted to the treatment of drug dependency, as well as public policies directed to prevention of injuries-particularly among recidivist motorcycle riders.

HHH Fellow: Flavio Pechansky, Brazil, 1993-1994

Bassols AM, De Boni R, Pechansky F. Alcohol, drugs, and risky sexual behavior

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are related to HIV infection in female adolescents. *Rev Bras Psiquiatr.* 2010 Dec; 32(4): 361-368.

The objective of this study was to examine associations between risk factors for HIV infection in a sample of young women who sought HIV testing in a city of southern Brazil. This was a Cross-sectional study with a consecutive convenience sample of 258 female adolescents aged 13 to 20 years evaluated in an anonymous testing site for HIV and sexually transmitted diseases in Brazil. Risk behavior for HIV was assessed with the Brazilian version of the Risk Assessment Battery and HIV status was assessed through ELISA (Enzyme Linked Immunosorbent Assay). Overall seropositivity rate was 7.4%. HIV-seropositive patients had significantly more sexual intercourse in exchange for money, higher rates of pregnancy and abortion, as well as earlier sexual debut. In multiple analyses with the inclusion of two composite variables (sex risk and drug risk), only drug risk was associated with positive HIV status (OR=4.178; CI 95%=1.476-11.827). The findings suggest that high HIV seropositivity among female adolescents seeking HIV testing in Brazil directly reflects the need for effective interventions specifically designed to prevent risk behaviors in order to halt the spread of HIV infection.

HHH Fellow: Jozsef Lango, Hungary, 1997-1998

Morisseau C, Bernay M, Escaich A, Sanborn JR, Lango J, Hammock BD. Development of fluorescent substrates for microsomal epoxide hydrolase and application to inhibition studies. *Anal Biochem.* 2011 Feb 28. [Epub ahead of print]

The microsomal epoxide hydrolase (mEH) plays a significant role in the metabolism of numerous xenobiotics. Additionally, it has a potential role in sexual development and bile acid transport, and it is associated with a number of diseases, such as emphysema, spontaneous abortion, eclampsia and several forms of cancer. Toward developing chemical tools to study mEH biological role, the authors designed and synthesized a series of absorbent and fluorescent substrates. The highest activity for both rat and human mEH was obtained with the fluorescent substrate cyano(6-methoxy-naphthalen-2-yl)methyl glycidyl carbonate (11). An in vitro inhibition assay using this substrate ranked a series of known inhibitors similarly to the assay that used radioactive cis-stilbene oxide, but with a greater discrimination between inhibitors. These results demonstrate that the new fluorescence-based assay is a useful tool for the discovery of structure-activity relationships among mEH inhibitors. Further, this substrate could also be used for the screening chemical library with high accuracy and with a Z' value about 0.7. This new assay permits a significant decrease in labor and cost as well as offering the advantage of a continuous readout. However, it should not be used with crude enzyme preparations due to interfering reactions.

HHH Fellow: Wei-Jen Tsai, Taiwan, 1992-1993

Mao YC, Tsai WJ, Wu ML, Ger J, Deng JF, Yang CC. Acute hemolysis following iodine tincture ingestion. *Hum Exp Toxicol.* 2011 Feb 7. [Epub ahead of print] Iodine tincture poisoning is uncommon regardless of its widespread use as an antiseptic in daily practice. Previously reported effects of iodine-containing antiseptic poisoning included topical irritation, corrosive effects, allergic response, and hepatic or renal injury, which mainly resulted from complications of topical use during surgical procedures. The authors herein reported an unusual case of severe hemolysis and acute renal failure following intentional ingestion of iodine tincture containing 60 mg/ml iodine and 40 mg/ml potassium iodide in 70% v/v ethanol. The patient completely recovered 8 weeks later after receiving supportive treatment, plasma exchange, and temporary hemodialysis.

HHH Fellows: Sergio Nicastrì, Brazil, 1993-1994; Arthur Guerra de Andrade; Brazil, 1991-1992; WHO/NIDA/CPDD International Traveling Fellow: Paulo J. Cunha, Brazil, 2005

Cunha PJ, Bechara A, de Andrade AG, Nicastrì S. Decision-making deficits

linked to real-life social dysfunction in crack cocaine-dependent individuals. *Am J Addict.* 2011 Jan; 20(1):78-86.

Crack cocaine-dependent individuals (CCDI) present abnormalities in both social adjustment and decision making, but few studies have examined this association. This study investigated cognitive and social performance of 30 subjects (CCDI x controls); CCDI were abstinent for 2 weeks. The authors used the Social Adjustment Scale (SAS), Wisconsin Card Sorting Test (WCST), and Iowa Gambling Task (IGT). Disadvantageous choices on the IGT were associated with higher levels of social dysfunction in CCDI, suggesting the ecological validity of the IGT. Social dysfunction and decision making may be linked to the same underlying prefrontal dysfunction, but the nature of this association should be further investigated.

HHH Fellow: Chung Tai Lee, South Korea 1994-1995

Lee SJ, Lee HK, Kweon YS, Lee CT, Lee KU. Deficits in facial emotion recognition in schizophrenia: a replication study with Korean subjects. *Psychiatry Investig.* 2010 Dec; 7(4):291-7. Epub 2010 Nov 23.

The authors investigated the deficit in the recognition of facial emotions in a sample of medicated, stable Korean patients with schizophrenia using Korean facial emotion pictures and examined whether the possible impairments would corroborate previous findings. Fifty-five patients with schizophrenia and 62 healthy control subjects completed the Facial Affect Identification Test with a new set of 44 colored photographs of Korean faces including the six universal emotions as well as neutral faces. Korean patients with schizophrenia showed impairments in the recognition of sad, fearful, and angry faces [$F(1,114)=6.26$, $p=0.014$; $F(1,114)=6.18$, $p=0.014$; $F(1,114)=9.28$, $p=0.003$, respectively], but their accuracy was no different from that of controls in the recognition of happy emotions. Higher total and three subscale scores of the Positive and Negative Syndrome Scale (PANSS) correlated with worse performance on both angry and neutral faces. Correct responses on happy stimuli were negatively correlated with negative symptom scores of the PANSS. Patients with schizophrenia also exhibited different patterns of misidentification relative to normal controls. These findings were consistent with previous studies carried out with different ethnic groups, suggesting cross-cultural similarities in facial recognition impairment in schizophrenia.

HHH Fellow: Chung Tai Lee, South Korea 1994-1995

Kim YR, Choi KH, Oh Y, Lee HK, Kweon YS, Lee CT, Lee KU. Elderly suicide attempters by self-poisoning in Korea. *Int Psychogeriatr.* 2011 Mar 1: 1-7. [Epub ahead of print]

Suicide is a major public health concern. The elderly have the highest rate of suicide and they make more lethal suicide attempts and have fewer psychiatric interventions than young people. Furthermore, they have old-age specific psychosocial difficulties. The present study investigated psychosocial risk factors and characteristics of an index suicide attempt of the elderly suicide attempters. Subjects included 388 patients who were admitted to the emergency room following self-poisoning. Two age groups were defined: younger patients (aged less than 65 years) and older patients (aged over 65 years). Data including demographic factors, suicidal risk factors and information about the current suicide attempt were obtained from a retrospective chart review. The number of suicide attempters over the age of 65 years old was 57, and their mean age was 73.5 ± 7.5 years. The elderly patients had more underlying medical illnesses than the under-65 group ($p < 0.001$). Depression was the most common psychiatric diagnosis. Psychotropics were the most commonly ingested drugs in both groups, but the use of pesticides was more notable in the elderly. The elderly suicide attempters had higher risk-rating scores ($p < 0.001$) and lower rescue-rating scores ($p = 0.014$) than the under-65 group. Male-to-female ratio of the elderly group was nearly 1:1 unlike the under-65 group ($p = 0.004$). Elderly suicide attempters had different psychosocial stressors such as physical illness and more lethal suicide attempts. This study suggests the need for development of specific

preventive strategies and management guidelines for the elderly suicide attempters.

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

Mravčík V, Skařupová K, Orliková B, Zábanský T, Karachaliou K, Schulte B. Use of gelatine capsules for application of methamphetamine: A new harm reduction approach. *Int J Drug Policy*. 2011 Jan 15.

In order to reduce injecting drug use, low-threshold facilities in the Czech Republic have started to distribute empty gelatine capsules as an oral alternative of drug application for those injecting methamphetamine. This report reviews implementation of this intervention and its possible benefits and limitations. Between December 2008 and January 2009, 109 low-threshold facilities were asked to complete a questionnaire about the capsule programs. Two focus groups were conducted, one with professionals involved in distribution and one with peer outreach workers who were interviewed on their experience of using the capsules. A total of 50 facilities (46%) responded to the questionnaire; 16 (32%) distributed the capsules regularly and 19 (38%) were planning to introduce this practice. The main target groups were injecting users of methamphetamine whose veins had been damaged, and methamphetamine users wishing to reduce injecting. The advantages of capsules, as perceived by service staff and peer outreach workers, were their easy use and the satisfactory effect of the oral application; health risks related to the oral use of methamphetamine were considered drawbacks. Capsule distribution is a promising harm reduction approach for injectors of methamphetamine or other stimulants; nonetheless its benefits and limitations should be further analyzed in an in-depth longitudinal study.

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

Research Findings - Intramural Research

Electrophysiology Research Section, Cellular Neurobiology Research Branch

Increased Nigrostriatal Function Precedes Behavioral Deficits In A Genetic Mitochondrial Model of Parkinson's Disease

Parkinson's disease (PD) involves progressive loss of nigrostriatal dopamine (DA) neurons over an extended period of time. Mitochondrial damage may lead to PD, and neurotoxins affecting mitochondria are widely used to produce degeneration of the nigrostriatal circuitry. Deletion of the mitochondrial transcription factor A gene (Tfam) in C57BL6 mouse DA neurons leads to a slowly progressing parkinsonian phenotype in which motor impairment is first observed at 12 wk of age. L-DOPA treatment improves motor dysfunction in these "MitoPark" mice, but this declines when DA neuron loss is more complete. To investigate early neurobiological events potentially contributing to PD, IRP scientists compared the neurochemical and electrophysiological properties of the nigrostriatal circuit in behaviorally asymptomatic 6- to 8-wk-old MitoPark mice and age-matched control littermates. Release, but not uptake of DA, was impaired in MitoPark mouse striatal brain slices, and nigral DA neurons lacked characteristic pacemaker activity compared with control mice. Also, hyperpolarization-activated cyclic nucleotide-gated (HCN) ion channel function was reduced in MitoPark DA neurons, although HCN messenger RNA was unchanged. This study demonstrates altered nigrostriatal function that precedes behavioral parkinsonian symptoms in this genetic PD model. A full understanding of these presymptomatic cellular properties may lead to more effective early treatments of PD. Good CH, Hoffman AF, Hoffer, BJ, Chefer, VI, Shippenberg TS, Bäckman CM, Larsson NG, Olson L, Gellhaar S, Galter D, Lupica CR. Increased nigrostriatal function precedes behavioral deficits in a genetic mitochondrial model of Parkinson's disease. *FASEB J.* 2011 Jan 13. [Epub ahead of print].

Neuroimaging Research Branch

Anatomical Differences and Network Characteristics Underlying Smoking Cue Reactivity

A distributed network of brain regions has been linked to drug-related cue responding that is generally similar across all classes of primary drug of choice. However, the relationships between cue-induced phasic activity and possible underlying differences in brain structure, tonic neuronal activity and connectivity between these brain areas are as yet unexplored. As such, IRP researchers exposed smokers and nonsmokers to cigarette-related pictures while obtaining multimodal MRI based data. The double contrast of [specific-control pictures] in [smokers vs. controls] yielded significant activation in 6 brain areas: dorsal lateral prefrontal cortex (dlPFC), dorsal medial prefrontal

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cortex (dmPFC), dorsal anterior cingulate cortex, rostral anterior cingulate cortex (rACC), occipital cortex, and insula. Secondary analyses based on these regions revealed that rsFC strength between rACC and dlPFC was positively correlated with cue-elicited activity in dlPFC. Similarly, rsFC strength between dlPFC and dmPFC predicted cue-elicited activity in dmPFC while rsFC strength between dmPFC and insula was negatively correlated with cue elicited activity in both dmPFC and insula, suggesting that these brain circuits may facilitate the response to the salient smoking cues. Further, gray matter density in dlPFC was reduced in smokers and correlated with cue-elicited activity in the dlPFC, suggesting a neurobiological mechanism for the impaired cognitive control associated with drug use. Taken together, these results begin to address the underlying neurobiology of smoking cue salience, and may speak to novel treatment strategies and targets for therapeutic interventions. Zhang, X, Salmeron BJ, Ross TJ, Gu H, Geng X, Yang Y, Stein EA. *Neuroimage* 2011; 54: 131-141.

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Molecular Neuropsychiatry Research Branch

Mutant DISC1 Affects Methamphetamine-Induced Sensitization and Conditioned Place Preference: A Comorbidity Model

Genetic factors involved in neuroplasticity have been implicated in major psychiatric illnesses such as schizophrenia, depression, and substance abuse. Given its extended interactome, variants in the Disrupted-In-Schizophrenia-1 (DISC1) gene could contribute to drug addiction and psychiatric diseases. Thus, IRP investigators evaluated how dominant-negative mutant DISC1 influenced the neurobehavioral and molecular effects of methamphetamine (METH). Control and mutant DISC1 mice were studied before or after treatment with non-toxic escalating dose (ED) of METH. In naïve mice, the authors assessed METH-induced conditioned place preference (CPP), dopamine (DA) D2 receptor density and the basal and METH-induced activity of DISC1 partners, AKT and GSK-3B in the ventral striatum. In ED-treated mice, 4 weeks after METH treatment, they evaluated fear conditioning, depression-like responses in forced swim test, and the basal and METH-induced activity of AKT and GSK-3B in the ventral striatum. The authors found impairment in METH-induced CPP, decreased DA D2 receptor density and altered METH-induced phosphorylation of AKT and GSK-3B in naïve DISC1 female mice. The ED regimen was not neurotoxic as evidenced by unaltered brain regional monoamine tissue content. Mutant DISC1 significantly delayed METH ED-produced sensitization and affected drug-induced phosphorylation of AKT and GSK-3B in female mice. These results suggest that perturbations in DISC1 functions in the ventral striatum may impact the molecular mechanisms of reward and sensitization, contributing to comorbidity between drug abuse and major mental diseases. Pogorelov V, Nomura J, Kim J, Kannan G, Yang C, Taniguchi Y, Abazyan B, Valentine H, Krasnova IN, Kamiya A, Cadet JL, Wong DF, Pletnikov MV. *Neuropharmacology* 2011 Feb 16; [Epub ahead of print].

