Director's Report to the National Advisory Council on Drug Abuse - May, 2010

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Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Research Findings - Basic Neuroscience Research

PDZ binding of PICK1

The protein PICK1 (protein that interacts with C kinase 1) functions as a scaffolding or anchoring protein for the assembly of various protein partners, including protein kinase Calpha, AMPA receptor subunits 2-4, metabatropic glutamate receptors, transmembrane transporters, ion channels, and G protein-coupled receptors. Its binding to these varied partners can affect their level of surface plasma membrane expression in various cells, or, in some cases, their intracellular levels. PICK1 is highly expressed in the brain, including neuronal synapses. For binding, PICK1 possesses a single so-called "PDZ domain" near its N-terminus, consisting of amino acid residues 22-105, which provides a binding pocket for the PDZ-binding region of other proteins, primarily accommodating only several residues of the C-terminus of these proteins, with low micromolar affinity constants. A recent report by Dr. Gether and colleagues described the discovery of a small molecule known as FSC231, which serves as an inhibitor of the PICK1 PDZ domain. This molecule was found in a chemical library of approximately 44,000 compounds, using a competition assay for the inhibition of fluorescence of Oregon green-labeled DAT13 (a 13 amino acid C-terminus peptide of the DAT). This research has provided evidence for the disruption of the PICK1 PDZ-GluR2 complex by a small molecule with moderate binding affinity in the micromolar range. It may provide a starting point for the development of additional small molecule inhibitors, which may have the property of reducing hippocampal LTP induced by cocaine exposure and reversing the resulting redistribution of synaptic GluR subunits. Thorsen TS, Madsen KL, Rebola N, Rathje M, Anggono V, Bach A, Moreira I S, Stuhr-Hansen N, Dyhring T, Peters D, Beuming T, Huganir R, Weinstein H, Mulle C, Stromgaard K, Ronn LCB, Gether U. Identification of a small-molecule inhibitor of the PICK1 PDZ domain that inhibits hippocampal LTP and LTD. PNAS. 2010; 107(1): 413-418.

Characterization of Tunable Piperidine and Piperazine Carbamates as Inhibitors of Endocannabinoid Hydrolases

Monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH) are two enzymes from the serine hydrolase superfamily that degrade the endocannabinoids 2-arachidonoylglycerol and anandamide, respectively. A group led by Dr. Benjamin Cravatt has recently discovered that MAGL and FAAH are both inhibited by carbamates bearing an N-piperidine/piperazine group. Piperidine/piperazine carbamates show excellent in vivo activity, raising brain endocannabinoid levels and producing CB1-dependent behavioral effects in mice, suggesting that they represent a promising class of inhibitors for studying the endogenous functions of MAGL and FAAH. Herein, they disclose a full account of the syntheses, structure-activity relationships, and inhibitory

activities of piperidine/piperazine carbamates against members of the serine hydrolase family. These scaffolds can be tuned for MAGL-selective or dual MAGL-FAAH inhibition by the attachment of an appropriately substituted bisarylcarbinol or aryloxybenzyl moiety, respectively, on the piperidine/piperazine ring. Modifications to the piperidine/piperazine ring ablated inhibitory activity, suggesting a strict requirement for a six-membered ring to maintain potency. Long JZ, Jin X, Adibekian A, Li W, Cravatt BF. Characterization of tunable piperidine and piperazine carbamates as inhibitors of endocannabinoid hydrolases. J Med Chem. 2010; 53: 1830-1842.

Synthesis and Pharmacological Evaluation of Highly Potent [Dmt1]DALDA Analogs

Chemical structure variation of the highly potent and μ-opioid selective, peripheral analgesic, DALDA ([D-Arg2, Lys4] dermorphin-(1,4)-amide) led to the synthesis of a new compound [Dmt1] DALDA which had 12 fold higher affinity than DALDA at μ-opioid receptors, and a potency 180 fold higher. Authors had access to protected analogs of [Dmt1] DALDA which they used to synthesize gram quantities of three antioxidant peptides: SS-02 (Dmt-D-Arg-Phe-Lys-NH2). SS-31 (D-Arg-Dmt-Lys-Phe-NH2), and SS-20 (Phe-D-Arg-Phe-Lys-NH2), and then examined their bioactivity. Synthesis of these three peptides involved routinely used side chain protecting groups for amino acid building blocks. Opioid activities and potency varied at the at μ-opioid and δ-opioid receptors among these chemical structures. Reddy PA, Lewin AH, Schiller PW. Synthesis and pharmacological evaluation of highly potent [Dmt1] DALDA analogs. Adv Exp Med Biol. 2009; 611:473-474.

PET Imaging of Cortical Activation During Cocaine Self-Administration and Extinction

Dr. Leonard Howell and his colleagues at Emory University and Yerkes National Primate Research Center were among the first to use functional brain imaging to show cocaine-induced changes in brain activity during active drug taking in primates. Using PET imaging with O15-labeled water to quantify changes in cerebral blood flow, the PI and his colleagues studied the effects of cocaine administered noncontingently in na•ve monkeys, and the effects when the animals self-administered the drug or later, when saline was substituted for the cocaine. They found that noncontingent drug administration was associated with robust activation of the dorsolateral regions of the prefrontal cortex; by contrast, the effects of the drug when self-administered were to activate anterior cingulate cortex. During times when saline was substituted for cocaine, the stimuli previously paired with cocaine also induced a similar robust activation in prefrontal cortex. Dr. Howell and his colleagues interpret these findings to indicate that the effects of cocaine and associated cues extend further than the limbic system and utilize brain areas involved in cognitive processes. The recognition that neural circuits underlie the direct pharmacological and conditioned stimulus effects of cocaine may provide important new clues for the development of medications for the treatment of cocaine abuse. Howell LL, Votow JR, Goodman MM, Lindsey KP. Cortical activation during cocaine use and extinction in rhesus monkeys. Psychopharmacology. 2010; 208: 191-199.

Cannabinoid Receptor Agonist, THC, Inhibits Macrophage Migration to the Tat Protein of HIV-1

Macrophages and macrophage-like cells are important targets of HIV-1 infection at peripheral sites and in the central nervous system. After infection, these cells secrete a plethora of toxic factors, including the viral regulatory trans-activating protein (Tat). This protein is highly immunogenic and also

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serves as a potent chemoattractant for monocytes. In the present study, the exogenous cannabinoids THC and CP55940 were shown to significantly inhibit migration of human U937 macrophage-like cells to the Tat protein in a concentration-related manner. The CB1 receptor-selective agonist ACEA had no effect on Tat-mediated migration. In contrast, the CB2 receptor-selective agonist O-2137 exerted a concentration-related inhibition of U937 cell migration in response to Tat. Pharmacological blockage of CB1 receptor signaling using the antagonist (SR141716A had no effect on CP55940-mediated inhibition of macrophage migration to Tat, whereas treatment with the CB2 receptor antagonist SR144528 reversed the CP55940-mediated inhibition of migration. In addition, THC had no inhibitory effect on U937 migration to Tat after small interfering RNA knockdown of the CB2 receptor. Collectively, the pharmacological and biochemical knockdown data indicate that cannabinoid-mediated modulation of macrophage migration to the HIV-1 Tat protein is linked to the CB2 cannabinoid receptor. Furthermore, these results suggest that the CB2 cannabinoid receptor has potential to serve as a therapeutic target for ablation of HIV-1-associated untoward inflammatory response. Raborn ES, Cabral GA. Cannabinoid inhibition of macrophage migration to the trans-activating (Tat) protein of HIV-1 Is linked to the CB2 cannabinoid receptor. J Pharm Exp Ther. 2010; Apr; 333(1): 319-327.