Chronic Methamphetamine Exposure Suppresses the Striatal Expression of Members of Multiple Families of Immediate Early Genes (IEGs) in the Rat: Normalization By An Acute Methamphetamine Injection

Repeated injections of cocaine cause blunted responses to acute cocaine challenge-induced increases in the expression of immediate early genes (IEGs). The aim of this study was to test if chronic methamphetamine (METH) exposure might cause similar blunting of acute METH-induced increases in IEG expression. Repeated saline or METH injections were given to rats over 14 days. After 1 day of withdrawal, they received a single injection of saline or METH (5 mg/kg). Acute injection of METH increased c-fos, fosB, fra2, junB, Egr1-3, Nr4a1 (Nur77), and Nr4a3 (Nor-1) mRNA levels in the striatum of saline-pretreated rats. Chronic METH treatment alone reduced the expression of AP1, Erg1-3, and Nr4a1 transcription factors below control levels. Acute

METH challenge normalized these values in METH-pretreated rats. Unexpectedly, acute METH challenge to METH-pretreated animals caused further decreases in Nr4a2 (Nurr1) mRNA levels. In contrast, the METH challenge caused significant but blunted increases in Nr4a3 and Arc expression in METH-pretreated rats. There were also chronic METH-associated decreases in the expression of cAMP responsive element binding protein (CREB) which modulates IEG expression via activation of the cAMP/PKA/CREB signal transduction pathway. Chronic METH exposure also caused significant decreases in preprotachykinin, but not in prodynorphin, mRNA levels. These results support the accumulated evidence that chronic administration of psychostimulants is associated with blunting of their acute stimulatory effects on IEG expression. The METH-induced renormalization of the expression of several IEGs in rats chronically exposed to METH hints to a potential molecular explanation for the recurrent self-administration of the drug by human addicts. McCoy MT, Jayanthi S, Wulu JA, Beauvais G, Ladenheim B, Martin TA, Krasnova IN, Hodges AB, Cadet JL. *Psychopharmacology (Berl)*. 2011 Jan 13; [Epub ahead of print].

NPY Promotes Chemokinesis and Neurogenesis in the Rat Subventricular Zone

The subventricular zone (SVZ) is a major reservoir for stem cells in the adult mammalian brain. Neural stem cells supply the olfactory bulb with new interneurons and provide cells that migrate towards lesioned brain areas. Neuropeptide Y (NPY), one of the most abundant neuropeptides in the brain, was previously shown to induce neuroproliferation on mice SVZ cells. In the present study, performed in rats, IRP scientists demonstrate the endogenous synthesis of NPY by cells in the SVZ that suggests that NPY could act as an autocrine/paracrine factor within the SVZ area. They observed that NPY promotes SVZ cell proliferation as previously reported in mice, but does not affect self-renewal of SVZ stem cells. Additionally, this study provides the first direct evidence of a chemokinetic activity of NPY on SVZ cells. Using pharmacological approaches, the authors demonstrate that both the mitogenic and chemokinetic properties of NPY involve Y1 receptor-mediated activation of the ERK1/2 MAP kinase pathway. Altogether, these data establish that NPY through Y1 receptors activation controls chemokinetic activity and, as for mice, is a major neuroproliferative regulator of rat SVZ cells. Thiriet N, Agasse F, Nicoleau C, Guégan C, Vallette F, Cadet JL, Jaber M, Malva JO, Coronas V. *J Neurochem*. 2011 Mar; 116(6): 1018-1027.

Differential Effects of Prenatal and Postnatal Expressions of Mutant Human DISC1 on Neurobehavioral Phenotypes in Transgenic Mice: Evidence for Neurodevelopmental Origin of Major Psychiatric Disorders

Strong genetic evidence implicates mutations and polymorphisms in the gene Disrupted-In-Schizophrenia-1 (DISC1) as risk factors for both schizophrenia and mood disorders. Recent studies have shown that DISC1 has important functions in both brain development and adult brain function. IRP researchers have described earlier a transgenic mouse model of inducible expression of mutant human DISC1 (hDISC1) that acts in a dominant-negative manner to induce the marked neurobehavioral abnormalities. To gain insight into the roles of DISC1 at various stages of neurodevelopment, the authors examined the effects of mutant hDISC1 expressed during (1) only prenatal period, (2) only postnatal period, or (3) both periods. All periods of expression similarly led to decreased levels of cortical dopamine (DA) and fewer parvalbumin-positive neurons in the cortex. Combined prenatal and postnatal expression produced increased aggression and enhanced response to psychostimulants in male mice along with increased linear density of dendritic spines on neurons of the dentate gyrus of the hippocampus, and lower levels of endogenous DISC1 and LIS1. Prenatal expression only resulted in smaller brain volume, whereas selective postnatal expression gave rise to decreased social behavior in male mice and depression-like responses in female mice as well as enlarged lateral ventricles and decreased DA content in the hippocampus of female mice, and

decreased level of endogenous DISC1. These data show that mutant hDISC1 exerts differential effects on neurobehavioral phenotypes, depending on the stage of development at which the protein is expressed. The multiple and diverse abnormalities detected in mutant DISC1 mice are reminiscent of findings in major mental diseases. Ayhan Y, Abazyan B, Nomura J, Kim R, Ladenheim B, Krasnova IN, Sawa A, Margolis RL, Cadet JL, Mori S, Vogel MW, Ross CA, Pletnikov MV. *Mol Psychiatry*. 2011 Mar;16(3):293-306. Epub 2010 Jan 5.

Clinical Pharmacology and Therapeutics

Incubation of Cue-Induced Cigarette Craving During Abstinence In Human Smokers

Abstinent drug users remain at risk for relapse for long periods of time, well after withdrawal symptoms subside. Reasons for this prolonged relapse susceptibility are poorly understood. Studies with laboratory animals indicate that responses to drug-related cues not only persist, but increase with abstinence duration. If this phenomenon, termed "incubation of craving" also occurs in humans, it may contribute to prolonged relapse risk. In this study IRP scientists investigated whether cue-elicited craving increases with duration of abstinence in cigarette smokers. Healthy, non-treatment-seeking, adult cigarette smokers (N = 86) were randomized to four groups and paid to abstain for 7 (Group 1), 14 (Group 2), or 35 (Groups 3, 4) days. Abstinence was biochemically verified daily. Groups 1, 2, and 3 underwent a cue exposure session to measure cue-elicited craving on the last day of abstinence (days 7, 14, or 35), whereas Group 4 underwent three repeated cue sessions (days 7, 14, and 35). In both between- and within- groups analyses of the results, cue-induced craving increased as a function of abstinence duration. Participants in Group 3 (35-day abstinence) reported significantly greater smoking-cue-elicited craving than did Group 1 participants (7-day abstinence). Participants in Group 4 (repeated cues) reported greater cue-elicited craving at 35 days than at 14 days. Time-dependent increases in conditioned craving occurred in the context of progressively decreasing baseline (non-provoked) craving. Here, the authors present the first evidence of incubation of craving in human drug users. These findings, which suggest that craving elicited by cues increase with abstinence even as daily "background" craving and nicotine withdrawal symptoms subside, have significant implications for treatment. 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):708-11.

Nicotine Psychopharmacology Section

Tobacco Craving in Smokers with and without Schizophrenia

IRP investigators examined tobacco craving and dependence in current smokers (18-65 years) with schizophrenia (N=100) and those without a psychiatric disorder (normal controls, N=100). During the 2-3 h visit participants completed demographic and smoking-related questionnaires and provided a breath CO sample. The Tobacco Craving Questionnaire-Short Form (TCQ-SF) was administered. Immediately after smoking one cigarette, no difference in TCQ-SF total score was noted (46.7 ± 19.5 schizophrenia, 42.8 ± 18.2 controls, $p=0.15$); however, after 15 min TCQ-SF total score was significantly higher in people with schizophrenia (50.0 ± 19.6) than in controls (38.6 ± 19.4) ($p=0.0014$). TCQ-SF factors of emotionality ($p=0.0015$), compulsivity ($p=0.0003$) and purposefulness ($p=0.0174$) were significantly greater in the schizophrenia group than the control group. FTND scores (5.5 ± 2.0 vs 5.3 ± 2.0 , $p=0.62$) number of cigarettes smoked daily (17.9 ± 11.6 vs. 17.0 ± 7.9), expired breath CO (28.0 ± 14.5 ppm vs. 22.0 ± 8.0 ppm) and age at smoking initiation (16.2 ± 5.4 vs. 15.6 ± 5.5 years, $p=0.44$) did not differ in the schizophrenia and control groups respectively. In conclusion, tobacco

craving as measured by the TCQ-SF was significantly greater in people with schizophrenia than controls 15 min post-smoking, despite similar scores in dependence and similar smoking histories and current smoking patterns. Lo S, Heishman SJ, Raley HG, Wright K, Wehring HJ, Moolchan ET, Feldman S, Liu F, McMahon RP, Richardson CM, Kelly DL. Tobacco craving in smokers with and without schizophrenia. *Schizophr Res.* 2011; 127: 241-245.

Chemical Biology Research Branch, Drug Design and Synthesis Section

Effects of Serotonin (5-HT)1A and 5-HT2A Receptor Agonists on Schedule-Controlled Responding In Rats: Drug Combination Studies

Indirect-acting serotonin (5-HT) receptor agonists (e.g., selective 5-HT reuptake inhibitors [SSRI]) stimulate multiple 5-HT receptors, although the role of particular receptors as well as interaction(s) among different receptors in the therapeutic effects of SSRIs is not fully understood. Relatively few studies have systematically examined direct-acting agonists in combination. This study examined the 5-HT(1A) receptor agonists 8-hydroxy-2-(di-n-propylamino) tetralin hydrochloride (8-OH-DPAT; 0.01-10.0 mg/kg) and 3-chloro-4-fluorophenyl-4-fluoro-4-[(5-methyl-6-methylamino-pyridin-2-ylmethyl)-amino]-methyl-piperidin-1-yl-methanone (F13714; 0.01-1.0 mg/kg) and the 5-HT(2A) receptor agonists 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM; 0.32-10.0 mg/kg) and dipropyltryptamine (DPT; 1.0-32.0 mg/kg), alone and in combination, in rats responding under a fixed ratio schedule of food presentation. When administered alone, each drug decreased the rate of responding in a dose-related manner with the potency order being F13714 > 8-OH-DPAT > DOM > DPT. WAY100635 (5-HT(1A) receptor antagonist; 0.01-0.1 mg/kg) attenuated the rate-decreasing effects of 8-OH-DPAT and F13714 while MDL100907 (5-HT(2A) receptor antagonist; 0.01-0.1 mg/kg) attenuated the rate-decreasing effects of DOM and DPT. Dose addition analysis showed that the interaction between 8-OH-DPAT and F13714, as well as the interaction between DOM and DPT, was additive. In contrast, the interaction between 8-OH-DPAT and DOM, as well as the interaction between F13714 and DOM, was infra-additive. This study shows that for some dose combinations, agonist actions at one 5-HT receptor subtype attenuate agonist actions at another 5-HT receptor subtype; thus, the combined neuropharmacological actions and therapeutic effects of indirect-acting agonists are not likely to be adequately characterized by examining in isolation activity at particular 5-HT receptor subtypes. Li JX, Crocker C, Koek W, Rice KC, France CP. *Psychopharmacology (Berl).* 2011 Feb; 213(2-3): 489-497. Epub 2010 Dec 21.

Effects of Direct- and Indirect-Acting Serotonin Receptor Agonists on the Antinociceptive and Discriminative Stimulus Effects of Morphine In Rhesus Monkeys

Serotonergic (5-HT) systems modulate pain, and drugs acting on 5-HT systems are used with opioids to treat pain. This study examined the effects of 5-HT receptor agonists on the antinociceptive and discriminative stimulus effects of morphine in monkeys. Morphine increased tail-withdrawal latency in a dose-related manner; 5-HT receptor agonists alone increased tail-withdrawal latency at 50°C but not 55°C water. The antinociceptive effects of morphine occurred with smaller doses when monkeys received an indirect-acting (fenfluramine) or direct acting (8-OH-DPAT, F13714, buspirone, quipazine, DOM, and 2C-T-7) agonist. The role of 5-HT receptor subtypes in these interactions was confirmed with selective 5-HT(1A) (WAY100635) and 5-HT(2A) (MDL100907) receptor antagonists. None of the 5-HT drugs had morphine-like discriminative stimulus effects; however, fenfluramine and 5-HT(2A) receptor agonists attenuated the discriminative stimulus effects of morphine and this attenuation was prevented by MDL100907. The 5-HT(1A) receptor agonists did not alter the discriminative stimulus effects of morphine. Thus, 5-HT receptor agonists increase the potency of morphine in an assay of antinociception, even under conditions

where 5-HT agonists are themselves without effect (i.e., 5 μ C water), without increasing (and in some cases decreasing) the potency of morphine in a drug discrimination assay. Whereas 5-HT(2A) receptor agonists increase the potency of morphine for antinociception at doses that have no effect on the rate of operant responding, 5-HT(1A) receptor agonists increase the potency of morphine only at doses that eliminate operant responding. These data suggest that drugs acting selectively on 5-HT receptor subtypes could help to improve the use of opioids for treating pain. Li JX, Koek W, Rice KC, France CP. *Neuropsychopharmacology*. 2011 Apr; 36(5): 940-949. Epub 2011 Jan 5.

Probes for Narcotic Receptor Mediated Phenomena. 41. Unusual Inverse K-Agonists And Potent K-Opioid Antagonists By Modification of the N-Substituent In Enantiomeric 5-(3-Hydroxyphenyl)Morphans

Conformational restraint in the N-substituent of enantiomeric 5-(3-hydroxyphenyl)morphans was conferred by the addition of a cyclopropane ring or a double bond. All of the possible enantiomers and isomers of the N-substituted compounds were synthesized. Opioid receptor binding assays indicated that some of them had about 20-fold higher μ -affinity than the compound with an N-phenylpropyl substituent ($K(i) = 2-450$ nM for the examined compounds with various N-substituents). Most of the compounds acted unusually as inverse agonists in the [(35)S]GTP- γ -S functional binding assay using nondependent cells that stably express the cloned human μ -opioid receptor. Two of the N-substituted compounds with a cyclopropane ring were very potent μ -opioid antagonists ((+)-29, $K(e) = 0.17$ and (-)-30, $K(e) = 0.3$) in the [(35)S]GTP- γ -S functional binding assay. By comparison of the geometry-optimized structures of the newly synthesized compounds, an attempt was made to rationalize their μ -opioid receptor affinity in terms of the spatial position of N-substituents. Cheng K, Lee YS, Rothman RB, Dersch CM, Bittman RW, Jacobson AE, Rice KC. *J Med Chem*. 2011 Feb 24; 54(4): 957-969. Epub 2011 Jan 19.

[(76) Br]BMK-152, A Non-Peptide Analogue, With High Affinity and Low Non-Specific Binding for the Corticotropin-Releasing Factor Type 1 Receptor (CRF(1) Receptor)

Corticotropin-releasing factor (CRF), a neuropeptide, regulates endocrine and autonomic responses to stress through G-protein coupled receptors, CRF(1) or CRF(2). A PET ligand able to monitor changes in CRF(1) receptor occupancy in vivo would aid in understanding the pathophysiology of stress related diseases as well as in the clinical development of non-peptide antagonists with therapeutic value. IRP scientists have radiolabeled the CRF(1) receptor ligand, BMK-152 ([8-(4-bromo-2,6-dimethoxyphenyl)-2,7-dimethylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-N,N-bis-(2-methoxyethyl)amine; $ClogP = 2.6$), at both the 3 and 4 position with [(76) Br]. Using in vitro autoradiography saturation studies the 4-[(76) Br]BMK-152 exhibited high affinity binding to both rat ($K(d) = 0.23 \pm 0.07$ nM; $n=3$) and monkey frontal cortex ($K(d) = 0.31 \pm 0.08$ nM; $n=3$) consistent with CRF(1) receptor regional distribution whereas with the 3-[(76) Br]BMK-152, the $K(d)$'s could not be determined due to high non-specific binding. In vitro autoradiography competition studies using [(125) I]Tyr(0)-o-CRF confirmed that 3-Br-BMK-152 ($K(i) = 24.4 \pm 4.9$ nM; $n=3$) had lower affinity (70 fold) than 4-Br-BMK-152 ($K(i) = 0.35 \pm 0.07$ nM; $n=3$) in monkey frontal cortex and similar studies using [(125) I]Savagine confirmed CRF(1) receptor selectivity. In vivo studies with P-glycoprotein (PGP) knockout mice (KO) and their wildtype littermates (WT) showed that the brain uptake of 3-[(76) Br]BMK/4-[(76) Br]BMK was increased < 2 fold in KO vs WT indicating that 3-[(76) Br]BMK-152/4-[(76) Br]BMK was not a Pgp substrate. Rat brain uptakes of 4-[(76) Br] BMK-152 from ex vivo autoradiography studies showed regional localization consistent with known published CRF(1) receptor distribution and potential as a PET ligand for in vivo imaging of CRF(1) receptors. Jagoda EM, Lang L, McCullough K, Contoreggi C, Kim BM, Ma Y, Rice KC, Szajek LP, Eckelman WC, Kiesewetter DO. *Synapse*. 2011 Feb 9. doi: 10.1002/syn.20919. [Epub ahead of print]

Stress-Induced Reinstatement of Alcohol-Seeking In Rats Is Selectively Suppressed by the Neurokinin 1 (NK1) Antagonist L822429

Genetic inactivation or pharmacological antagonism of neurokinin 1 (NK1) receptors blocks morphine and alcohol reward in rodents, while NK1 antagonism decreases alcohol craving in humans. The role of the NK1 system for relapse-like behavior has not previously been examined. Divergence between human and rodent NK1 receptors has limited the utility of NK1 antagonists developed for the human receptor species for preclinical studies of addiction-related behaviors in rats. Here IRP scientists used L822429, an NK1 antagonist specifically engineered to bind at high affinity to the rat receptor, to assess the effects of NK1 receptor antagonism on alcohol-seeking behaviors in rats. L822429 (15 and 30 mg/kg) was used to examine effects of NK1 receptor antagonism on operant self-administration of 10% alcohol in 30-min daily sessions, as well as intermittent footshock stress- and cue-induced reinstatement of alcohol-seeking after extinction of lever responding. At the doses used, L822429 did not significantly affect alcohol self-administration or cue-induced reinstatement, but potently and dose dependently suppressed stress-induced reinstatement of alcohol seeking, with an essentially complete suppression at the highest dose. The effect of L822429 on stress-induced reinstatement was behaviorally specific. The drug had no effect on conditioned suppression of operant responding following fear conditioning, locomotor activity, or self-administration of a sucrose solution. To the degree that the reinstatement model provides a model of drug relapse, the results provide support for NK1 antagonism as a promising mechanism for pharmacotherapy of alcoholism, acting through suppression of stress-induced craving and relapse. Schank JR, Pickens CL, Rowe KE, Cheng K, Thorsell A, Rice KC, Shaham Y, Heilig M. *Psychopharmacology (Berl)*. 2011 Feb 22. [Epub ahead of print]

Activation of σ -Receptors Induces Binge-like Drinking in Sardinian Alcohol-Preferring Rats

Sigma (σ) receptors have been implicated in the behavioral and motivational effects of alcohol and psychostimulants. Sigma receptor antagonists reduce the reinforcing effects of alcohol and excessive alcohol intake in both genetic (alcohol-preferring rats) and environmental (chronic alcohol-induced) models of alcoholism. The present study tested the hypothesis that pharmacological activation of σ -receptors facilitates ethanol reinforcement and induces excessive, binge-like ethanol intake. The effects of repeated subcutaneous treatment with the selective σ -receptor agonist 1,3-di-(2-tolyl)guanidine (DTG; 15 mg/kg, twice a day for 7 days) on operant ethanol (10%) self-administration were studied in Sardinian alcohol-preferring (sP) rats. To confirm that the effect of DTG was mediated by σ -receptors, the effects of pretreatment with the selective σ -receptor antagonist BD-1063 (7 mg/kg, subcutaneously) were determined. To assess the specificity of action, the effects of DTG on the self-administration of equally reinforcing solutions of saccharin or sucrose were also determined. Finally, gene expression of opioid receptors in brain areas implicated in ethanol reinforcement was analyzed in ethanol-naive sP rats treated acutely or repeatedly with DTG, because of the well-established role of the opioid system in alcohol reinforcement and addiction. Repeatedly administered DTG progressively and dramatically increased ethanol self-administration in sP rats and increased blood alcohol levels, which reached mean values close to 100 mg% in 1 h drinking sessions. Repeated DTG treatment also increased the rats' motivation to work for alcohol under a progressive-ratio schedule of reinforcement. BD-1063 prevented the effects of DTG, confirming that σ -receptors mediate the effects of DTG. Repeated DTG treatment also increased the self-administration of the non-drug reinforcers saccharin and sucrose. Naive sP rats repeatedly treated with DTG showed increased mRNA expression of μ - and δ -opioid receptors in the ventral tegmental area. These results suggest a key facilitatory role for σ -receptors in the reinforcing effects of alcohol and identify a potential mechanism that contributes to binge-like and excessive drinking. Sabino V, Cottone P, Blasio A,

Iyer MR, Steardo L, Rice KC, Conti B, Koob GF, Zorrilla EP.
Neuropsychopharmacology. 2011 Feb 23. [Epub ahead of print]

Effects of the Delta-Opioid Agonist SNC80 on the Abuse Liability of Methadone In Rhesus Monkeys: A Behavioral Economic Analysis

Delta-opioid agonists enhance the antinociceptive efficacy of methadone and other mu-opioid agonists. However, relatively little is known about the degree to which delta agonists might enhance the abuse-related effects of mu agonists. This study used a behavioral economic approach to examine effects of the delta agonist SNC80 [(+)-4-[(α R)- α -((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide] on the reinforcing effects of methadone in a drug self-administration assay. Interactions between SNC80 and cocaine were also examined for comparison. Rhesus monkeys (n=4), surgically implanted with indwelling intravenous catheters, were tested in two phases. In phase 1, drug self-administration dose-effect curves for methadone (0.0032-0.1 mg/kg/injection (inj)) and cocaine (0.0032-0.32 mg/kg/inj) alone were determined under a fixed-ratio 10 (FR 10) schedule of reinforcement. In phase 2, FR values were increased every 3 days (FR 1-FR 1800) during availability of methadone alone (0.032 mg/kg/inj) and in combination with varying proportions of SNC80 (0.1:1, 0.3:1, and 0.9:1 SNC80/methadone) or of cocaine alone (0.032 mg/kg/inj) and in combination with varying proportions of SNC80 (0.33:1, 1:1, and 3:1 SNC80/cocaine). Demand curves related drug intake to FR price, and measures of reinforcement were derived. Methadone and cocaine alone each functioned as a reinforcer. SNC80 did not alter measures of reinforcement for either methadone or cocaine. SNC80 at proportions previously shown to enhance methadone-induced antinociception did not enhance the abuse-related effects of methadone. These results support the proposition that delta agonists may selectively enhance mu agonist analgesic effects without enhancing mu agonist abuse liability. Banks ML, Roma PG, Folk JE, Rice KC, Negus SS. Psychopharmacology (Berl). 2011 Mar 3. [Epub ahead of print].

Translational Pharmacology Research Section

Opioid Receptor Probes Derived From Cycloaddition of the Hallucinogen Natural Product Salvinorin A

As part of IRP scientists' continuing efforts toward more fully understanding the structure-activity relationships of the neoclerodane diterpene salvinorin A, the authors report the synthesis and biological characterization of unique cycloadducts through [4+2] Diels-Alder cycloaddition. Microwave-assisted methods were developed and successfully employed, aiding in functionalizing the chemically sensitive salvinorin A scaffold. This demonstrates the first reported results for both cycloaddition of the furan ring and functionalization via microwave-assisted methodology of the salvinorin A skeleton. The cycloadducts yielded herein introduce electron-withdrawing substituents and bulky aromatic groups into the C-12 position. Kappa opioid (KOP) receptor space was explored through aromatization of the bent oxanorbornadiene system possessed by the cycloadducts to a planar phenyl ring system. Although dimethyl- and diethylcarboxylate analogues 5 and 6 retain some affinity and selectivity for KOP receptors and are full agonists, their aromatized counterparts 13 and 14 have reduced affinity for KOP receptors. The methods developed herein signify a novel approach toward rapidly probing the structure-activity relationships of furan-containing natural products. Lozama A, Cunningham CW, Caspers MJ, Douglas JT, Dersch CM, Rothman RB, Prisinzano TE. J Nat Prod 2011 Feb 21 [Epub ahead of print].

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 16 $\mu\text{mol/kg}$ (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 8 $\mu\text{mol/kg}$. 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 Jan 21 [Epub ahead of print].

Probes for Narcotic Receptor Mediated Phenomena. 41. Unusual Inverse Mu-Agonists and Potent Mu-Opioid Antagonists by Modification of the N-Substituent In Enantiomeric 5-(3-Hydroxyphenyl)Morphans

Conformational restraint in the N-substituent of enantiomeric 5-(3-hydroxyphenyl) morphans was conferred by the addition of a cyclopropane ring or a double bond. All of the possible enantiomers and isomers of the N-substituted compounds were synthesized. Opioid receptor binding assays indicated that some of them had about 20-fold higher μ -affinity than the compound with an N-phenylpropyl substituent ($K(i) = 2\text{-}450$ nM for the examined compounds with various N-substituents). Most of the compounds acted unusually as inverse agonists in the $[(35)\text{S}]\text{GTP-}\gamma\text{-S}$ functional binding assay using nondependent cells that stably express the cloned human μ -opioid receptor. Two of the N-substituted compounds with a cyclopropane ring were very potent μ -opioid antagonists ((+)-29, $K(e) = 0.17$ and (-)-30, $K(e) = 0.3$) in the $[(35)\text{S}]\text{GTP-}\gamma\text{-S}$ functional binding assay. By comparison of the geometry-optimized structures of the newly synthesized compounds, an attempt was made to rationalize their μ -opioid receptor affinity in terms of the spatial position of N-substituents. Cheng K, Lee YS, Rothman RB, Dersch CM, Bittman RW, Jacobson AE, Rice KC. *J Med Chem* 2011 Feb 24; 54(4): 957-969.

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, IRP researchers evaluated the pharmacology of amphetamine analogs (m-fluoroamphetamine, p-fluoroamphetamine, m-methylamphetamine, p-methylamphetamine) which display similar in vitro potency as DA releasers ($\text{EC}_{50} = 24$ to 52 nM) but differ in potency as 5-HT releasers ($\text{EC}_{50} = 53$ to 1937 nM). In vivo microdialysis was used to assess the effects of drugs on extracellular DA and 5-HT in rat n. accumbens, while simultaneously measuring ambulation (i.e., forward locomotion) and stereotypy (i.e., repetitive movements). Rats received two i.v. injections of drug, 1 mg/kg at time zero followed by 3 mg/kg 60 min later. All analogs produced dose-related increases in dialysate DA and 5-HT, but 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., % DA increase divided by % 5-HT increase) ($p < 0.029$). Collectively, these 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 B, Rothman RB. *J. Pharmacol. Exp. Ther.* 2011 Jan 12. [Epub ahead of print].

Neuropsychopharmacology Section

Neuronal Mechanisms Underlying Gamma-Vinyl GABA's Anti-Addiction Actions

IRP scientists have previously found that the drug gamma-vinyl GABA (GVG), an inhibitor of GABA transaminase in the brain, shows a promising anti-addiction profile in preclinical animal models related to addiction (e.g., Peng X-Q, Li X, Gilbert JG, Pak AC, Ashby CR Jr, Brodie JD, Dewey SL, Gardner EL, Xi Z-X. Gamma-vinyl GABA inhibits cocaine-triggered reinstatement of drug-seeking behavior in rats by a non-dopaminergic mechanism. *Drug Alcohol Depend.* 2008 Oct 1; 97(3): 216-225). GABA (gamma-aminobutyric acid) is an inhibitory neurotransmitter in the brain. These researchers have also reported that GVG elevates extracellular GABA but fails to alter dopamine release in the nucleus accumbens (NAc). Now, these researchers have investigated the mechanism(s) by which GVG elevates extracellular GABA levels and whether GVG also alters glutamate (another important brain chemical linked to addiction) in the NAc. In vivo brain microdialysis was used to simultaneously measure extracellular NAc GABA and glutamate before and after GVG administration in freely moving rats. The authors found that systemic administration of GVG or intra-NAc local perfusion of GVG significantly increased extracellular NAc GABA and glutamate. GVG-enhanced GABA was completely blocked by intra-NAc local perfusion of 5-nitro-2,3-(phenylpropylamino)-benzoic acid (NPPB), a selective anion channel blocker and partially blocked by SKF89976A, a type 1 GABA transporter inhibitor. GVG-enhanced glutamate was completely blocked by NPPB or SKF89976A. Tetrodotoxin, a voltage-dependent Na(+)-channel blocker, failed to alter GVG-enhanced GABA and glutamate. These findings suggest that GVG-enhanced extracellular GABA and glutamate are mediated predominantly by the opening of anion channels and partially by the reversal of GABA transporters, thus increasing understanding of specific neuronal mechanisms by which GVG may exert its anti-addiction effects. Peng X-Q, Gardner EL, Xi Z-X. Gamma-vinyl GABA increases nonvesicular release of GABA and glutamate in the nucleus accumbens in rats via action on anion channels and GABA transporters. *Psychopharmacology (Berl)*. 2010 Mar; 208(4): 511-519.