Supraspinal Inactivation of Mitochondrial Superoxide Dismutase is a Source of Peroxynitrite in the Development of Morphine Antinociceptive Tolerance

Effective treatment of chronic pain with morphine is limited by decreases in the drug's analgesic action with chronic administration (antinociceptive tolerance). Because opioids are mainstays of pain management, restoring their efficacy has great clinical importance. It has been reported that formation of peroxynitrite in the dorsal horn of the spinal cord plays a critical role in the development of morphine antinociceptive tolerance and that nitration and enzymatic inactivation of mitochondrial superoxide dismutase (MnSOD) at that site provides a source for this nitroxidative species. These researchers report for the first time that antinociceptive tolerance in mice is also associated with the inactivation of MnSOD at supraspinal sites. Inactivation of MnSOD led to nitroxidative stress as evidenced by increased levels of products of oxidative DNA damage and activation of the nuclear factor poly (ADP-ribose) polymerase in whole brain homogenates. Co-administration of morphine with potent Mn porphyrin-based peroxynitrite scavengers, restored the enzymatic activity of MnSOD, (2) attenuated PN-derived nitroxidative stress, and (3) blocked the development of morphine-induced antinociceptive tolerance. A more lipophilic analogue was able to cross the blood-brain barrier and was about 30-fold more efficacious. Collectively, these data suggest that PN-mediated enzymatic inactivation of supraspinal MnSOD provides a source of nitroxidative stress, which in turn contributes to central sensitization associated with the development of morphine antinociceptive tolerance. Thus, PN-targeted therapeutics may have potential as adjuncts to opiates in pain management. Doyle T, Bryant L, Batinic-Haberle I, Little J, Cuzzocrea S, Masini E, Spasojevic I, Salvemini D. Supraspinal inactivation of mitochondrial superoxide dismutase is a source of peroxynitrite in the development of morphine antinociceptive tolerance. Neuroscience 2009; Dec. 164:702-710.

Opioids Activate Brain Analgesic Circuits through Cytochrome P450/Epoxygenase Signaling

Activation of μ opioid receptors by morphine in the brainstem and spinal cord produces analgesia, but the relevant post-receptor mechanisms are not known. In the brainstem, opioid-induced stimulation of descending circuits from the ventrolateral periaqueductal gray (PAG) and rostral ventromedial medulla (RVM) produces powerful inhibition of spinal nociceptive transmission. In the

PAG, μ-opioid receptors activate these circuits by increasing a presynaptic, voltage-dependent potassium conductance that inhibits GABA release. Biochemical and electrophysiological studies have suggested that phospholipase A2 and its product, arachidonic acid, are important for such analgesic signaling. These researchers evaluated the arachidonate epoxygenase pathway, which uses P450s to produce up to four distinct epoxyeicosatrienoic acid isomers, as a brain μ opioid analgesic transduction mechanism. To assess the importance of brain cytochrome P450 (P450) activity in mu opioid analgesic action, these investigators generated mutant mice with brain neuron-specific reductions in P450 activity. These mice showed highly attenuated morphine antinociception compared with controls. Pharmacological inhibition of brain P450 arachidonate epoxygenases also blocked morphine antinociception in mice and rats. These findings indicate that a neuronal P450 epoxygenase mediates the pain-relieving properties of morphine. Conroy JL, Fang C, Gu J, Zeitlin SO, Yang W, Yang J, VanAlstine MA, Nalwalk JW, Albrecht PJ, Mazurkiewicz JE, Snyder-Keller A, Shan Z, Zhang SZ, Wentland MP, Behr M, Knapp BI, Bidlack JM, Zuiderveld OP, Leurs R, Ding X, Hough LB. Opioids activate brain analgesic circuits through cytochrome P450/epoxygenase signaling. Nat Neurosci. 2010; 13: 284-286.

The Beta-lactam Antibiotic, Ceftriaxone, Prevents Relapse to Cocaine Seeking by Restoring Glutamate Transport

The cystine-glutamate exchanger (xCT) is downregulated in the brain after chronic cocaine, resulting in reduced extracellular levels of nucleus accumbens glutamate. The importance of cocaine-induced loss of glutamate homeostasis is revealed by N-acetylcysteine restoring cystine-glutamate exchange and attenuating reinstatement to cocaine seeking. Another regulator of extracellular glutamate is the glial glutamate transporter (GLT-1). Dr. Kalivas and his colleagues hypothesized that cocaine self-administration reduces GLT-1 and that GLT-1 upregulation inhibits cocaine seeking. The authors measured [(3)H] glutamate uptake and protein expression of GLT-1 and xCT, the catalytic subunit of the cystine-glutamate exchanger, following cocaine self-administration and 3 weeks of extinction training. They also examined the affect of ceftriaxone (previously shown to increase GLT-1) and N-acetylcysteine treatment on the expression of GLT-1 and xCT. Ceftriaxone was also tested for the capacity to inhibit cue- and cocaine-induced relapse. Results indicated that self-administration reduced glutamate uptake and the expression of both GLT-1 and xCT. Ceftriaxone restored GLT-1 and xCT levels and prevented cue- and cocaine-induced reinstatement of drug seeking. N-acetylcysteine also restored GLT-1 and xCT levels. These results indicate that glutamate transport and cystine-glutamate exchange may be coregulated and provide further evidence that targeting glutamate homeostasis is a potential method for treating cocaine relapse. Knackstedt LA, Melendez RI, Kalivas PW. Ceftriaxone restores glutamate homeostasis and prevents relapse to cocaine seeking. Biol Psychiatry. 2010 Jan 1; 67(1): 81-84.

Benzodiazepines Promote Addiction by Increasing VTA Dopamine Firing through Disinhibition of Interneuron GABA Release

Addictive drugs increase the levels of dopamine and also trigger long-lasting synaptic adaptations in the mesolimbic reward system that ultimately may induce the pathological behaviour. Addictive drugs can be classified into three groups according to the mechanism through which they increase mesolimbic dopamine; 1) indirectly increasing dopamine neuron firing rates by reducing inhibitory neuron input, 2) directly activating dopamine neurons, or 3) altering dopamine transporter function. However, it is unclear whether these mechanisms can account for the addiction liability of benzodiazepines. This paper shows that benzodiazepines indirectly increase firing of dopamine neurons of the ventral tegmental area through the positive modulation of

GABA(A) (gamma-aminobutyric acid type A) receptors in nearby interneurons. Such disinhibition, which relies on alpha1-containing GABA(A) receptors expressed in these cells, triggers drug-evoked synaptic plasticity in excitatory afferents onto dopamine neurons and underlies drug reinforcement. Taken together, the data provide evidence that benzodiazepines share defining pharmacological features of addictive drugs through cell-type-specific expression of alpha1-containing GABA(A) receptors in the ventral tegmental area. The data also indicate that subunit-selective benzodiazepines sparing alpha1 may be devoid of addiction liability. Tan KR, Brown M, Labou be G, Yvon C, Creton C, Fritschy JM, Rudolph U, LŸscher C. Neural bases for addictive properties of benzodiazepines. Nature 2010 Feb 11; 463(7282): 769-774.

Muscarinic Acetylcholine Type M2 and GABA(B) R2 Receptors Form Novel Heterodimer Receptors that Enhance Cholinergic Signaling in the Brain

Chronic stimulation of muscarinic M2 receptors [M(2)R] has previously been shown to promote internalization of G-protein-activated inwardly rectifying potassium channels (GIRKs) which results in loss of function. However, emerging evidence is showing that G-protein-coupled receptors (GPCRs) can form heterodimeric receptor complexes that generate new GPCR signaling properties within the brain. This paper now reports that coexpression of GABA(B) R2 receptors (GBR2s) rescues both surface expression and function of muscarinic M2 receptors, including M(2)R-induced activation of G-protein-activated inwardly rectifying potassium channels (GIRKs). GBR2 showed significant association with M(2)R at the plasma membrane but not with other GPCRs (such as M(1)R, mu-opioid receptor), as detected by fluorescence resonance energy transfer (FRET). Unique regions of the proximal C-terminal domains of GBR2 and M(2)R mediate specific binding between M(2)R and GBR2. In the brain, GBR2, but not GBR1, biochemically coprecipitates with M(2)R and overlaps with M(2)R expression in cortical neurons. This novel heteromeric association between M(2)R and GBR2 provides a possible mechanism for altering muscarinic signaling in the brain and represents a previously unrecognized role for GBR2. Boyer SB, Clancy SM, Terunuma M, Revilla-Sanchez R, Thomas SM, Moss SJ, Slesinger PA. Direct interaction of GABAB receptors with M2 muscarinic receptors enhances muscarinic signaling. J Neurosci 2009 Dec 16; 29(50): 15796-15809.