Activation of Type 7 Metabotropic Glutamate Receptors (mGlu7s) in the Brain Inhibits Relapse to Cocaine-Seeking Behavior

IRP scientists have previously found that activation of Type 7 metabotropic glutamate receptors (mGlu7s) in the brain inhibits cocaine's rewarding effects, inhibits intravenous cocaine self-administration, and inhibits motivation to self-administer cocaine (e.g., Li X, Li J, Peng X-Q, Spiller K, Gardner EL, Xi Z-X. Metabotropic glutamate receptor 7 modulates the rewarding effects of cocaine in rats: involvement of a ventral pallidal GABAergic mechanism. *Neuropsychopharmacology*. 2009 Jun; 34(7):1783-1796). Up to now, however, the role of brain mGlu7s in relapse to drug-seeking behavior after successful achievement of abstinence from the drug-taking habit has been unexplored and unknown. Now these researchers have found that systemic administration of AMN082, a selective mGlu7 allosteric agonist, dose-dependently inhibits cocaine-induced relapse to drug-seeking behavior. Furthermore, the exact brain locus of this action has been identified. Intracranial microinjections of AMN082 into the nucleus accumbens (NAc) or ventral pallidum, but not the dorsal striatum, inhibited cocaine-triggered relapse to cocaine-taking behavior,

an effect that was blocked by local co-administration of MMPIP, a selective mGluR7 antagonist. In vivo brain microdialysis demonstrated that cocaine priming significantly increased extracellular dopamine in the NAc, ventral pallidum and dorsal striatum, while increasing extracellular glutamate in the NAc only. AMN082 alone failed to alter extracellular dopamine, but produced a slow-onset long-lasting increase in extracellular glutamate in the NAc only. Pre-treatment with AMN082 dose-dependently blocked both cocaine-enhanced NAc glutamate and cocaine-induced reinstatement, an effect that was blocked by MMPIP or LY341497 (a selective mGluR2/3 antagonist). These data suggest that mGluR7 activation inhibits relapse to drug-seeking behavior by a glutamate-mGluR2/3 mechanism in the NAc. Thus, these findings support the potential use of mGluR7 agonists for the treatment of cocaine addiction - thus opening up a new avenue for the development of anti-addiction, anti-craving, anti-relapse medications. Li X, Li J, Gardner EL, Xi Z-X. Activation of mGluR7s inhibits cocaine-induced reinstatement of drug-seeking behavior by a nucleus accumbens glutamate-mGluR2/3 mechanism in rats. *J Neurochem.* 2010 Sep 1; 114(5): 1368-1380.

Slow-Onset Long-Acting Dopamine Reuptake Inhibitors As Potential Anti-Addiction, Anti-Craving and Anti-Relapse Medications for the Treatment of Addiction

IRP scientists have previously synthesized two chemical classes of molecules that produce slow-onset and long-acting inhibition of presynaptic dopamine reuptake in the addiction-related synapses of the nucleus accumbens of the forebrain (e.g., Froimowitz M, Wu K-M, Moussa A, Haidar RM, Jurayj J, George C, Gardner EL. Slow-onset, long-duration 3-(3',4'-dichlorophenyl)-1-indanamine monoamine reuptake blockers as potential medications to treat cocaine abuse. *J Med Chem.* 2000 Dec 28; 43(26): 4981-4992). By analogy to methadone treatment for heroin addiction and nicotine-substitution treatment for nicotine dependence, it has been suggested that such slow-onset long-duration dopamine reuptake blockers may have utility as maintenance pharmacotherapies for cocaine, amphetamine, and/or methamphetamine addiction. However, careful testing - by IRP scientists - of these compounds in preclinical animal models with good face-, construct-, and predictive-validity to the human disease of addiction showed that such compounds were pro-addictive rather than being anti-addictive (e.g., Gardner EL, Liu X, Paredes W, Giordano A, Spector J, Lepore M, Wu K-M, Froimowitz M. A slow-onset, long-duration indanamine monoamine reuptake inhibitor as a potential maintenance pharmacotherapy for psychostimulant abuse: effects in laboratory rat models relating to addiction. *Neuropharmacology.* 2006 Oct; 51(5):993-1003). This was puzzling, given the clinical success of methadone and nicotine replacement therapies, for opiate and nicotine dependence respectively. Therefore, IRP scientists embarked upon a careful parametric study of methadone pretreatment on heroin's effects in the same preclinical models being used to test the slow-onset long-acting dopamine transporter blockers. In the 45 years since the introduction of methadone for the treatment of heroin addiction, no such preclinical studies had ever previously been carried out. The findings from these new studies are extremely interesting and important. At low doses of methadone (analogous to clinically non-effective doses of methadone), the effects of methadone and heroin were found to summate - i.e., to produce a bigger opiate addiction-like effect than either methadone or heroin alone. But at higher doses of methadone (analogous to clinically effective anti-addiction doses of methadone), methadone pretreatment blocked heroin's effects. This has very important implications - methadone (although it is an opiate agonist) does not exert its anti-heroin therapeutic effects by mere agonist substitution, as has been widely assumed in the addiction medicine field for more than 45 years. Rather, at high doses, methadone actually produces a function antagonism of heroin's effects (probably by internalizing the mu opioid receptor into the neuronal cell membrane, thus hiding the receptor and making it inaccessible to subsequently administered heroin). With this breakthrough insight, IRP scientists now know, for the first time, what is necessary for a

slow-onset long-acting anti-cocaine therapy to be successful - it must substitute as a substrate for cocaine within the dopamine transporter to relieve cocaine craving, but must also conformationally change the dopamine transporter (perhaps by flipping it from an external-facing conformation to an inward-facing conformation within the neuronal cell membrane) such that subsequent cocaine is rendered ineffectual. Peng X-Q, Xi Z-X, Li X, Spiller K, Li J, Chun L, Wu K-M, Froimowitz M, Gardner EL. Is slow-onset long-acting monoamine transport blockade to cocaine as methadone is to heroin? Implication for anti-addiction medications. *Neuropsychopharmacology*. 2010 Dec; 35(13): 2564-2578.

A New and Highly-Selective Novel Dopamine D3 Receptor Antagonist Markedly Inhibits Methamphetamine's Addictive Effects in Animal Models of Addiction

Use and abuse of methamphetamine in the United States has reached epidemic proportions. Two recent national surveys give ample testimony to this fact. The first survey - "The Effect of Meth on Hospital Emergency Rooms" - found that 47% of all responding hospitals reported that methamphetamine is the top illicit drug responsible for emergency room presentations, that 73% of all hospitals report that emergency room presentations due to methamphetamine have increased over the last 5 years, and that 56% of all hospitals report that costs have increased at their facilities due to the growing use and abuse of methamphetamine. The emergency room presentations revealed by this first survey are serious medical emergencies - convulsions, malignant hyperthermia, strokes, cardiac arrhythmias, heart attacks, severe psychotic behavior, and out-of-control rages. The second survey - "The Challenges of Treating Meth Abuse" - found that 54% of all responding treatment programs report that treatment success for methamphetamine addiction is markedly lower than for other addictive drugs, that 44% of treatment programs report that relapse is higher for methamphetamine addiction than for any other drug addiction, that 63% of treatment programs report that their program lacks sufficient capacity to handle the numbers of methamphetamine addicts referred to their program, and that 69% of treatment programs report an urgent and increasing need for additional treatment options for methamphetamine-addicted patients. These facts prompted the United States Congress to declare methamphetamine use and abuse to be a national epidemic, and to pass the "Combat Methamphetamine Epidemic Act of 2005" (Title VII, Public Law 109-177). IRP scientists have previously found that blockade of dopamine D3 receptors in the brains of laboratory mice and rats produces remarkable anti-addiction effects in animal models of addiction. D3 receptors are neuroanatomically restricted to drug-reward, drug-seeking, drug-craving, and drug-relapse circuits in the brain. The highly selective dopamine D3 receptor antagonists SB277011A and NGB2904 markedly attenuate enhanced brain-reward, drug-seeking behavior, motivation to self-administer, incubation of craving, and drug-, stress-, and environmental cue-triggered relapse to drug-seeking behavior for cocaine, heroin, alcohol, and nicotine (for reviews, see Heidbreder CA, Gardner EL, Xi Z-X, Thanos PK, Mugnaini M, Hagan JJ, Ashby CR Jr. The role of central dopamine D3 receptors in drug addiction: a review of pharmacological evidence. *Brain Res Rev*. 2005 Jul; 49(1): 77-105; Xi Z-X, Gardner EL. Pharmacological actions of NGB 2904, a selective dopamine D3 receptor antagonist, in animal models of drug addiction. *CNS Drug Rev*. 2007 Summer; 13(2): 240-259. Now, these researchers have studied the effects of a novel D3 receptor antagonist - PG01037, designed and synthesized at the IRP - on intravenous methamphetamine self-administration, methamphetamine-enhanced brain stimulation reward, and environmental cue-triggered relapse to methamphetamine-seeking behavior. They found that PG01037 blocked methamphetamine-enhanced brain stimulation reward, blocked motivation to intravenously self-administer methamphetamine under progressive-ratio reinforcement conditions, and blocked methamphetamine-associated cue-triggered relapse to methamphetamine-seeking behavior. These findings now extend the potential anti-addiction pharmacotherapeutic actions of highly

selective dopamine D3 receptor antagonists to methamphetamine, which some addiction medicine experts had previously believed to be so powerfully addictive that no anti-addiction pharmacotherapy could prove effective against it. Higley AE, Spiller K, Grundt P, Newman AH, Kiefer SW, Xi Z-X, Gardner EL. PG01037, a novel dopamine D3 receptor antagonist, inhibits the effects of methamphetamine in rats. *J Psychopharmacol.* 2011 Feb; 25(2): 263-273.

A New and Highly-Selective Novel Dopamine D3 Receptor Antagonist Markedly Inhibits Cocaine's Addictive Effects In Laboratory Rat and Mouse Models of Addiction

IRP scientists have previously found that blockade of brain dopamine D3 receptors in laboratory mice and rats produces remarkable anti-addiction effects against cocaine in animal models of addiction (e.g., Vorel SR, Ashby CR Jr, Paul M, Liu X, Hayes R, Hagan JJ, Middlemiss DN, Stemp G, Gardner EL. Dopamine D3 receptor antagonism inhibits cocaine-seeking and cocaine-enhanced brain reward in rats. *J Neurosci.* 2002 Nov 1; 22(21):9595-603; Xi Z-X, Gilbert J, Campos AC, Kline N, Ashby CR Jr, Hagan JJ, Heidbreder CA, Gardner EL. Blockade of mesolimbic dopamine D3 receptors inhibits stress-induced reinstatement of cocaine-seeking in rats. *Psychopharmacology (Berl).* 2004 Oct; 176(1):57-65; Gilbert JG, Newman AH, Gardner EL, Ashby CR Jr, Heidbreder CA, Pak AC, Peng X-Q, Xi Z-X. Acute administration of SB-277011A, NGB 2904, or BP 897 inhibits cocaine cue-induced reinstatement of drug-seeking behavior in rats: role of dopamine D3 receptors. *Synapse.* 2005 Jul; 57(1):17-28; Xi Z-X, Gilbert JG, Pak AC, Ashby CR Jr, Heidbreder CA, Gardner EL. Selective dopamine D3 receptor antagonism by SB-277011A attenuates cocaine reinforcement as assessed by progressive-ratio and variable-cost-variable-payoff fixed-ratio cocaine self-administration in rats. *Eur J Neurosci.* 2005 Jun; 21(12):3427-38; Xi Z-X, Newman AH, Gilbert JG, Pak AC, Peng X-Q, Ashby CR Jr, Gitajn L, Gardner EL. The novel dopamine D3 receptor antagonist NGB 2904 inhibits cocaine's rewarding effects and cocaine-induced reinstatement of drug-seeking behavior in rats. *Neuropsychopharmacology.* 2006 Jul; 31(7):1393-405; Xi Z-X, Yang Z, Li SJ, Li X, Dillon C, Peng X-Q, Spiller K, Gardner EL. Levo-tetrahydropalmatine inhibits cocaine's rewarding effects: experiments with self-administration and brain-stimulation reward in rats. *Neuropharmacology.* 2007 Nov; 53(6):771-82; Peng X-Q, Ashby CR Jr, Spiller K, Li X, Li J, Thomasson N, Millan MJ, Moca'r E, Mu'noz C, Gardner EL, Xi Z-X. The preferential dopamine D3 receptor antagonist S33138 inhibits cocaine reward and cocaine-triggered relapse to drug-seeking behavior in rats. *Neuropharmacology.* 2009 Mar; 56(4):752-60). However, the proof-of-concept D3 antagonist compounds used in those previous studies will never progress to human trials due to pharmacokinetic and/or toxicological problems. Now, therefore, IRP scientists have designed and synthesized an entirely novel D3 receptor antagonist - YQA14 - and tested it against intravenous cocaine self-administration in laboratory rats and mice. This new compound has superior efficacy, potency, and selectivity as a D3 receptor antagonist compound as compared to those previously tested. In the present experiments, YQA14 was found to markedly inhibit intravenous cocaine self-administration in rats and mice, but not in mice lacking the D3 receptor due to specific gene deletion (D3 knockout mice). These experiments not only introduce a new and highly promising anti-cocaine medication into the field of anti-addiction medication development, but confirm - using specific gene-deletion techniques - that the observed anti-cocaine-addiction effects are mediated via the dopamine D3 receptor, thus emphasizing the validity of this anti-cocaine medication development strategy. Song R, Yang R-F, Gou H-Y, Wu N, Su R-B, Li J, Peng X-Q, Li X, Xi Z-X, Gardner EL. YQA14: a novel dopamine D3 receptor antagonist that inhibits cocaine self-administration in rats and mice, but not in D3-knockout mice. Paper presented at meetings of the Society for Neuroscience, San Diego, California, November 2010 (Abstract published in 2010 Abstract Viewer/Itinerary Planner CD-ROM, the Fortieth Annual Meeting of the Society for Neuroscience, San Diego, California, November 13-17, 2010, Society for Neuroscience, Washington DC, Abstract Number 770.10).