Glutamate or Norepinephrine-mediated Synaptic Plasticity within the Extended Amygdala Involve Different Cellular Mechanisms and are Differentially Affected in Response to Stress

Changes in the amygdala have been proposed as potential mechanisms underlying the development of addictive behaviors. Long-term depression (LTD), a form of synaptic plasticity, is an important synaptic mechanism for limiting excitatory influence over circuits subserving cognitive and emotional behavior. A major means of LTD induction is through the recruitment of signaling via G-protein coupled receptors [GPCR] activated by norepinephrine (NE) and glutamate. Receptors from these transmitter families have been proposed to converge on a common postsynaptic LTD mechanism to produce similar alterations in glutamate synapse efficacy. This paper reports that in the bed nucleus of the stria terminalis (BNST), a structure within the extended amygdala, recruitment of G-protein coupled receptors by glutamate or NE initiates mechanistically distinct forms of postsynaptically maintained LTD. Furthermore, the LTDs produced are differentially regulated by stress exposure. In particular, although both glutamate [mGluR5] and norepinephrine [alpha(1)-adrenergic receptor (AR)]-dependent LTDs involve postsynaptic endocytosis, norepinephrine-initiated LTD exclusively involves modulation of signaling through calcium-permeable AMPA receptors. Further, norepinephrine, but not glutamate, dependent LTD is disrupted by restraint stress. These data

suggest that in the BNST, NE- and glutamate-activated GPCR pathways differentially tune glutamate synapse efficacy in response to stress. McElligott ZA, Klug JR, Nobis WP, Patel S, Grueter BA, Kash TL, Winder DG. Distinct forms of Gq-receptor-dependent plasticity of excitatory transmission in the BNST are differentially affected by stress. Proc Natl Acad Sci USA 2010 Feb 2; 107(5): 2271-2276.

Differential Modulation of Mu- and Delta-Opioid Receptor Agonists by Endogenous RGS4 Protein in SH-SY5Y Cells

Regulator of G-protein signaling (RGS) proteins are a family of molecules that control the duration of G protein signaling. A variety of RGS proteins are thought to modulate opioid receptor signaling. Here Dr. Traynor of University of Michigan Medical School and his research team show that RGS4 is abundantly expressed in human neuroblastoma SH-SY5Y cells that endogenously express mu- and delta-opioid receptors and test the hypothesis that the activity of opioids in these cells is modulated by RGS4. Endogenous RGS4 protein was reduced by approximately 90% in SH-SY5Y cells stably expressing short hairpin RNA specifically targeted to RGS4. In these cells, the potency and maximal effect of delta-opioid receptor agonist (SNC80)-mediated inhibition of forskolin-stimulated cAMP accumulation was greater than that seen in control cells. Transient transfection of a stable RGS4 mutant (HA-RGS4C2S) reversed this effect. Further, the delta opiate agonist increased MAPK activation in cells with less RGS4, but there was no change in the mu-opioid (morphine) response at adenylyl cyclase or MAPK. FLAG-tagged opioid receptors and HA-RGS4C2S were transiently expressed in HEK293T cells, and co-immunoprecipitation experiments showed that the delta-opioid receptor but not the mu-opioid receptor could be precipitated together with the stable RGS4. The use of delta- and mu-opioid receptor chimeras indicated that the C-tail and third intracellular domain of the delta-opioid receptor could be the sites of interaction with RGS4. The findings demonstrate a role for endogenous RGS4 protein in modulating delta-opioid receptor signaling in SH-SY5Y cells and provide evidence for a receptor-specific effect of RGS4. Wang, Q, Liu-Chen, L-Y, Traynor, JR. Differential modulation of mu- and delta-opioid receptor agonists by endogenous RGS4 protein in SH-SY5Y cells. J Biol Chem 2009; 284(27): 18357-18367.

Mu-Opioid Receptor Endocytosis Prevents Adaptations in Ventral Tegmental Area GABA Transmission Induced During Naloxone-Precipitated Morphine Withdrawal

Chronic morphine drives adaptations in synaptic transmission thought to underlie opiate dependence. Here Dr. Whistler and colleagues at the Ernest Gallo Clinic and Research Center examine the role of mu-opioid receptor (MOR) trafficking in one of these adaptations, specifically, changes in GABA transmission in the ventral tegmental area (VTA). To address this question, they used a knock-in mouse, RMOR (for recycling MOR), in which genetic change in the MOR promotes morphine-induced receptor desensitization and endocytosis in GABA interneurons of the VTA. In wild-type mice repeated injections of morphine (10 mg/kg, s.c., twice daily for 5 d), induced a cAMP-dependent increase in the probability of GABA release onto VTA dopamine neurons. The increased GABA release frequency correlated with physical dependence on morphine measured by counting somatic signs of morphine withdrawal, such as, tremors, jumps, rears, wet-dog shakes, and grooming behavior precipitated by subcutaneous administration of naloxone. This adaptation in GABA release was prevented in RMOR mice given the same morphine treatment, implicating MOR trafficking in this morphine-induced change in plasticity. Importantly, treatment with the cAMP activity inhibitor rp-cAMPS [(R)-adenosine, cyclic 3',5'-(hydrogenphosphorothioate) triethylammonium] directly to the VTA attenuated somatic withdrawal signs to

systemic morphine produced by intra-VTA naloxone, directly linking enhanced cAMP-driven GABA release to naloxone-precipitated morphine withdrawal in the VTA. Madhavan A, He L, Stuber GD, Bonci A, Whistler JL. Mu-opioid receptor endocytosis prevents adaptations in ventral tegmental area GABA transmission induced during naloxone-precipitated morphine withdrawal. J Neurosci. 2010 Mar 3; 30(9): 3276-3286.

The Quantal Size of Dopamine Release is Regulated by Glutamate in Dopamine Neurons that Co-Release Glutamate

Recent evidence strongly suggests that a subset of dopamine neurons in the ventral tegmental area (VTA) release not only dopamine but also release the excitatory neurotransmitter glutamate. To assess a physiological role for glutamate co-release, these researchers disrupted the expression of vesicular glutamate transporter 2 selectively in dopamine neurons. This conditional knockout abolishes glutamate release from midbrain dopamine neurons in culture and severely reduces their excitatory synaptic output in mesoaccumbens slices. Baseline motor behavior is not affected, but stimulation of locomotor activity by cocaine is impaired, along with a selective reduction of dopamine stores in the projection of VTA neurons to ventral striatum. Glutamate co-entry promotes dopamine storage by increasing the pH gradient that drives vesicular monoamine transport. Low concentrations of glutamate acidify synaptic vesicles more slowly, but to a greater extent, than equimolar Cl-, indicating a distinct, presynaptic mechanism to regulate dopamine quantal size Hnasko TS, Chuhma N, Zhang H, Goh GY, Sulzer D, Palmiter RD, Rayport S, Edwards RH. Vesicular glutamate transport promotes dopamine storage and glutamate corelease in vivo. Neuron 2010 Mar 11; 65(5): 643-656.

Cocaine-induced Regulation of Striatal Dopamine Transporter uptake is Different in Rats with High and Low Locomotor Responsivity to Cocaine

While cocaine use is a serious public health issue, only 10-15% of initial users develop addiction to the drug. Previously, Dr. Zahniser had identified SD rats that responded with increased (HCR, high cocaine responders) or decreases (LCR, low cocaine responders) and sought to identify the neurochemical bases of their individual differences. She found that 30 min after a single injection of cocaine, the uptake of DA into striatal synaptosomes of HCRs was greater than that of LCRs. She extended the observation time in this study and found that HCRs exhibited a marked initial locomotor activation that returned to baseline by 120 min post-injection. While LCRs exhibited a >50% lower maximal locomotor response, this increase was sustained, lasting approximately 33% longer than in HCRs. At 25 min post-cocaine, maximal velocity (of [(3)H]DA uptake was significantly higher by 25% in HCRs than LCRs, with no difference in affinity. Despite the difference in the rate of uptake, however, DAT surface expression did not differ between LCRs and HCRs. These findings suggest that, compared to LCRs, HCRs have an enhanced ability to rapidly up-regulate DAT function in response to acute cocaine, which may be related to their cocaine-induced locomotor activation. Mandt BH, Zahniser NR. Low and high cocaine locomotor responding male Sprague-Dawley rats differ in rapid cocaine-induced regulation of striatal dopamine transporter function. Neuropharmacology. 2010 Mar; 58(3): 605-612. Epub 2009 Dec 4.

Meta-analysis of 15 Genome-wide Linkage Scans of Smoking Behavior

A genetic contribution to smoking behavior is well-established. To identify loci that increase the risk for smoking behavior, many genome-wide linkage scans have been performed with various smoking behavior assessments. Numerous

putative susceptibility loci have been identified, but only a few of these were replicated in independent studies. Dr. Gelernter and colleagues used genome search meta-analysis (GSMA) to identify risk loci by pooling all available independent genome scan results on smoking behavior. Additionally, to minimize locus heterogeneity, subgroup analyses of the smoking behavior assessed by the Fagerstrom Test for Nicotine Dependence (FTND) and maximum number of cigarettes smoked in a 24-hour period (MaxCigs24) were carried out. Samples of European ancestry were also analyzed separately. A total number of 15 genome scan results were available for analysis, including 3404 families with 10,253 subjects. Overall, the primary GSMA across all smoking behavior identified a genome-wide suggestive linkage in chromosome 17q24.3-q25.3 (p(SR) = .001). A secondary analysis of FTND in European-ancestry samples (625 families with 1878 subjects) detected a genome-wide suggestive linkage in 5q33.1-5q35.2 (p(SR) = .0076). Subgroup analysis of MaxCigs24 (966 families with 3273 subjects) identified a genome-wide significant linkage in 20q13.12-q13.32 (p(SR) = .00041, p(OR) = .048), where a strongly supported nicotine dependence candidate gene, CHRNA4, is located. The regions identified in the current study deserve close attention and will be helpful for candidate gene identification or target re-sequencing studies in the future. Han S, Gelernter L, Luo X, Yang BZ. Biol Psychiatry. Meta-analysis of 15 genome-wide linkage scans of smoking behavior. 2010 Jan 1; 67(1):12-19.

Histone Dimethylation is Essential for Cocaine-induced Neuronal and Behavioral Plasticity

Cocaine can induce behavioral changes by altering expression of neuronal genes through mechanisms that have been somewhat unclear. One possible mechanism is to modify histone proteins associated with DNA to form chromatin, the structural scaffold for chromosome. By modifying and thereby altering the structural conformation of histones, protein factors that turn off or on a gene can gain access or be prevented from gaining acesss to the DNA sequence encoding a gene. Dr. Nestler, Dr. Greengard, and colleagues observed that histone methylation levels are reduced in the nucleus accumbens (NAc) of rodents. To further explore this phenomenon, Dr. Nestler investigated the gene expression levels of the histone dimethyltransferases and demethylases that regulate this chromatin modification and found that levels of the G9a and GLP histone dimethyltransferases are downregulated upon cocaine administration. Dr. Nestler then looked at the effect of G9a manipulation in the NAc on the behavioral effects of cocaine. He found that overexpression of G9a decreased the rewarding properties of cocaine, while knockdown of G9a increased the rewarding properties of cocaine. Dr. Nestler showed that these behavioral changes were correlated with concomitant changes in G9a levels and global histone dimethylation. Looking upstream of G9a, Dr. Nestler presented evidence that repeated cocaine exposure increases the levels of the transcription factor deltafosB leading to decreased G9a levels. Looking downstream, Dr. Nestler showed that many of the genomic targets of histone dimethylation are involved in regulation of dendritic plasticity and further that dendritic spine density is altered by G9a levels. Overall Dr. Nestler and colleagues have elucidated an elegant multistep molecular pathway leading from repeated cocaine exposure to deltafosB activation, downregulation of G9a, and reduction in global histone demethylation levels. Histone demethylation is normally associated with gene silencing, so decreased histone methylation leads to increased expression of genes that regulate dendritic plasticity. This change in gene expression leads to increased dendritic spine density and ultimately increased behavioral preference for cocaine. Small molecules that target the activities of histone demethylases or histone dimethyltransferases could have potential efficacy as therapeutic agents for treating cocaine addiction. Maze I, Covington HE 3rd, Dietz DM, LaPlant Q, Renthal W, Russo SJ, Mechanic M, Mouzon E, Neve RL, Haggarty SJ, Ren Y, Sampath SC, Hurd YL, Greengard P, Tarakhovsky A, Schaefer A, Nestler EJ. Essential role of the

histone methyltransferase G9a in cocaine-induced plasticity. Science. 2010; 327(5962): 213-216.

Functional Impact of a Single-nucleotide Polymorphism in the OPRD1 Promoter Region

The delta-opioid receptor mediates rewarding effects of many substances of abuse. Dr. Zhang and colleagues reported an increased frequency of the minor G-allele of single-nucleotide polymorphism (SNP) rs569356 (the only variant identified so far in the promoter region of the delta-opioid receptor gene (OPRD1)) in subjects with opioid dependence. In this study, Dr. Zhang and colleagues examined the functional significance of this variant. OPRD1 promoter region harboring SNP rs569356 was amplified by PCR and inserted into a firefly luciferase reporter vector. HEK293 cells were co-transfected with these constructs and a renilla luciferase vector to control for transfection efficiency. Expression of firefly luciferase (driven by the OPRD1 promoter) was measured by a dual luciferase reporter assay and normalized by renilla luciferase expression. Moreover, alleles altering expression were further assessed for binding of human brain nuclear proteins by electrophoretic mobility shift assay (EMSA). The minor G-allele was associated with significantly greater expression levels of firefly luciferase than the major A-allele of SNP rs569356 (P=0.003). EMSA also showed specific gel shift bands, suggesting that SNP rs569356 is situated in the binding site of potential transcription factors. These results suggest that the minor G-allele of SNP rs569356 may enhance transcription factor binding and increase OPRD1 expression. Zhang H, Gelernter J, Gruen JR, Kranzler HR, Herman AI, Simen AA. Functional impact of a single-nucleotide polymorphism in the OPRD1 promoter region. J Hum Genet. 2010 Mar 19 [Epub ahead of print].

Genetic Variation in Nicotine Metabolism Predicts the Efficacy of Extended-duration Transdermal Nicotine Therapy

CYP2A6 is the primary metabolizer of nicotine to cotinine, and cotinine to 3'-hydroxycotinine. Genetic variants have been identified that cause reduced-activity and inactive variants of the CYP2A6 gene associated with slower nicotine clearance. A phenotypic assay that measures the plasma 3'-hydroxycotinin/cotinine nicotine metabolite ratio (NMR) levels in smokers is used as a biomarker to predict the efficacy of transdermal nicotine. In the study presented here, Dr. Lerman and her colleagues tested the hypothesis that the reduced metabolizer subgroup, defined by either CYP2A6 genotype or NMR, would be more likely to benefit from a 6-month therapy with transdermal nicotine than from the standard 8 week therapy, as compared with normal metabolizers of nicotine. The results show that smokers with reduced nicotine metabolism benefit more than normal metabolizers from extended (6-month) transdermal nicotine therapy as compared to standard therapy. The group-by-treatment interaction was significant only for the genotype and NMR measure for reduced metabolizers but not the normal metabolizers. The benefit, however, dissipates once treatment ends, suggesting that the benefits may be enhanced with longer treatment. These results suggest that determining the NMR or genotyping CYP2A6 can be used to tailor the type, dose, and length of smoking cessation treatment in clinical practice. Lerman C, Jepson C, Wileyto EP, Patterson F, Schnoll R, Mroziewicz M, Benowitz N, and Tyndale RF. Genetic variation in nicotine metabolism predicts the efficacy of extended-duration transdermal nicotine therapy. Clin Pharm Ther. 2010 Mar 24 [epub ahead of print].