Cannabinoid CB1 Receptor Neural Antagonists As Potential Anti-Addiction, Anti-Craving and Anti-Relapse Medications for the Treatment of Addiction

IRP scientists have previously found that the selective cannabinoid CB1 receptor antagonists SR141716A and AM251 inhibit cocaine-enhanced brain reward, and cocaine- or cue-triggered relapse to cocaine-seeking behavior. However, all CB1 receptor antagonists tested for anti-addiction efficacy to date - both at IRP and elsewhere - are CB1 receptor inverse agonists rather than true neutral antagonists. Now, therefore, IRP scientists have designed and synthesized a true neutral CB1 receptor antagonist - PIMSR1 - and have tested it against cocaine-enhanced brain reward. PIMSR1 proved to markedly attenuate cocaine-enhanced brain-stimulation reward. Importantly, when tested at doses up to 100-fold higher than the lowest effective anti-cocaine dose, PIMSR1 by itself did not alter brain-stimulation reward electrophysiological thresholds. This is an extremely important finding, as it suggests that neutral CB1 receptor antagonists may be devoid of the dysphorigenic effects shown both in laboratory animals and humans by some CB1 receptor inverse agonists such as SR141716A. Thus, the present experiments open up an entirely new and novel class of compounds - neutral CB1 receptor antagonists - for exploration as potentially promising anti-addiction, anti-craving, and anti-relapse medication for drug abuse. Chun L, Bi G, Seltzman HH, Regio PH, Xi Z-X, Gardner EL. The novel CB1 receptor antagonist PIMSR1 attenuates cocaine's rewarding effects in rats. Paper presented at meetings of the Society for Neuroscience, San Diego, California, November 2010 (Abstract published in 2010 Abstract Viewer/Itinerary Planner CD-ROM, the Fortieth Annual Meeting of the Society for Neuroscience, San Diego, California, November 13-17, 2010, Society for Neuroscience, Washington DC, Abstract Number 770.18).

Cannabinoid CB2 Receptors are Found In the Reward and Relapse Circuitry of the Brain

Cannabinoid CB1 receptors are widely distributed in the brain. Cannabinoid CB2 receptors are widely distributed in the periphery - most especially in the immune system. Therefore, it has heretofore been generally believed that the behavioral, psychotropic, and addictive effects of cannabinoids are CB1-mediated. However, recent studies have called that accepted dogma into question (e.g., Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, Stella N, Makriyannis A, Piomelli D, Davison JS, Marnett LJ, Di Marzo V, Pittman QJ, Patel KD, Sharkey KA. Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science*. 2005 Oct 14; 310(5746): 329-332). Now, IRP scientists have used real-time PCR and immunohistochemistry to examine CB2 mRNA expression in various brain regions, and to study specific neuronal distributions of CB2 receptors in brain of wild-type, CB1 knockout, and CB2 knockout mice. The authors found that CB2 receptor mRNA is detected in the brains of wild-type and CB1 knockout, but not CB2 knockout mice. They also found that CB2 receptors are expressed on dopaminergic neurons in the ventral tegmental area of wild-type and CB1 knockout mice, while being present at significantly lower densities in CB2 knockout mice. CB2 receptors were also found on cortical GABAergic and glutamatergic neurons. CB2A and CB2B mRNA was detected in cortex, striatum, and midbrain in all three mouse strains using CB2A and CB2B Taqman probes that target undeleted receptor regions in CB2 knockout mice. However, when a specific CB2 probe that targets the CB2 receptor gene-deleted region was used, CB2 receptor mRNA was detectable only in wildtype and CB1 knockout mice, but not in CB2 knockout mice. These findings suggest that CB2 receptors are present in brain, and are specifically present on neurons in the reward, craving, and relapse circuitry of the brain. This strongly raises the possibility that CB2 receptor-mediated neural signaling may play a role in drug addiction. Zhang H, Li X, Liu Q-R, Yang H, Xu H, Gardner EL, Xi Z-X. Expression and cellular distributions of cannabinoid CB2 receptor in mouse

brain. Paper presented at meetings of the Society for Neuroscience, San Diego, California, November 2010 (Abstract published in 2010 Abstract Viewer/Itinerary Planner CD-ROM, the Fortieth Annual Meeting of the Society for Neuroscience, San Diego, California, November 13-17, 2010, Society for Neuroscience, Washington DC, Abstract Number 772.2).

Activation of Brain Cannabinoid CB2 Receptors Inhibits Cocaine Self-Administration and Cocaine-Enhanced Nucleus Accumbens Dopamine

IRP scientists have been investigating the possible existence and addiction-related function(s) of cannabinoid CB2 receptors in the brain (see immediately above). On a parallel track of research, the same IRP scientists have been exploring the effects of highly selective cannabinoid CB2 receptor agonist and antagonist pharmaceutical agents in animal models relating to addiction. The selective CB2 receptor agonist JWH133 significantly and dose-dependently inhibited intravenous cocaine self-administration in wild-type and CB1 receptor knockout mice, but not in CB2 receptor knockout mice. This inhibition was blocked by AM630, a selective CB2 receptor antagonist, but not by AM251, a selective CB1 receptor antagonist. Furthermore, the selective CB2 receptor agonist GW405833 also dose-dependently inhibited intravenous cocaine self-administration in mice. Additionally, JWH133 significantly lowered the progressive-ratio breakpoint for intravenous cocaine self-administration, indicating a significant lowering of incentive motivation to self-administer cocaine. These effects with JWH133 were duplicated by intra-nasal administration of micro-quantities of JWH133, while intravenous microinjection of the same micro-quantities of JWH133 were without effect - suggesting a effect mediated by passage of JWH133 through the cribiform plate directly into the brain. JWH133 also dose-dependently inhibited cocaine-enhanced locomotion in wild-type and CB1 receptor knockout mice, but not in CB2 receptor knockout mice. Finally, JWH133 significantly and dose-dependently lowered extracellular dopamine in the reward- and relapse-related nucleus accumbens, and significantly attenuated cocaine-enhanced extracellular nucleus accumbens dopamine in wild-type and CB1 receptor knockout mice, but not in CB2 receptor knockout mice. The effects on nucleus accumbens dopamine were blocked by AM630, a selective CB2 receptor antagonist. These findings suggest that CB2 receptors in brain modulate cocaine's rewarding and locomotor-stimulating effects, likely by inhibiting cocaine-enhanced dopamine in the nucleus accumbens. These findings also suggest that brain cannabinoid CB2 receptors may constitute a new and novel target for medication development for the treatment of addictive diseases. Xi Z-X, Peng X-Q, Li X, Li J, Gardner EL. Activation of brain CB2 receptors inhibits cocaine self-administration and cocaine-enhanced nucleus accumbens dopamine in mice. Paper presented at meetings of the Society for Neuroscience, San Diego, California, November 2010 (Abstract published in 2010 Abstract Viewer/Itinerary Planner CD-ROM, the Fortieth Annual Meeting of the Society for Neuroscience, San Diego, California, November 13-17, 2010, Society for Neuroscience, Washington DC, Abstract Number 772.3).

Medications Discovery Research Branch, Medicinal Chemistry Section

Influence of Cocaine History on the Behavioral Effects of Dopamine D3 Receptor-Selective Compounds In Monkeys

While dopamine D3 receptors have been associated with cocaine abuse, little is known about the consequences of chronic cocaine on functional activity of D3 receptor-preferring compounds. The present study examined the behavioral effects of D3 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 was a potent D3 antagonist in the mitogenesis assay but a fully efficacious agonist in the adenylyl cyclase assay, NGB 2904 was a selective D3 antagonist, whereas

CJB090 exhibited a partial agonist profile in both in vitro assays. In behavioral studies, the D3 preferential agonist quinpirole (0.03-1.0 mg/kg, i.v.) dose-dependently elicited yawns in both groups of monkeys. PG 619 and CJB090 elicited yawns only in monkeys with an extensive history of cocaine, while 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 (0.03-1.0 mg/kg/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 prior to a cocaine prime, PG 619 decreased cocaine-elicited reinstatement. These findings suggest (1) an incongruence between in vitro and in vivo assays and (2) a history of cocaine self-administration can affect in vivo efficacy of D3 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. Influence of cocaine history on the behavioral effects of dopamine D3 receptor-selective compounds in monkeys. *Neuropsychopharmacology*. 2011, e-pub Feb 2.

Design and Synthesis of Substituted N-(1,3-Diphenyl-1H-Pyrazol-5-Yl)Benzamides As Positive Allosteric Modulators of the Metabotropic Glutamate Receptor Subtype 5

Based on SAR in the alkyne class of mGlu5 receptor negative allosteric modulators and a set of amide-based positive allosteric modulators, optimized substitution of the aryl 'b' ring was used to create substituted N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamides. Results from an mGlu5 receptor functional assay, using calcium fluorescence, revealed varying efficacies and potencies that provide evidence that subtle changes in compounds within a close structural class can have marked effects on functional activity including switches in modes of efficacy (i.e., negative to positive allosteric modulation). Zou M.-F, Cao J, Rodriguez AL, Conn PJ, Newman AH. Design and synthesis of substituted N-(1,3-Diphenyl-1H-pyrazol-5-yl)benzamides as positive allosteric modulators of the metabotropic glutamate receptor subtype 5. *Bioorg. Med. Chem. Lett*. 2010, e-pub Dec 28.

Behavioral Neuroscience Branch, Preclinical Pharmacology Section

Comparison of the Effects of Methamphetamine, Bupropion, and Methylphenidate on the Self-Administration of Methamphetamine By Rhesus Monkeys

The effectiveness of methadone as a treatment for opioid abuse and nicotine preparations as treatments for tobacco smoking has led to an interest in developing a similar strategy for treating psychostimulant abuse. The current study investigated the effects of three such potential therapies on intravenous methamphetamine self-administration (1 - 30 µg/kg/injection) in rhesus monkeys. When given as a pre-session intramuscular injection, a high dose of methamphetamine (1.0 mg/kg) decreased intravenous methamphetamine self-administration but did not affect responding for a food reinforcer during the same sessions. However, the dose of intramuscular methamphetamine required to reduce intravenous methamphetamine self-administration exceeded the cumulative amount taken during a typical self-administration session, and pretreatment with a low dose of methamphetamine (0.3 mg/kg) actually increased self-administration in some monkeys at the lower self-administration dose. Like pretreatment with methamphetamine, pretreatment with bupropion (3.2 mg/kg) decreased methamphetamine self-administration but did not affect responding for food. Pretreatment with methylphenidate (0.56 mg/kg) did not significantly alter methamphetamine self-administration. These results suggest that some agonist-like agents can decrease methamphetamine self-administration. Although the most robust effects occurred with a high dose of

methamphetamine, safety and abuse liability considerations suggest that bupropion should also be considered for further evaluation as a methamphetamine addiction treatment. (PsycINFO Database Record (c) 2011 APA, all rights reserved). Schindler CW, Gilman JP, Panlilio LV, McCann DJ, Goldberg SR. *Experimental and Clinical Psychopharmacology*. 2011; Feb; 19(1): 1-10.

Striatal Pre- and Postsynaptic Profile of Adenosine A(2A) Receptor Antagonists

Striatal adenosine A(2A) receptors (A(2A)Rs) are highly expressed in medium spiny neurons (MSNs) of the indirect efferent pathway, where they heteromerize with dopamine D(2) receptors (D(2)Rs). A(2A)Rs are also localized presynaptically in cortico-striatal glutamatergic terminals contacting MSNs of the direct efferent pathway, where they heteromerize with adenosine A(1) receptors (A(1)Rs). It has been hypothesized that postsynaptic A(2A)R antagonists should be useful in Parkinson's disease, while presynaptic A(2A)R antagonists could be beneficial in dyskinetic disorders, such as Huntington's disease, obsessive-compulsive disorders and drug addiction. The aim of this work was to determine whether selective A(2A)R antagonists may be subdivided according to a preferential pre- versus postsynaptic mechanism of action. The potency at blocking the motor output and striatal glutamate release induced by cortical electrical stimulation and the potency at inducing locomotor activation were used as *in vivo* measures of pre- and postsynaptic activities, respectively. SCH-442416 and KW-6002 showed a significant preferential pre- and postsynaptic profile, respectively, while the other tested compounds (MSX-2, SCH-420814, ZM-241385 and SCH-58261) showed no clear preference. Radioligand-binding experiments were performed in cells expressing A(2A)R-D(2)R and A(1)R-A(2A)R heteromers to determine possible differences in the affinity of these compounds for different A(2A)R heteromers. Heteromerization played a key role in the presynaptic profile of SCH-442416, since it bound with much less affinity to A(2A)R when co-expressed with D(2)R than with A(1)R. KW-6002 showed the best relative affinity for A(2A)R co-expressed with D(2)R than co-expressed with A(1)R, which can at least partially explain the postsynaptic profile of this compound. Also, the *in vitro* pharmacological profile of MSX-2, SCH-420814, ZM-241385 and SCH-58261 was in accordance with their mixed pre- and postsynaptic profile. On the basis of their preferential pre-versus postsynaptic actions, SCH-442416 and KW-6002 may be used as lead compounds to obtain more effective antidyskinetic and antiparkinsonian compounds, respectively. Orru M, Bakešová J, Brugarolas M, Quiroz C, Beaumont V, Goldberg SR, Llu's C, Cortés A, Franco R, Casadó V, Canela EI, Ferré S. *PLoS One*. 2011 Jan 11; 6(1): e16088.