Interaction of the Mu-opioid Receptor with GPR177 (Wntless) Inhibits Wnt Secretion: Potential Implications for Opioid Dependence

Opiate agonists such as morphine and heroin exert their actions by activating the mu opioid receptor. Chronic use of opiate agonists can lead to addiction and to tolerance. Chronic use is associated with morphological changes in neurons. Now, Dr. Jin and his colleagues have identified an orphan G coupled receptor called GPR177, the mammalian ortholog of Drosophila Wntless/Evi/Sprinter that associates with the mu opiate receptor that regulates the secretion of the wnt protein. Wnts play a significant role in pattern formation during development, regulate dendritic arborizaton, and regulate neurogenesis in hippocampus. Jin and his colleagues show that antibodies selective for the mu opioid receptor precipitate the mu opioid receptor/GPR177 complex from a rat pheochromocytoma cell line and from rat brain. Experiments using immunoelectron microscopy suggest that the mu opioid receptor and the GPR177 are co-localized in the same neurons in the striatum. Treatment of HEK293 cells that express both the mu opioid receptor and GPR177 with morphine leads to the formation GPR177-mu opioid receptor complex at the cell surface, resulting in suppression of wnt release. The suppression of wnt release could be overcome by either overexpressing GPR177 or by blocking the effects of morphine with either CTAP or naloxone, both opiate antagonists. Jin and his colleagues suggest that the suppression of the wnt could explain the loss of the dendritic tree seen with chronic morphine. Jin also suggests that morphine, which delays internalization of the mu opiate receptor suppresses the release of wnts by trapping the GPR177 receptor at the cell surface. GPR177 unable to internalize to the Golgi, required for wnt release, prevents secretion. These findings suggest a novel role for GPR177 in mediating opiate dependence. Jin J, Kittanakom S, Wong V, Reyes BA, Van Bockstaele EJ, Stagljar I, Berrettini W, Levenson R. BMC Neurosci. Interaction of the mu-opioid receptor with GPR177 (Wntless) inhibits Wnt secretion: potential implications for opioid dependence BMC Neurosci. 2010 Mar 9; 11: 33.

A Major QTL on Chromosome 11 Influences Psychostimulant and Opioid Sensitivity in Mice

C57Bl/6 mouse strain shows significantly greater locomotor response to methamphetamine and to the opiate agonist, fentanyl, than does the AJ strain of mouse. Bryant and his colleagues mapped this trait to chromosome 11 using a genetic strategy that substitutes chromosome 11 from the C57BL/6 strain of mouse with chromosome 11 from the AJ strain of mouse. To further map the genetic loci on chr 11 responsible for enhanced locomotor response to methamphetamine a B6 x (AJ chromosome 11 substitution) F2 intercross was conducted. In other words of B6 mice carrying 1 substituted AJ chromosome 11 were mated with B6 mice to produce the F1 generation. These mice have one AJ chromosome 11 and one B6 chromosome. Brother-sister matings of the B6 x AJ chromosome 11 substitution is then conducted. As a result of this mating there is random recombination between homologous chromosomes. By looking at which part of chromosome 11 is B6 or AJ across the different progeny, the trait can be better localized on the chromosome. The response to methamphetamine mapped to 40 to 60 centimorgans on chromosome 11. Examining how the genes in this region vary with a function in a given strain, a large number of genes are identified. Bryant and his colleagues suggest based on anatomical localization in the striatum that Cacna1g, which encodes the alpha 1 G subunit of the t-type calcium channel CaV3.1t, Cacng5, which encodes the voltage-dependent calcium channel subunit, syntaxin binding protein 4 (Stxbp4) and sorting nexin 11 (Snx11) are of greatest interest. All are involved in the secretion of neurotransmitter from neurons. In summary, this work suggests a common locus of action for both psychostimulants and opiates and will lead to a better understanding of individual differences in response to abused drugs. Bryant CD, Chang HP, Zhang J, Wiltshire T, Tarantino LM, Palmer AA. A major QTL on chromosome 11 influences psychostimulant and opioid sensitivity in mice. Genes Brain Behav. 2009 Nov;

8(8): 795-905.

Thrombospondin May Promote Synaptogenesis through Gabapentin Receptor in CNS

Neuronal synapses are modified cell adhesions with specialized presynaptic and postsynaptic membrane structures for neuronal transmission. The cellular and molecular events that initiate various synaptogenesis are not well defined. Dr. Ben Barres, a NIDA supported researcher at Stanford University, and his group previously reported that astrocyte-derived thrombospondin is responsible for the initiation of excitatory synapse formation in CNS. They now report that a neuronal membrane receptor with known pharmacological roles may also be the receptor for thrombospondin during brain development and repair. The identified neuronal thrombospondin receptor involved in CNS synapse formation is alpha2delta-1, the receptor for the anti-epileptic and analgesic drug gabapentin. They show that the VWF-A domain of alpha2delta-1 interacts with the epidermal growth factor-like repeats common to all thrombospondins. Alpha2delta-1 overexpression increases synaptogenesis in vitro and in vivo and is required postsynaptically for thrombospondin- and astrocyte-induced synapse formation in vitro. Gabapentin antagonizes thrombospondin binding to alpha2delta-1 and powerfully inhibits excitatory synapse formation in vitro and in vivo. These findings identify alpha2delta-1 as a receptor involved in excitatory synapse formation and suggest that gabapentin may function therapeutically by blocking new synapse formation. Eroglu C, Allen NJ, Susman MW, O'Rourke NA, Park CY, Ozkan E, Chakraborty C, Mulinyawe SB, Annis DS, Huberman AD, Green EM, Lawler J, Dolmetsch R, Garcia KC, Smith SJ, Luo ZD, Rosenthal A, Mosher DF, Barres BA. Gabapentin receptor alpha2delta-1 is a neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis. Cell. 2009; 139: 380-392.

Non-coding RNA Switches Oligodendrocyte Proliferation to Differentiation during CNS Myelination

During brain development the genetic mechanisms that switch undifferentiated precursor cells of neurons and glia to differentiating and functional mature cells are not clear. This is particularly important for neuronal axon myelination which is the function of oligodendrocytes. Oligodendrocytes proliferate along the growing axons. Upon the cessation of proliferation the differentiation and myelination is initiated. It is known that the location and myelination in the CNS is regulated mainly by controlling the progression of oligodendrocyte differentiation. A NIDA researcher, Dr. Ben Barres, and his group at the Stanford University report that non-coding RNAs are required for oligodendrocytes to switch from proliferation to differentiation during CNS development. MicroRNAs (miRNAs) are small, noncoding RNA molecules generated from longer hairpin-loop RNA sequences, which are trimmed to functional 19-21 mers by successive cleavages by the obligate miRNA processing enzymes Drosha and Dicer1, then incorporated into an RNA-induced silencing complex (RISC). When a RISC-loaded miRNA recognizes a complementary sequence, it either represses RNA translation or directly promotes the degradation of the associated mRNA. To investigate the role of microRNAs in regulating oligodendrocyte differentiation and myelination, Dr. Barres utilized transgenic mice in which microRNA processing was disrupted in oligodendrocyte precursor cells by targeted deletion of Dicer1. They found that inhibition of miRNA processing disrupts normal CNS myelination and that oligodendrocyte precursor cells lacking mature miRNAs fail to differentiate normally in vitro. They further identified three miRNAs (miR-219, miR-138, and miR-338) that are induced 10-100x during oligodendrocyte differentiation; the most strongly induced of these, miR-219, is necessary and sufficient to promote the differentiation, and partially rescues differentiation defects caused by total miRNA loss. They found miR-219 directly represses the expression of

PDGFRalpha, Sox6, FoxJ3, and ZFP238 proteins, all of which normally help to promote OPC proliferation. Together, these findings show that miR-219 plays a critical role in coupling differentiation to proliferation arrest in the oligodendrocyte lineage, enabling the rapid transition from proliferation to myelination. Dugas JC, Cuellar TL, Scholze A, Ason B, Ibrahim A, Emery B, Zamanian JL, Foo LC, McManus MT, Barres BA. Dicer1 and miR-219 are required for normal oligodendrocyte differentiation and myelination. Neuron. 2010; 65: 597-611.

MicroRNA Shrinks Fat Spines

The fine regulation of the number, morphology and protein composition of dendritic spines by neuronal activity constitutes a structural basis for synaptic plasticity during learning and memory. The microRNA pathway has been implicated in the regulation of synaptic protein synthesis and ultimately in dendritic spine morphogenesis, although, the particular microRNAs (miRNAs) involved are largely unknown. Siegel and colleagues demonstrate, by performing a functional screen, that a small non-coding RNA, microRNA-138, decreases the size of dendritic spines through local downregulation of acyl protein thioesterase 1 (APT1). They used microarrays to identify miRNAs that are enriched in the immediate proximity of synapses, isolating RNA from synaptosomes as a source of synaptic miRNA and comparing miRNA levels in this fraction with those in total brain extracts. They identified several miRNAs consistently enriched in the synaptic compartment. After confirming the neuronal expression and dendritic localization of candidate miRNAs, the authors set out to investigate the role of these miRNAs in regulating dendritic spine morphology, an indicator of synaptic plasticity. For this, the authors used antisense oligoribonucleotides that inhibit the action of target miRNAs. Expression of antisense oligoribonucleotides against two candidates resulted in an increase in dendritic spine volume. The physiological function of one of the two candidates, miRNA-138, is unknown in the nervous system. Using duplex RNA, the authors found that overexpression of miRNA-138 decreased spine volume without affecting other dendrite characteristics, such as spine density and dendrite branching. As expected when spine size is decreased, the authors were able to correlate the overexpression of miRNA-138 with a decrease in AMPA receptor cluster size and the miniature excitatory postsynaptic currents (mEPSCs) mediated by these receptors. The specific effect of miRNA-138 on dendritic spine size suggests a potential role in regulating synaptic plasticity rather than in regulating other characteristics of neuronal function. A key feature of this work was to identify relevant target(s) for miRNA-138. Using reporter constructs containing their 3'm untranslated region (3'UTR) after the luciferase coding region, the most striking effect of miRNA-138 overexpression was observed with the 3'UTR of the depalmitoylation enzyme APT1. Palmitoylation has only recently been implicated in the regulation of synaptic plasticity, and changes in spine structure have been linked to a dynamic balance between the addition of palmitate to, and removal from, synaptic proteins. Therefore, the authors hypothesized that APT1 may regulate spine morphology in response to neuronal activity. Other findings confirmed APT1 as a target of miRNA-138. This study by Siegel and colleagues is the first to show a direct link between miRNA and the dynamic regulation of post-translational modification of synaptic proteins leading to changes in spine morphology. Siegel G, Obernosterer G, Fiore R, Oehmen M, Bicker S, Christensen M, Khudayberdiev S, Leuschner PF, Busch CJ, Kane C, HŸbel K, Dekker F, Hedberg C, Rengarajan B, Drepper C, Waldmann H, Kauppinen S, Greenberg ME, Draguhn A, Rehmsmeier M, Martinez J, Schratt GM. A functional screen implicates microRNA-138-dependent regulation of the depalmitoylation enzyme APT1 in dendritic spine morphogenesis. Nat Cell Biol. 2009 Jun; 11(6): 705-716.

Timing of Birth and Differential Gene Regulation Determines

Neuronal Fates during Limbic System Development

The striatum is the inhibitory center of the telencephalon that is vital for movement and impulse control. The amygdala is a key area modulating fear, aggression and emotionality. These two important limbic system components are formed by highly diversified types of inhibitory and excitatory neurons during brain development. How and where various types of neurons are derived and how their fates are determined have not been well understood. Joshua Corbin, a NIDA researcher at the Children's National Medical Center in Washington DC, reports that a specific lineage of neural progenitors marked by Emx1 differentially contribute to excitatory and inhibitory neurons in the striatum and amygdala. Using a combination of approaches, including genetic fate mapping, cell birth dating, cell migration assays, and electrophysiology, Corbin found that cells derived from the Emx1 lineage contribute to two distinct neuronal populations in the mature basal forebrain: inhibitory medium spiny neurons in the striatum and functionally distinct subclasses of excitatory neurons in the amygdala. Their cell birth-dating studies reveal that these two populations are born at different times during early neurogenesis, with the amygdala population born before the MSNs. In the striatum, Emx1-lineage neurons represent a unique subpopulation of MSNs: they are disproportionately localized to the dorsal striatum, are found in dopamine receiving, reelin-positive patches, and are born throughout striatal neurogenesis. In addition, Corbin's data suggest that a subpopulation of these Emx1-lineage cells originate in the pallium and subsequently migrate to the developing striatum and amygdala. An intersectional fate-mapping analysis further reveals that Emx1-lineage cells that coexpress Dlx exclusively generate MSNs but do not contribute to the excitatory neurons in the amygdala. Thus, both the timing of neurogenesis and differential combinatorial gene expression appear to be key determinants of striatal versus amygdala fate decisions of Emx1-lineage cells. Cocas LA, Miyoshi G, Carney RS, Sousa VH, Hirata T, Jones KR, Fishell G, Huntsman MM, Corbin JG. Emx1-lineage progenitors differentially contribute to neural diversity in the striatum and amygdala. Journal of Neuroscience. 2009; 29:15933-15946.

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Research Findings - Basic Behavioral Research

Stress System Mediation of the "Dark Side" of Compulsive Eating

Some types of obesity and eating disorders can be characterized as chronic relapsing disorders, similar to drug addiction. That is, periods of abstinence from "forbidden" highly palatable foods alternate with relapse to compulsive eating that continues despite negative consequences. Pietro Cottone and his colleagues investigated the role of negative reinforcement and the CRF system in this cycle, in a rat model. As opposed to positive reinforcement, negative reinforcement is the increased probability of a behavioral response produced by the removal of an aversive stimulus, e.g., the intake of palatable food to relieve a negative emotional state produced by abstinence. Rats were provided regular chow for 5 days, followed by a sugary diet for 2 days in a repeating cycle for 7 weeks (Chow/Palatable rats). Control rats had access to regular chow only. This regimen leads to undereating of chow and overeating of the preferred, highly palatable food. Rats then received a CRF1 receptor antagonist (R121919) in varying doses one hour before the switch from chow to palatable food or vice versa. The antagonist dose-dependently decreased palatable diet intake and increased chow intake in the Chow/Palatable rats, without affecting intake in chow controls. Thus, the CRF antagonist blunted the effect of diet cycling. The researchers then tested whether CRF1 receptors were involved in this negative emotional behavior that follows withdrawal from palatable food. After the 7-week feeding cycle, rats that are switched to chow show increased anxiety-like behavior, as measured by reduced time spent in the open arms of an elevated plus maze. However, treatment with the CRF1 antagonist normalized this behavior. In a final behavioral test, they found that the CRF1 antagonist reversed motivational deficits in responding for regular chow in a progressive ratio test exhibited by Chow/Palatable rats. Next, they measured CRF mRNA and peptide levels in the central nucleus of the amygdala. When Chow/Palatable rats were withdrawn from the palatable food, CRF mRNA expression increased five-fold and peptide levels were 70% higher. These measures were not significantly altered in other brain areas, including the hypothalamus, and they returned to baseline when rats regained access to the palatable food. Importantly, they did not observe changes in CRF after only one diet cycle, indicating that the CRF-CRF1 system is recruited progressively by diet history. These withdrawal-induced effects on CRF are similar to findings for drug and ethanol withdrawal. The authors propose that recruitment of anti-reward extrahypothalamic CRF-CRF1 systems during withdrawal from palatable food, analogous to abstinence from abused substances, promotes compulsive selection of palatable food, undereating of a more balanced diet, and a negative emotional state when intake of the palatable food is prevented. Cottone P, Sabino V, Roberto M, Bajo M, Pockros L, Frihauf JB, Fekete EM, Steardo L, Rice KC, Grigoriadis DE, Conti B, Koob GF, Zorrilla EP. CRF system recruitment mediates dark side of compulsive eating. Proc Natl Acad Sci USA.