Dopamine D1-Histamine H3 Receptor Heteromers Provide a Selective Link to MAPK Signaling in Gabaergic Neurons of the Direct Striatal Pathway

Previously, using artificial cell systems, IRP scientists identified receptor heteromers between the dopamine D(1) or D(2) receptors and the histamine H(3) receptor. In addition, they demonstrated two biochemical characteristics of the dopamine D(1) receptor-histamine H(3) receptor heteromer. They have now extended this work to show the dopamine D(1) receptor-histamine H(3) receptor heteromer exists in the brain and serves to provide a novel link between the MAPK pathway and the GABAergic neurons in the direct striatal efferent pathway. Using the biochemical characteristics identified previously, the authors found that the ability of H(3) receptor activation to stimulate p44 and p42 extracellular signal-regulated MAPK (ERK 1/2) phosphorylation was only observed in striatal slices of mice expressing D(1) receptors but not in D(1) receptor-deficient mice. On the other hand, the ability of both D(1) and H(3) receptor antagonists to block MAPK activation induced by either D(1) or H(3) receptor agonists was also found in striatal slices. Taken together, these data indicate the occurrence of D(1)-H(3) receptor complexes in the striatum and, more importantly, that H(3) receptor agonist-induced ERK 1/2

phosphorylation in striatal slices is mediated by D(1)-H(3) receptor heteromers. Moreover, H(3) receptor-mediated phospho-ERK 1/2 labeling co-distributed with D(1) receptor-containing but not with D(2) receptor-containing striatal neurons. These results indicate that D(1)-H(3) receptor heteromers work as processors integrating dopamine- and histamine-related signals involved in controlling the function of striatal neurons of the direct striatal pathway. Moreno E, Hoffmann H, Gonzalez-Sepolveda M, Navarro G, Casadó V, Cortés A, Mallol J, Vignes M, McCormick PJ, Canela EI, Llu's C, Moratalla R, Ferré S, Ortiz J, Franco R. *Journal of Biological Chemistry*. 2011 Feb 18; 286(7): 5846-5854.

Neurobiology of Relapse Section

Role of Dorsal Medial Prefrontal Cortex Dopamine D1-Family Receptors in Relapse to High-Fat Food Seeking Induced by the Anxiogenic Drug Yohimbine

In humans, relapse to maladaptive eating habits during dieting is often provoked by stress. In rats, the anxiogenic drug yohimbine, which causes stress-like responses in humans and nonhumans, reinstates food-seeking in a relapse model. Here, IRP researchers studied the role of medial prefrontal cortex (mPFC) dopamine D1-family receptors, previously implicated in stress-induced reinstatement of drug-seeking, in yohimbine-induced reinstatement of food seeking. They trained food-restricted rats to lever press for 35% high-fat pellets every other day (9-15 sessions, 3-h each); pellet delivery was accompanied by a discrete tone-light cue. They then extinguished the operant responding for 10-16 days by removing the pellets. Subsequently, they examined yohimbine's (2 mg/kg, i.p) effect on reinstatement of food seeking and Fos (a neuronal activity marker) induction in mPFC. They then examined the effect of systemic injections of the D1-family receptor antagonist SCH23390 (10 µg/kg, s.c) on yohimbine-induced reinstatement and Fos induction, and mPFC SCH23390 (0.5, and 1.0 µg/site) injections on this reinstatement. Yohimbine-induced reinstatement was associated with strong Fos induction in dorsal mPFC and weaker Fos induction in ventral mPFC. Systemic SCH23390 injections blocked both yohimbine-induced reinstatement and mPFC Fos induction. Dorsal, but not ventral, mPFC injections of SCH23390 decreased yohimbine-induced reinstatement of food-seeking. Additionally, dorsal mPFC SCH23390 injections decreased pellet-priming-induced reinstatement, but had no effect on ongoing high-fat pellet self-administration or discrete-cue-induced reinstatement. Results indicate a critical role of dorsal mPFC dopamine D1-family receptors in stress-induced relapse to palatable food-seeking, as well as relapse induced by acute re-exposure to food taste, texture, and smell. Nair SG, Navarre BM, Cifani C, Pickens CL, Bossert JM, Shaham Y. *Role of dorsal medial prefrontal cortex dopamine D1-family receptors in relapse to high-fat food seeking induced by the anxiogenic drug yohimbine. Neuropsychopharmacology*. 2011; 36: 497-510.

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

Program Activities

New NIDA PAs and RFAs

On February 3, 2011, NIDA issued a Program Announcement (PA) entitled **Pre-Application for the 2011 NIDA Translational Avant-Garde Award for Medication Development for Diseases of Addiction (X02) PAR-11-102**. 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 diseases of addiction. Through this FOA, NIDA is committed to making significant advances in the development of safe and efficacious products for the treatment of disorders stemming from tobacco, cannabis, cocaine, methamphetamine, heroin, or prescription opiate use or abuse. Open Date: February 17, 2011. Application Due Date: March 17, 2011, by 5:00 PM local time of applicant organization.

On February 9, 2011, NIDA issued a PA entitled **Grand Opportunity in Medications Development for Substance-Related Disorders (U01) (PAR-11-109)**. The purpose of this FOA is to accelerate the development of medication for the treatment of Substance-Related Disorders (SRDs) by soliciting research applications to support a diverse array of preclinical and/or clinical research projects. The goal is to fund medication studies that will have high impact and quickly yield the necessary results to advance medications closer to FDA approval. It is expected that these U01s will be short-term (funded for up to 3 years) and large (up to \$5 million per year) cooperative agreements with close monitoring and significant scientific involvement of NIDA staff. This funding mechanism will enable critical medications development studies that would not be feasible using the traditional R01 mechanism. Letter of Intent Due Date(s): April 26, 2011, July 26, 2011, February 27, 2012, June 27, 2012, February 27, 2013, June 26, 2013; Application Due Date(s): May 26, 2011, August 26, 2011, March 27, 2012, July 27, 2012, March 27, 2013, July 26, 2013, by 5:00 PM local time of applicant organization.

On February 3, 2011, NIDA issued an RFA entitled **2011 NIDA Translational Avant-Garde Award for Medication Development for Diseases of Addiction (DP1) (RFA-DA-11-009)**. 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 diseases of addiction. Through this funding FOA, NIDA is committed to making significant advances in the development of safe and efficacious products for the treatment of disorders stemming from tobacco, cannabis, cocaine, methamphetamine, heroin, or prescription opiate use or abuse. These products can be pharmaceuticals ("small molecules") or biologics. Biologics include medicinal products such as vaccines and recombinant therapeutic proteins created by biological processes. Applications may focus on the pharmaco-therapy of one or various disorders. Applications may also focus on the specific symptoms of the disorder such as withdrawal, craving or relapse. Testing of new formulations of marketed medications that are available for other indications, or new combinations of existing medications, which may be promising candidates for the treatment of diseases of addiction is within the scope of this FOA. The 2011 Translational Avant-Garde Award competition will proceed in two phases. The first phase is a pre-application phase in response to PAR-11-102. Applications will be evaluated by a group of external reviewers. Those investigators whose submissions are judged to be the most outstanding will be notified by April 26 of the opportunity to submit full applications

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under this FOA (DP1). The 2011 Avant-Garde awardees will be selected from this group of applicants. Application Due Date: June 27, 2011, by 5:00 PM local time of applicant organization.

On February 4, 2011, NIDA issued an RFA entitled **Predictive Animal Models for Smoking Cessation Medications (U54) (RFA-DA-11-014)**. This FOA solicits grant applications for a multi-project research program to develop a weighted battery of animal behavioral tests for preclinical development of smoking cessation medications. This research program seeks to significantly improve the predictive validity of in vivo screening of drug candidates. Since people smoke for many different reasons-withdrawal relief, pleasure, taste, improvement in concentration, weight control, stress control, irritability reduction, etc.-one approach to generating predictive models is to assess effects of effective anti-smoking pharmacotherapies on specific components of tobacco dependence. Applications are expected to include animal behavior tests only. The critical part of this initiative is the establishment of a biostatistical/computational modeling core and individual project nodes, arranged according to behavioral paradigms being studied. The behavioral assessments used to model various domains of tobacco dependence should capture essential features of these processes. Funding would be provided through a cooperative center agreement mechanism (U54). Applications will be solicited for centers that include core and node activities. Applicants are responsible for arranging the agreements between different laboratories which will service all centers' activities, including the statistical/administrative core as well as the behavioral nodes activities. Letter of Intent Due Date: March 1, 2011. Application Due Date: March 31, 2011.

On February 22, 2011, NIDA issued an RFA entitled **Medication Initiative for Tobacco Dependence (MITD): A New Product Development Partnership (PDP)(UH2/UH3) (RFA-DA-11-015)**. Through this FOA, NIDA invites cooperative agreement applications from qualified non-profit, private and academic researchers/organizations to participate in the planning and execution of a new public-private partnership (PPP). The purpose of a one-year planning phase (UH2) is to provide support for the systematic study directed toward fuller scientific understanding of the opportunities in the area of drug discovery and development for tobacco dependence, with the ultimate goal of establishing a PPP, specifically, a Product Development Partnership (PDP). The mission of the PDP is to develop safe and effective medications for the treatment of tobacco dependence, including aids for smoking cessation. Phase two (UH3) funding will be utilized to support the implementation and execution phase of the PDP, with one selected cooperative agreement recipient assuming the role of the PDP's Managing Partner. In this subsequent phase, the PDP will conduct a wide array of research and development (R&D) projects aimed at the fulfillment of regulatory requirements for approval for marketing in the US. Letter of Intent Due Date: March 26, 2011. Application Due Date: April 26, 2011 by 5:00 PM local time of applicant organization.

On February 16, 2011, NIDA issued an RFA entitled **HIV/AIDS Implementation Science Targeting Drug Using Populations: A Collaboration with PEPFAR (R01) RFA-AI-12-002**. NIDA, in collaboration with the Office of the Global AIDS Coordinator, is soliciting applications for support for implementation science projects that will inform the President's Emergency Program for AIDS Relief (PEPFAR) as they develop more efficient and cost-effective methods to deliver HIV prevention, treatment, and care for drug using populations. Letter of Intent Due Date: July 1, 2011. Application Due Date: August 1, 2011 by 5:00 PM local time of applicant organization.

On March 17, 2011, NIDA issued an RFA entitled **Exploring Drugs of Abuse and Transgenerational Phenotypes (R01) (RFA-DA-12-006)**. The purpose of this FOA is to support research investigating whether or not exposure to drugs of abuse leads to behavioral, molecular, physiological or other phenotypic effects in subsequent generations. Letter of Intent Due Date: June 29, 2011. Application Due Date: July 29, 2011, by 5:00 PM local time of applicant organization.

On March 29, 2011, NIDA issued an RFA entitled **Medications Development Program Projects for Substance-Related Disorders (P01) (RFA-DA-12-005)**. With this FOA, NIDA solicits investigator-initiated program project (P01) grant applications that advance the discovery/development of new or existing therapeutics for the treatment of substance-related disorders (SRDs). Research projects in a program project grant must be closely related to a central theme that can be conducted effectively and efficiently through a coordinated collaborative approach using common resources, facilities, and instruments. Each research project within the P01 award must be supportable on its own merit. The scientific merit of each research

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project is assessed independently as well as within the context of the whole program. This initiative is designed to support an array of translational research programs, each comprised of at least three interrelated preclinical and/or clinical projects. As part of the program project, applicants are encouraged to develop synergistic collaborations with industry that enhance and strengthen the overall developmental potential of the proposed work. While the inclusion of an Administrative Core or other core is optional, it is expected that the PD/PI (or a multi-PI-coordinating group) will be responsible for the overall coordination of the program project and communication between components. Program projects can focus on the development of any sort of novel treatment strategies for cocaine, methamphetamine, cannabis, nicotine or opioid SRDs. Letter of Intent Due Date: June 29, 2011. Application Due Date: July 29, 2011.

Additional PAs/RFAs Issued with Other NIH/HHS Components

On February 3, 2011, NIDA, in collaboration with a number of other NIH components, issued a PA entitled **International Neuroscience Fellowship (F05) (PAR-11-106)**. The goal of the International Neuroscience Fellowship (INF) is to advance the training of qualified foreign neuroscientists and clinicians at the early or mid-career level, by enhancing their basic, translational or clinical research skills in a research setting in the United States. This program aims to strengthen the intellectual capital of neuroscience research in international institutions. Awardees are expected to pursue future independent and productive careers, which stimulate research in the neurosciences on a global scale. Eligible individual applicants include non-immigrant foreign scientists at the early or mid-career level. All applicants must have a doctoral or equivalent degree, and an endorsement from their home institution, with a guaranteed appointment upon completion of the fellowship. Applicants must be proficient in English and must have a sponsor in the U.S. who is affiliated with an eligible U.S. organization. All applicants must be from a low- to middle-income country based on Gross National Income per capita classified by the World Bank (<http://go.worldbank.org/K2CKM78CC0>). All applications for the INF must be submitted from the U.S. Sponsoring Institution. Open Date: July 16, 2011. Letter of Intent Receipt Date: July 16, 2011. Application Due Date: August 16, 2011, 2012, by 5:00 PM local time of applicant organization.

On February 9, 2011, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Developmental Centers for AIDS Research (P30) (PAR-11-108)**. This FOA encourages applications for the Centers for AIDS Research (CFAR) program to provide administrative and shared research support to enhance HIV/AIDS research. Applications are being solicited for both standard CFARs and for developmental CFARs (D-CFARs). Standard and D-CFARs provide core facilities, expertise, resources, and services not readily obtained otherwise through more traditional funding mechanisms. Additionally, D-CFARs provide support to assist investigators in the development of a competitive standard CFAR. The program emphasizes interdisciplinary collaboration, especially between basic and clinical investigators, translational research between the laboratory and the clinic, inclusion of investigators from diverse backgrounds, and inclusion of prevention and behavioral change research. Letter of Intent Due Date: May 13, 2011, May 14, 2012 and May 14, 2013. Application Due Date: May 13, 2011, May 14, 2012 and May 14, 2013, June 14, 2011, June 14, 2012 and June 14, 2013, by 5:00 PM local time of applicant organization.

On February 10, 2011, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral MD/PhD and Other Dual Doctoral Degree Fellows (Parent F30) (PA-11-110)**. The purpose of the Ruth L. Kirschstein National Research Service Awards (Kirschstein-NRSA) is to provide support to individuals for combined MD/PhD and other dual doctoral degree training (e.g. DO/PhD, DDS/PhD, AuD/PhD). The participating Institutes award this Kirschstein-NRSA individual fellowship (F30) to qualified applicants with the potential to become productive, independent, highly trained physician-scientists and other clinician-scientists, including patient-oriented researchers in their scientific mission areas. This funding opportunity supports individual predoctoral F30 fellowships with the expectation that these training opportunities will increase the number of future investigators with both clinical knowledge and skills in basic, translational or clinical research. Open Date: March 13, 2011.