2009 Nov 24; 106(47): 20016-20020.

Orexin A/Hypocretin-1 Selectively Promotes Motivation for High Salient Positive Rewards

A number of recent studies have indicated that the activation of orexin A/hypocretin-1 neurons in the hypothalamus, and activation of ox/hcrt-1 receptors in the VTA, are linked with drug reward and reinstatement to drug seeking behavior. The new report by Stephanie Borgland, Antonello Bonci, and colleagues shows that oxA/hcrt-1 signaling has a selective role in motivation for highly salient reinforcers. They trained different cohorts of rats to press a lever to obtain cocaine, regular food, or high-fat chocolate pellets and then tested them using a progress ratio procedure (PR) to assess the amount of effort the rats were willing to expend to obtain their respective reinforcers. Specifically, the PR procedure requires animals to press a lever an increasing number of times to obtain a reward and measures the "breakpoint" at which they are no longer willing to press. When ox/hcrt-1 receptor signaling was blocked, the breakpoints for the cocaine and high-fat pellet reinforcers decreased, while the breakpoint for regular food remained unchanged. To further test whether blocking this receptor affected motivation only for highly salient reinforcers, they placed high-fat pellets in one arm of a T maze and regular food in the other. Untreated rats were willing to climb over a significant inclined plane barrier to reach the high-fat pellets, but rats treated with an ox/hcrt-1 antagonist were more likely to take the easy path to the regular food. Next, they performed several electrophysiological studies on brain slices containing the VTA. Their previous studies had shown that oxA/hcrt-1 potentiates glutamate receptor responses in the VTA. In the new studies, they found that this oxA/hcrt-1-induced plasticity was significantly enhanced in rats with a history of cocaine or high-fat self-administration, but not in the rats trained with regular food. OxA/hcrt-1 mediated excitatory synaptic transmission was not, however, potentiated by arousing, aversive stimuli. This series of studies indicates that the oxA/hcrt-1 system may provide a unique opportunity to design novel therapies that selectively reduce excessive drive for highly salient positive reinforcers. Borgland SL, Chang SJ, Bowers MS, Thompson JL, Vittoz N, Floresco SB, Chou J, Chen BT, Bonci A. Orexin A/hypocretin-1 selectively promotes motivation for positive reinforcers. J Neurosci. 2009 Sep 9; 29(36): 11215-11225.

Sex Differences in the Effects of Allopregnanolone on Yohimbine-induced Reinstatement of Cocaine Seeking in Rats

Recent studies have shown that the gonadal hormones estrogen and progesterone play opposite roles in cocaine self-administration in rodent models. Dr. Marilyn Carroll and colleagues at the University of Minnesota, for example, found that whereas estrogen facilitated escalation of cocaine self-administration in ovariectomized female rats, progesterone prevented escalation (Larson et al., 2007). They also found that in females progesterone has an inhibitory effect on reinstatement of cocaine-primed responding, a commonly used model of relapse (Anker et al, 2007), whereas estrogen has previously been shown to play a facilitatory role. They subsequently showed that progesterone's suppression of cocaine-primed reinstatement was mediated by its metabolite allopregnanolone (ALLO), and that suppression by ALLO occurred only in females (Anker et al., 2009). More recently, they examined the effects of ALLO on stress-induced reinstatement of responding. Stress was produced by administration of the pharmacologic stressor yohimbine. They found that yohimbine-priming injections produced more reinstatement responding in females than males. Further, as previously found with cocaine-primed reinstatement, ALLO blocked yohimbine-induced reinstatement only in females. Collectively, these studies point to the potential clinical use of compounds that target progesterone, ALLO, or related compounds in the

Planned Meetings

Publications

Staff Highlights

Grantee Honors

treatment of cocaine addiction. Higher doses may be required in males than in females. Anker JJ, Carroll ME. Sex differences in the effects of allopregnanolone on yohimbine-induced reinstatement of cocaine seeking in rats. Drug Alcohol Depend. 2010 Mar 1;107(2-3):264-7. Epub 2009 Dec 14.

The Medial Preoptic Area is Necessary for Motivated Choice of Pup- over Cocaine-associated Environments in Early Postpartum Rats

The motivation to seek cocaine during the postpartum period is significantly affected by the competing incentive of offspring, a stimulus unique to this life stage. The present study investigated the functional role of the medial preoptic area (mPOA), a critical site involved in maternal responsiveness, on processing incentive value of pup-associated cues, and directing response allocation for pup- over cocaine-associated environments. The study involved a concurrent pup/cocaine choice conditioned place preference (CPP) paradigm. Early postpartum females with bilateral guide cannulae near the mPOA or control sites were conditioned, from postpartum days (PPD) 4 to 7, to associate environments with pups or cocaine. CPP was tested on PPD8 following intra-mPOA infusions of either 2% bupivacaine to transiently inactivate the mPOA or saline vehicle. In separate experiments, the researchers examined effects of intra-mPOA infusions of bupivacaine on expression of conditioned responding induced by environments associated with either pups or cocaine. Bupivacaine infusion into the mPOA selectively blocked conditioned preferences for pup-associated environments, significantly contrasting the robust pup-CPP seen in non-surgical and intra-mPOA vehicle-treated females. Conversely, mPOA inactivation failed to alter cocaine-CPP in postpartum females. When given a choice between environments associated with pups or cocaine, transient functional inactivation of the mPOA altered choice behavior, biasing the preference of females toward cocaine-associated environments, such that almost all preferred cocaine- and none the pup-associated option. Anatomical specificity was revealed when inactivation of adjacent regions to the mPOA did not affect CPP responses for pups. These findings support a critical role for the mPOA in mediating pup-seeking behavior. They further suggest that competing properties of pups over alternative incentives, including drugs of abuse, rely on mPOA integrity to provide relevant pup-related information to the circuitry underlying the choice behavior between pups and alternative stimuli during the early postpartum period. Pereira M, Morrell JI. The medial preoptic area is necessary for motivated choice of pup- over cocaine-associated environments by early postpartum rats. Neurosci. 2010 Feb 12; [Epub ahead of print].

Stress-coping Profile of Opioid Dependent Individuals Entering Naltrexone Treatment: A Comparison with Healthy controls

Stress increases addiction vulnerability and risk of relapse to substance use. This study compared opioid dependent individuals entering naltrexone treatment with healthy controls on measures of stress, coping, and social support and examined the relative contribution of group membership, coping, and social support to stress within the sample. The results revealed that opioid dependent subjects reported greater stress, less use of adaptive coping, but comparable use of maladaptive/avoidant coping, as compared with their control counterparts. However, no differences were found between the two groups with respect to social support. Perceived stress was predicted by group membership, low social support, and greater use of maladaptive/avoidant coping, and the prediction by social support and maladaptive/avoidant coping did not differ by group. Findings suggest that novel treatment approaches that decrease maladaptive/avoidant coping and improve social support are important aspects of decreasing stress during early recovery from opioid addiction. Hyman SM, Hong KI, Chaplin TM, Dabre Z, Comegys AD, Simmerling A, Sinha R. A stress-coping profile of opioid dependent individuals entering

naltrexone treatment: A comparison with healthy controls. Psychol Addict Behav. 2009; 23: 613-619.

"Emotional numbing" Associated with Heavy Smoking Among Veterans

There is a strong association between posttraumatic stress disorder (PTSD) and cigarette smoking, as individuals suffering from PTSD are approximately twice as likely to smoke as the general population. Although some research has examined the association between PTSD and smoking, there has been little investigation into the particular aspects of PTSD that may be responsible for this association. Therefore, NIDA grantee Dr. Jessica Cook and colleagues investigated overall PTSD severity, as well as symptom clusters, for their relationship to smoking status and heaviness of smoking in Iraq and Afganistan combat veterans. Smoking status was measured and subjects were classified as non-smokers, light (1-9 cigarettes per day; cpd), moderate (10-19 cpd) or heavy smokers (³20 cpd). Most subjects were light or moderate smokers. The PTSD Checklist Military version was used to assess PTSD, and the Patient History Questionnaire was used to evaluate depression. Results indicate that the PTSD factors of reexperiencing, effortful avoidance, emotional numbing and hyperarousal were significantly positively correlated as symptom clusters (or "factors") of PTSD. The higher the PTSD symptom severity, the more likely that smoking was endorsed. Severity predicted heavy smoking, but not light or moderate smoking. Of the four PTSD factors, none were associated with light or moderate smoking and only emotional numbing was associated with heavy smoking. Like emotional numbing, depression also predicted heavy smoking. Because these two are also correlated with each other, both were included in a regression model. Neither depression nor emotional numbing predicted heavy smoking, suggesting that they may "cancel out" individual contributions toward heavy smoking. Therefore, the authors suggest that mechanisms maintaining smoking in both PTSD and depression are similar. One explanation for this association is that smoking elevates blunted positive emotions -- a symptom of both emotional numbing and depression. If this is the case, then perhaps early interventions aimed at treating PTSD (and/or depression) may decrease the likelihood of either initiating smoking, or escalating smoking. Cook J, Jakupcak M, Rosenheck R, Fontana A, McFall M. Influence of PTSD symptom clusters on smoking status among help-seeking Iraq and Afganistan veterans. Nic Tob Res. 2009; 10: 1189-1195.