On February 10, 2011, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellows (Parent F31) (PA-11-111)**. The purpose of this individual predoctoral research training fellowship is to provide support for promising

doctoral candidates who will be performing dissertation research and training in scientific health-related fields relevant to the missions of the participating NIH Institutes and Centers (ICs) during the tenure of the award. Open Date: March 8, 2011.

On February 10, 2011, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellowships to Promote Diversity in Health-Related Research (Parent F31-Diversity) (PA-11-112)**. The purpose of this individual predoctoral research training fellowship is to improve the diversity of the health-related research workforce by supporting the training of predoctoral students from groups that have been shown to be underrepresented. Such candidates include individuals from underrepresented racial and ethnic groups, individuals with disabilities, and individuals from disadvantaged backgrounds. Open Date: March 13, 2011.

On February 10, 2011, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Ruth L. Kirschstein National Research Service Awards (NRSA) for Individual Postdoctoral Fellows (Parent F32) (PA-11-113)**. The purpose of this individual postdoctoral research training fellowship is to provide support to promising Fellowship Applicants with the potential to become productive, independent investigators in scientific health-related research fields relevant to the missions of participating NIH Institutes and Centers. Open Date: March 8, 2011.

On February 26, 2011, NIDA, in collaboration with numerous other NIH components issued a PA entitled **Lab to Marketplace: Tools for Brain and Behavioral Research (SBIR [R43/R44]) (PA-11-134)**. The NIH Blueprint for Neuroscience Research is a framework to enhance cooperative activities among the NIH Office of the Director and 15 NIH Institutes and Centers that support research on the nervous system. This FOA is released in affiliation with the Neuroscience Blueprint, with Institutes and Centers participating independently, and with participation by Institutes and Centers that are not part of the Blueprint. This FOA encourages the translation of technologies for brain or behavioral research from academic and other non-small business research sectors to the marketplace. Encouraged from Small Business Concerns (SBCs) are Small Business Innovation Research (SBIR) grant applications that propose to further develop, make more robust, and make more user-friendly such technologies in preparation for commercial dissemination. It is expected that this activity will require partnerships and close collaboration between the original developers of these technologies and SBCs, which may be accomplished in any of a number of ways, including the use of multiple principle investigators. Open Date: March 5, 2011.

On March 14, 2011, NIDA in collaboration with numerous other NIH components, issued a PA entitled **Nanoscience and Nanotechnology in Biology and Medicine (R01) (PA-11-148)**. This initiative encourages applications from institutions/organizations that apply nanoscience and nanotechnology approaches to address problems in biology and medicine. The purpose of this FOA is to provide support for cutting-edge nanoscience and nanotechnology research that can lead to biomedical breakthroughs and new investigations into the diagnosis, treatment and management of an array of diseases and traumatic injuries. Nanoscience and nanotechnology have the capacity to drive a new wave of medical innovation through the engineering of bioactive nanoscale structures, processes and systems based on the advancement of our understanding of biology at the nanoscale. Therefore, this FOA will also support research projects that develop new or improved nanotechnology and nanoscience-based tools, methods, concepts, and devices that lead to a better understanding of basic biology in addition to conducting translational biomedical studies. Open Date: May 5, 2011.

On March 14, 2011, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Nanoscience and Nanotechnology in Biology and Medicine (R21) (PA-11-149)**. This initiative encourages applications from institutions/organizations that apply nanoscience and nanotechnology approaches to address problems in biology and medicine. The purpose of this FOA is to provide support for cutting-edge nanoscience and nanotechnology research that can lead to biomedical breakthroughs and new investigations into the diagnosis, treatment and management of an array of diseases and traumatic injuries. Nanoscience and nanotechnology have the capacity to drive a new wave of medical innovation through the engineering of bioactive nanoscale structures, processes and systems based on the advancement of our understanding of biology at the nanoscale. Therefore, this FOA will also support research projects that develop new or improved nanotechnology

and nanoscience-based tools, methods, concepts, and devices that lead to a better understanding of basic biology in addition to conducting translational biomedical studies. Because this FOA utilizes the R21 grant mechanisms, applications that focus on novel or exploratory approaches that are risky but have potentially a high impact are encouraged as well as proposed discovery research that may lead to new areas of biomedical investigations. Open Date: May 16, 2011.

On March 24, 2011, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Research on Ethical Issues in Biomedical, Social and Behavioral Research (R01) (PA-11-180)**. The purpose of this FOA is to support investigator-initiated Research Project Grant (R01) applications that propose to study high priority bioethical challenges and issues associated with the types of biomedical, social, and behavioral research supported by the participating NIH Institutes/Centers. The Office of Behavioral and Social Sciences Research (OBSSR) joins this FOA as part of its efforts to promote research on the behavioral and social aspects of health and illness. However, only participating ICs will provide direct grant support under this FOA. Open Date: May 5, 2011.

On March 24, 2011, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Research on Ethical Issues in Biomedical, Social, and Behavioral Research (R03) (PA-11-181)**. The purpose of this FOA is to support investigator-initiated Small Research Grant Award (R03) applications that propose to study high priority bioethical challenges and issues associated with the types of biomedical, social and behavioral research supported by the participating NIH Institutes/Centers. The Office of Behavioral and Social Sciences Research (OBSSR) joins this FOA as part of its efforts to promote research on the behavioral and social aspects of health and illness. However, only participating ICs will provide direct grant support under this FOA. May 16, 2011.

On March 24, 2011, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Research on Ethical Issues in Biomedical, Social, and Behavioral Research (R21) (PA-11-182)**. The purpose of this FOA is to support investigator-initiated Exploratory/Developmental Research Grant Award (R21) applications that propose to study high priority bioethical challenges and issues associated with the types of biomedical, social, and behavioral research supported by the participating NIH Institutes/Centers. The Office of Behavioral and Social Sciences Research (OBSSR) joins this FOA as part of its efforts to promote research on the behavioral and social aspects of health and illness. However, only participating ICs will provide direct grant support under this FOA. Open Date: May 16, 2011.

On March 30, 2011, NIDA, in collaboration with numerous other NIH components issued a PA entitled **Genetic Screens to Enhance Zebrafish Research (R01) (PAR-11-130)**. This FOA encourages investigator-initiated NIH Research Project Grant (R01) applications designed to exploit the power of the zebrafish as a vertebrate model for biomedical and behavioral research. Applications proposing to develop new genetic screens of high priority to the zebrafish community that will advance the detection and characterization of genes, pathways, and phenotypes of interest in development and aging, organ formation, neural processes, behavior, sensory processes, physiological processes, and disease processes are welcome. In addition, applications for pilot projects seeking to adapt existing phenotypic screening to support high-throughput characterization of mutants generated by large-scale mutagenesis projects are encouraged. This effort stems from an NIH initiative developed by the Institutes and Centers of the Trans-NIH Zebrafish Coordinating Committee (TZCC; <http://www.nih.gov/science/models/zebrafish/>) under the co-chairmanship of NICHD and NIDDK. Letter of Intent Due Date: August 19, 2011, August 19, 2012 and August 19, 2013. Application Due Date: September 19, 2011; September 19, 2012; September 19, 2013, by 5:00 PM local time of applicant organization.

On March 30, 2011, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Enhancing Zebrafish Research with Research Tools and Techniques (R01) (PAR-11-131)**. This FOA encourages investigator-initiated applications designed to exploit the power of the zebrafish as a vertebrate model for biomedical and behavioral research. Applications proposing to develop new research tools or techniques that are of high priority to the zebrafish community and that will advance the detection and characterization of genes, pathways, and phenotypes of interest in development and aging, organ formation, neural processes, behavior, sensory processing, physiological processes, and disease processes are welcome. This effort stems from an NIH initiative developed by the Institutes and Centers of the Trans-NIH Zebrafish Coordinating Committee (TZCC) under the co-chairmanship of

NICHD and NIDDK. Open Date: August 19, 2011. Application Due Date: September 19, 2011; September 19, 2012; September 19, 2013, by 5:00 PM local time of applicant organization.

On February 2, 2011, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Lasker Clinical Research Scholars Program (SI2) (RFA-OD-11-001)**. This FOA solicits applications for the Lasker Clinical Research Scholars Program, for the purpose of supporting the research activities during the early stage careers of independent clinical researchers. The program offers the opportunity for a unique bridge between the NIH intramural and extramural research communities, and contains two phases. In the first phase, Lasker scholars will receive appointments for up to 5-7 years as tenure-track investigators within the NIH Intramural Research Program with independent research budgets. In the second phase, successful scholars will be eligible to apply for up to 5 years of NIH support for their research at an extramural research facility; or, the scholar can be considered to remain as an investigator within the intramural program. Letter of Intent Due Date: March 4, 2011. Application Due Date: April 4, 2011.

On February 10, 2011, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Blueprint for Neuroscience Research Science Education Award (R25) (RFA-DA-11-013)**. This FOA solicits applications focused on improving kindergarten through twelfth grade science education in areas related to the NIH Blueprint for Neuroscience Research. Applications must be innovative, creative, and have a clear plan for improving science knowledge and enthusiasm for science among the targeted students or teachers. Plans for evaluation must be included in the application. Partnerships between educators and scientists in the development of the science education project are highly encouraged. Letter of Intent Due Date: March 11, 2011. Application Due Date: April 11, 2011, by 5:00 PM local time of applicant organization.

On February 17, 2011, NIDA, in collaboration with NIAAA and NCCAM, issued an RFA entitled **The Placebo Effect: Mechanisms and Methodology (R01) (RFA-DA-12-003)**. This FOA will use the National Institutes of Health (NIH) research project grant (R01) award mechanism to stimulate basic research to elucidate the underlying biological pathways that lead to placebo effects and to better understand how to recognize and enhance the therapeutic benefits of placebo effects in clinical research and practice. The goal of this initiative is two-fold: [1] to stimulate cross-cutting, integrative research aimed at delineating the behavioral processes and neurobiological mechanisms by which a placebo leads to its ultimate physiological and psychological effects; and [2] to stimulate clinical research that can improve detection of placebo effects, as well as an understanding of how to manipulate (i.e., reduce or enhance) and control them. In the context of this initiative, integrative research is defined as the combined use of approaches from several scientific disciplines such as psychology, neuroscience, physiology, genetics, and/or molecular biology to investigate the mechanisms underlying placebo effects. Further understanding of the placebo effect also has important implications for clinical trials. To determine the efficacy of pharmacological, procedural, or behavioral interventions, clinical trials methodology must be designed to account for placebo effects. In particular, it is important to distinguish placebo effects from the actual treatment being tested, as well as effects promoted by measurement and methodological factors. Thus, the current initiative is focused on using scientific advances within the field of placebo research to ultimately improve the ability to develop effective therapies. However, the assessment of therapeutic interventions is not the goal of this initiative. As such, applications submitted in response to the current FOA will be considered unresponsive if they propose a randomized clinical trial. Letter of Intent Due Date: April 24, 2011. Application Due Date: May 24, 2011, by 5:00 PM local time of applicant organization.

On March 16, 2011, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **NIH Blueprint for Neuroscience Research Grand Challenge: Developing Novel Drugs for Disorders of the Nervous System (U01) (RFA-NS-12-002)**. Through this FOA, NIH announces a unique opportunity for investigators working with small molecule compounds to gain access to a robust 'virtual pharma' drug development network to develop neurotherapeutic drugs. Successful applicants to this FOA will become collaborative participants in this network, receiving both funding and no-cost access to contracted drug development services that are not typically available to the academic research community. Funding will be provided through a U01 cooperative agreement mechanism to conduct biological testing of compound analogs in disease assays and models in the investigator's laboratory. No-cost drug development services will also be provided, including medicinal chemistry optimization, IND-directed pharmacology and

toxicology, and Phase I clinical testing. Researchers in possession of disease assays and small molecule compounds that show promise for treating nervous system and psychiatric disorders, but that are not yet suitable for clinical testing, are strongly encouraged to apply. Letter of Intent Due Date(s): May 10, 2011 and November 15, 2011. Application Due Date(s): June 10, 2011 and December 15, 2011, by 5:00 PM local time of applicant organization.

On April 5, 2011, NIDA, in collaboration with a number of other NIH components, issued an RFA entitled **NIH/PEPFAR Collaboration for Implementation Science and Impact Evaluation (R01) (RFA-AI-11-003)**. The NIH, in collaboration with the Office of the Global AIDS Coordinator, is soliciting applications for support for implementation science projects that will inform the President's Emergency Plan for AIDS Relief (PEPFAR) as they develop more efficient and cost-effective methods to deliver HIV prevention, treatment, and care on a large scale. Letter of Intent Due Date: June 7, 2011. Application Due Date: July 7, 2011, by 5:00 PM local time of applicant organization.

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, 24 ancillary studies have been supported by CTN and non-CTN funds. Over 12,000 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 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 0029**, A Pilot Study of Osmotic-Release Methylphenidate (OROS MPH) in Initiating and Maintaining Abstinence in Smokers with ADHD.
- **Protocol CTN 0030A2**, Effects of Chronic Opioids in Subjects with a History of Opioid Use

In addition, the following protocols have submitted primary paper:

- **Protocol CTN 0014**, Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT)
- **Protocol CTN 0020**, Job-Seekers Training for Patients with Drug Dependence
- **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 0030**, Prescription Opioid Addiction Treatment Study (POATS)
- **Protocol CTN 0032**, HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the U.S.

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 (DPMCD). 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 Gudyish, 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 0036-Ot**, Epidemiology and Ethnographic Survey of "Cheese" Heroin Use among Hispanics in Dallas County. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and is being conducted in the Texas Node.

The following protocols have 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 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 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.

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 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.
- **Protocol CTN 0045-Ot**, Rates of HIV Testing and Barriers to Testing in African Americans Receiving Substance Abuse Treatment. This is an observational study seeking to: (1) Compare the proportion of African American and non-African Americans receiving treatment at substance abuse treatment clinics that have been tested for HIV within the past 12 months; (2) Observe relationships between rates of African Americans who have not been tested and a) the types of testing offered at substance abuse treatment clinics and b) the types of outreach strategies used to engage persons in HIV testing; and (3) assess African American clients' self-reported barriers to accessing HIV testing, in relation to other ethnicities.
- **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:

- **Protocols CTN 0037A1, CTN-0044A1, CTN0046A1, and CTN0047A1**, Organizational and Practitioner Influences on Patient Outcomes. This series of ancillary studies is assessing associations between site organizational and practitioner variables and site

differences in clinical trial outcomes.

- **Protocol CTN 0049**, Project HOPE (Hospital Visit as Opportunity for Prevention and Engagement for HIV-Infected Drug Users). This study is under development. 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 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 0050**, START Follow-Up Study. This concept has been approved for further development into a protocol. 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.
- **Protocol CTN 0051**, Vivitrol. This study is under development.
- **Protocol CTN 0052**, BRAC, A Randomized Controlled Trial of Buspirone for Relapse-Prevention in Adults with Cocaine Dependence. This study is under development. The objective of this study is to evaluate the efficacy of buspirone, relative to placebo, in preventing relapse in cocaine-dependent adults in inpatient/residential treatment who are planning to enter outpatient treatment upon inpatient/residential discharge. This protocol is under development.

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).

There are also approximately 45 funded studies supported by independent grants that use CTN studies as a platform.

Dr. James Bjork, DCNBR, coordinated a Request for Information (RFI) in response to the NIDA Advisory Council's interest in a centralized neuroimaging data repository: "NOT-DA-11-008: Creation of a Consortium-Based Repository of fMRI-Based Connectivity Brain Scans from Substance-Using or Abusing Clinical Research Participants." This RFI was active from February 15, 2011 to March 15, 2011.

The Recruitment and Training Program for Under-represented Populations (RTURP) is accepting applications for the summer of 2011.

2011

Abraham, Soman N. -- Duke University

Nasal Adjuvant to Enhance Anti-Cocaine Vaccines

Aksenov, Micheal -- University of South Carolina at Columbia

Methamphetamine and HIV-1: NMDAR/D1 Mediated Neurologic Effects

Anderson, Beth Marie -- Hartford Hospital

Simulated Driving Under the Influence of Marijuana: An fMRI Study

Anderson, David J. -- California Institute of Technology

Imaging Neuromodulation in the Brain

Anokhin, Andrey P. -- Washington University

Neurocognition, Genetics, and Adolescent Substance Abuse

Anokhin, Andrey P. -- Washington University

The Functional Neuroanatomy of the Response Inhibition: Integrating ERP & FMRI Data

Aronson, Ian David -- National Development and Research Institutes

Optimizing Computer-Based Video to Increase HIV Testing in Emergency Departments

Bachtell, Ryan K. -- University of Colorado at Boulder

Effects of Adenosine Signaling on Cocaine Reward and Relapse

Biederer, Thomas -- Yale University

Mechanisms of SynCAM-Induced Synapse Formation

Binswanger, Ingrid A. -- University of Colorado Denver

Drug-Related Risk for Death After Release from Prison

Brewer, Judson A. -- Yale University

Mindfulness Training for Smoking Cessation

Buckner, Julia D. -- Louisiana State University A&M College Baton Rouge

Multi-method Assessment of Affective and Situational Antecedents of Marijuana Use

Busemeyer, Jerome R. -- Indiana University, Bloomington

Model Generalization & Parameter Consistency for Cognitive Models of Decision Making

Cabral, Guy A. -- Virginia Commonwealth University

Cannabinoid Modulation of Microglial Response to the HIV Protein Tat

Chang, Yung -- Arizona State University - Tempe Campus

Tunable Nicotine DNA-Nanovaccines

Chavkin, Charles -- University of Washington

p38 MAPK Mechanisms of Kappa Opioid-Induced Aversion

Chen, Yulong -- State University of New York, Binghamton

Genome-wide Protein-DNA Interactions Responding to Chronic Opioid Treatment

Chu, Lawrence F. -- Stanford University

5HT3 Antagonists to Treat Opioid Withdrawal and to Prevent the Progression

Corbin, Joshua G. -- Children's Research Institute

Development of the Basal Telencephalic Limbic System

Cottone, Pietro -- Boston University Medical Campus

Neurobiology of Compulsive Eating

Cowan, Christopher William -- University of Texas Southwest Medical

Center/Dallas

Transcriptional Mechanisms of Addiction-Related Neural Plasticity

Cucullo, Luca -- Cleveland Clinic Lerner College of Medicine-CWRU

Testing Tobacco Smoke Toxicity at the Blood-Brain Barrier

Cunningham, Chinazo -- Albert Einstein College of Medicine Yeshiva University

Development of a Community-Based Buprenorphine Treatment Intervention

D'Aunno, Thomas -- Columbia University Health Sciences

Testing a Comprehensive Model of the Diffusion of Evidence-Based Practices

- Dave, Rajnish S.** -- Temple University
Genomic Adaptation to HIV Infection of the CNS in Opioid-Abusers
- Deyoung, Colin G.** -- University of Minnesota Twin Cities
Neural and Genetic Mechanisms of Cognition in Externalizing Behavior
- Dhillon, Navneet Kaur** -- University of Kansas Medical Center
PDGF-Receptor regulation in Cocaine and Tat mediated Smooth Muscle Hyperplasia
- Dickson-Gomez, Julia B.** -- Medical College of Wisconsin
High Risk Crack Use Settings and HIV in El Salvador
- Dong, Yan** -- Washington State University
Labeling of Cocaine-generated Nascent Excitatory Synapses
- Dong, Yan** -- Washington State University
The Accumbens NMDA Receptor in HIV-induced Motivational Disorders
- Dracheva, Stella** -- Mount Sinai School of Medicine
Probing the Link between RNA Editing and Drug Addiction
- Evins, A. Eden** -- Massachusetts General Hospital
Proof-of-Concept Trial of an Alpha-7 Nicotinic Agonist for Nicotine Dependence
- Fairchild, Amanda Jane** -- University of South Carolina at Columbia
Mediation in Survival and Onset-to-Growth Models Applied to Youth Substance Onset
- Festinger, David S.** -- Treatment Research Institute, Inc. (TRI)
Delivering HIV Risk Reduction Services in Drug Court
- Filipeanu, Catalin** -- Louisiana State University Health Science Center New Orleans
The Regulation of Cannabinoid Receptors in Microglial Cells During HIV Infection
- Foltin, Richard W.** -- New York State Psychiatric Institute
Hypocretin Antagonists as a Novel Approach to Medication Development
- Frazier, Charles J.** -- University of Florida
CB1R Independent Effects of Cannabinoids on Synaptic Physiology in the CNS
- Fricker, Lloyd D.** -- Albert Einstein College of Medicine Yeshiva University
Neuropeptides, Processing Enzymes, and Drug Abuse
- Geurts, Aron M.** -- Medical College of Wisconsin
CRE Rat for Psychiatric Disorders
- Geyer, Mark A.** -- University of California San Diego
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- Gould, Thomas J.** -- Temple University
Nicotine Addiction: Learning, Neural & Genetic Process
- Green, Thomas Arthur** -- University of Texas Medical Branch Galveston
Molecular Mechanisms of Environmental Enrichment
- Greengard, Paul** -- Rockefeller University
Drugs of Abuse - Role of Protein Phosphorylation
- Griffiths, Roland R.** -- Johns Hopkins University
Licit Abused Drugs
- Grigson, Patricia Sue** -- Pennsylvania State University Hershey Medical Center
Drugs of Abuse and Learned Aversions: Solving a Paradox
- Grimm, Jeffrey W.** -- Western Washington University
Incubation of Craving: Abstinence and Environmental Enrichment-mediated Molecular
- Guan, Yongtao** -- Yale University
Statistical Methods for Understanding Heterogeneity in Cocaine Relapse
- Gulley, Joshua M.** -- University of Illinois Urbana-Champaign
Mechanisms of Amphetamine-induced Plasticity in Adolescents Compared to Adults
- Gurevich, Eugenia V.** -- Vanderbilt University
The Role of Receptor Desensitization Machinery in Psychostimulant Addiction
- Hook, Michelle A.** -- Texas A&M University System

Morphine Undermines Recovery of Function after SCI: Neurobiological Mechanisms

Hruby, Victor J. -- University of Arizona
Novel Non-Peptide Opioid Ligands for Pain

Hull, Mark -- University of British Columbia
Stop HIV in DUs

Hurt, Richard D. -- Mayo Clinic
Varenicline Treatment for Active Alcoholic Smokers

Ilggen, Mark Andrew -- University of Michigan at Ann Arbor
Psychosocial Pain Management During Addictions Treatment to Improve Outcomes

Ingersoll, Karen S. -- University of Virginia Charlottesville
Text Messaging Adherence Assessment & Intervention Tool for Rural HIV+ Drug Users

Jarrett, Traci -- West Virginia University
The Environmental Context of Smoking: Measuring Social Capital in College

Johnson, Alexander W. -- Johns Hopkins University
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Kogan, Steven M. -- University of Georgia (UGA)
HIV-Related Behavior among Rural African American, Young Adult Men

Koob, George F. -- Scripps Research Institute
Effects of Deep Brain Stimulation on Compulsive Drug Intake

Kumar, Mahendra -- University of Miami School of Medicine
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Latkin, Carl A. -- Johns Hopkins University
An RCT to Train Black MSM as Peer Health Educator for HIV Testing and Prevention

Lelutiu-Weinberger, Corina Teodora -- Hunter College
An Innovative HIV Prevention Intervention Using Social Networking Technology

Li, Guohua -- Columbia University Health Sciences
Effectiveness of Mandatory Prescription Drug Monitoring

Li, Jianghong -- Institute for Community Research
IDU Peer Recruitment Dynamics and Network Structure in Respondent Driven Sampling

Longstreth, James Alvan -- U.S. Worldmeds, LLC
NDA-Enabling Phase I Lofexidine Program

Lowe, John R. -- Florida Atlantic University
Testing a Substance Abuse Prevention Intervention for Cherokee Early Adolescents

Manning-Bog, Amy Beatrice -- SRI International
DJ-1-Dopamine Transporter Interactions in Models of Addiction

Mash, Deborah C. -- University of Miami School of Medicine
Carbon-14 Birth Dating of Neurons in Addiction

McCabe, Sean Esteban -- University of Michigan at Ann Arbor
Trajectories of Nonmedical Prescription Drug Misuse

Medina, Krista Lisdahl -- University of Cincinnati
Effects of Physical Activity & Marijuana Use on Frontolimbic Functioning

Melloni, Richard H. -- Northeastern University
Adolescent Anabolic Steroids, Vasopressin and Aggression

Mimiaga, Matthew James -- Massachusetts General Hospital
Behavioral Activation and HIV Risk Reduction for MSM with Crystal Meth Abuse

Moore, David J. -- University of California San Diego
Personalized Text Messages to Improve ART Adherence in HIV+ Meth Users

Nestler, Eric J. -- Mount Sinai School of Medicine
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Niv, Yael -- Princeton University

fMRI Investigations of How We Learn what is Relevant for a Decision

Novak, Scott -- Research Triangle Institute
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Odum, Amy -- Utah State University
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Okamoto, Scott Kiyoshi -- Hawaii Pacific University
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Ostlund, Sean Bjorn -- University of California Los Angeles
Cocaine-Seeking and the Transfer of Behavioral Control

Palfai, Tibor P. -- Boston University
Implementing Web-Based SBI for Marijuana Use in College Student Health Centers

Poduska, Jeanne Marie -- American Institutes for Research
Prevention Services for Early Drug Abuse Risk: Teachers Implement, Sustain, Adapt

Pope, Harrison G. -- McLean Hospital, Belmont, MA
Medical Consequences of Long-Term Anabolic-Androgenic Steroid Abuse

Pratt, Wayne E. -- Wake Forest University
Meso-accumbens Serotonergic Involvement in Appetitive and Consummatory Behaviors

Prescot, Andrew -- University of Utah
MRS Changes in Marijuana Using Adolescents: 2D MRS with Prior Knowledge Fitting

Reynolds, Elizabeth Keats -- University of Maryland College Park Campus
Analogue Study of Peer Influence on Risk Taking Behavior in Older Adolescents

Rich, Josiah D. -- Miriam Hospital
Prisoner Overdose Training and Naloxone Upon Release

Robertson, Angela A. -- Mississippi State University
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Rotheram-Borus, Mary J. -- University of California Los Angeles
Structural Pathways for South African Men to Reduce Substance Abuse & HIV

Roy, Sabita -- University of Minnesota Twin Cities
Role of microRNAs in Opioid Drug Abuse Induced Persistent Inflammation and HIV

Salas, Ramiro -- Baylor College of Medicine
Functional Imaging of the Habenula in Tobacco Smokers

Sandler, Irwin N. -- Arizona State University - Tempe Campus
Multi-Court Trial of NBP to Prevent Substance Abuse and Mental Health Disorder

Schulz, Daniela -- Brookhaven Science Association—Brookhaven Laboratories
PET Imaging in Behaving Animals: A New Research Paradigm for Neuroscience

Schwartz, Robert P. -- Friends Research Institute, Inc.
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Sofuoglu, Mehmet -- Yale University
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Suh, Jesse Jongshik -- University of Pennsylvania
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Recruitment Methods for Surveying Populations at Risk for HIV: Secondary Analysis

Tricomi, Elizabeth -- Rutgers The State University of New Jersey Newark
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Tsoh, Janice Y. -- University of California San Francisco
A Family Intervention to Reduce Smoking Among Chinese and Vietnamese Men

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Weinstein, Harel -- Weill Medical College of Cornell University
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Whistler, Jennifer L. -- Ernst Gallo Clinic and Research Center
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Reversal of AMPA Receptor Plasticity Underlying Incubation of Cocaine Craving

Wood, Ruth I. -- University of Southern California
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Yantis, Steven G. -- Johns Hopkins University
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Yin, Deling -- East Tennessee State University
Role of Opioids Signaling in Immune Suppression

Zhang, Chenming M. -- Virginia Polytechnic Institute and State University
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Director's Report to the National Advisory Council on Drug Abuse - May, 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)

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- 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 DPMCA

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.

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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 -

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

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

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

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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.

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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

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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.

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

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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, DPMCD, 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, DPMCD 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 Epidemiology, 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.

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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.

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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

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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. Alfiere 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.

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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](#)

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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](#)

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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 - May, 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 addiction.

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

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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.

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Director's Report to the National Advisory Council on Drug Abuse - May, 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 professionals 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.

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[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

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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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Zhang X, Ross TJ, Geng X, Salmeron BJ, Yang Y, Stein EA. Factors underlying prefrontal and insula structural alterations in smokers. *Neuroimage*. 2011 Jan 1; 54(1): 42-48.

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Director's Report to the National Advisory Council on Drug Abuse - May, 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, DPMCD, 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. Rodriguez Bores Ramirez is currently completing her medical residency in Psychiatry at the Universidad Nacional Autónoma de México, Instituto Nacional de Psiquiatría 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

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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.

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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."

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