Potential Pharmacotherapy for Methamphetamine Abuse and Attention Deficit Hyperactivity Disorder (ADHD) Differentially Affects Male and Female Periadolescent Rats

Lobeline is currently being tested in clinical trials for the treatment of methamphetamine abuse and ADHD. It is a nicotinic α4β2 receptor antagonist and is believed to disrupt vesicular monoamine transporters. Lobeline has been tested in animal models of substance use disorders and is neither rewarding nor reinforcing. However, it has not been tested in animal models of ADHD. It has also not been explicitly tested in comparisons between male and female animals. NIDA Grantee Steven Harrod and M. Lee Van Horn treated periadolescent male and female rats with one of five doses of lobeline (0, 1, 2, 5.6, or 10 mg/kg) for seven consecutive days, followed by a saline challenge, and examined drug effects on locomotor activity. Periadolescent rats were chosen in order to avoid the activational effects of gonadal hormones and locomotor activity was chosen because it has been previously shown to be sensitive to lobeline. As was seen in previous studies using adult rats, lobeline acutely reduced locomotor activity counts and distance traveled in a dose-dependent manner, with tolerance occurring over the seven lobeline sessions. Females developed tolerance more slowly than males at 5.6 mg/kg dose of lobeline. The saline challenge, administered one day after the seventh lobeline

treatment, produced hyperactivity that was positively correlated with previous doses of lobeline. That is, the larger the dose of previous lobeline treatment, the greater the locomotor activity seen following the saline challenge. This suggests that cessation of chronic lobeline may have behavior consequences. In conclusion, the current results suggest that female patients taking lobeline may experience greater motor-depressant effects, although more animal behavior research, particularly with adult animals, is needed. Harrod SB, Van Horn ML. Sex differences in tolerance to the locomotor depressant effects of lobeline in periadolescent rats. Pharm Biochem Behav. 2009; 94: 296-304.

Alcohol Changes Men's, but not Women's, Smoking Behavior

Both epidemiological and laboratory studies have shown a strong positive relationship between alcohol drinking and cigarette smoking, and there is growing evidence of sex differences in these interactions. NIDA grantee, Dr. Andrea King, and colleagues further examined this interaction by exploring the role of nicotine. In this laboratory study, heavy social drinkers participated in a two-session, double-blind study that included a 15-min drinking period followed by 3 hours of post-drink assessment (measuring subjective effects and smoking behavior). The within-subjects factor was nicotinized versus denicotinized cigarettes (smoked through a topography device), and a between-subjects factor was alcohol (equivalent to 4-5 standard alcoholic drinks) versus placebo beverage. For both males and females, alcohol increased "urge to smoke", which was significantly correlated with subsequent smoking behavior, regardless of whether smoking nicotinized or denicotinized cigarettes. Sex differences emerged when looking at beverage type. In men, alcohol significantly increased smoking choice and three smoking topography measures (puff count, puff volume, puff duration). In women, there were no differences in whether they smoked, or in smoking topography, when comparing alcohol and placebo beverages. Alcohol selectively increased men's, but not women's, smoking behavior. The failure to find a preference for either nicotinized or denicotinized cigarettes was surprising and the authors postulate that non-nicotinic sensory factors significantly contributed to this finding. These findings suggest that the interactions among alcohol, cigarettes, and sex differences may be more complex than previously thought. King A, McNamara P, Conrad M, Cao D. Alcohol-induced increases in smoking behavior for nicotinized and denicotinized cigarettes in men and women. Psychopharmacol. 2009; 207:107-117.

Plasticity of Composite Stimulus Control of Motivated Behavior

Stimuli in the environment that are paired with positive reinforcers, such as food or drug, are capable of eliciting drug seeking behavior and act as triggers for continued drug taking and relapse. These cues also act as signals for reward availability and thus provide information that food or drug is available. Via the same associative processes, it is possible to learn that a discriminative cue (DS) signals reward unavailability. Thus, in a human drug abuse situation, stimuli in the home environment may provide discriminative cues that nicotine reward is available, whereas stimuli in the workplace signal that drug reward is unavailable. Research using animal models of operant behavior (performing responses to receive reward) have demonstrated that discriminative stimuli signaling reward availability (DS+) increase responding, whereas signals for extinction (no reward, DS-) reduce responding. Dr. Stanley Weiss of American University has demonstrated the ability of environmental stimuli to control responding for reward can be predicted by the sum of DS+ and DS- influences. Whereas animal models of drug abuse and relapse typically study the single discrete stimulus cues, this research on Ôcomposite stimuli' (bundled collections of reward-referenced cues) controlling behavior offers a more ecologically valid model of human addiction, where multiple environmental stimuli most likely influence complex behavior. It is also likely that composite

stimuli controlling behavior include not only the presence of particular cues, but also the absence of other cues in the environment. Thus, the absence of a cue may also provide a signal that reward is available (DS+) or that reward is unavailable (DS-). The composite-stimulus control model accounts for combinations of these stimulus signals by conceptualizing cues in a Ôbinary' manner - cues are either present (an "on state") or absent ("off state") and an organism can learn that either state signals reward (DS+) or extinction (DS-). Previously, Dr. Weiss demonstrated that DS- cues act as conditioned inhibitors, capable of reducing ongoing reinforced behavior when added to a composite set of cues. This suggests that the use of conditioned inhibitors may be a useful therapeutic approach in addiction treatment. However, as continued drug-taking in addiction is believed to be an automatic behavior, generated from circuits controlling habit learning, these over-trained responses may not be malleable. In a recent study, Dr. Weiss trained rats until they were under stimulus control by a composite that elicited responding for food reward, and a composite that signaled extinction - reducing responding to almost zero. Then, he retrained groups of rats with this history of different DS+ and DS- stimulus combinations (including the presence and absence of discrete cues), switching the stimuli in the composites that signaled extinction. He found that rats were able to learn a new stimulus combinations that signaled extinction, and the new composite became capable of reducing responding to very low rates as well. (For example, rats learning that absence of light + absence of tone signaled extinction, were switched to presence of light + presence of tone signaled extinction). This demonstration of reversibility in stimulus control of over-trained reward reinforced behavioral patterns suggests that stimulus-response associations contributing to drug taking may be malleable. Additional research with drug rewards should extend these findings. Weiss, SJ, Kearns, DN, Antoshina, M. Within-subject reversibility of discriminative function in the composite-stimulus control of behavior. J Exp Anal Behav. 2009; 92: 367-377.

N-methyl-D-aspartate (NMDA) Glycine-site Antagonists Produce Distinct Subjective Effects When Compared to Other NMDA Antagonists

N-methyl-D-aspartate antagonists have a variety of potential clinical uses, including the treatment of pain, depression and stroke. However, they also produce side effects that limit their clinical usefulness. NMDA glycine-site antagonists may be less likely to produce these effects than other NMDA antagonists. NIDA-grantee Dr. Robert Balster (Virginia Commonwealth University) and colleagues compared the discriminative stimulus effects of NMDA glycine-site drugs to those of channel blocking and competitive NMDA antagonists. Rats were trained in a drug discrimination paradigm with saline versus the NMDA channel blocker PCP (2 mg/kg i.p.) or the NMDA competitive antagonist NPC17742 (4 mg/kg i.p.) using a standard two-lever operant conditioning procedure under a FR32 (fixed ratio 32) operant schedule. Neither of the partial glycine-site agonists nor antagonists tested produced greater than 50% PCP-lever selection, although high doses that produced motor deficits were tested. Similarly, the partial agonists and antagonists tested did not consistently substitute for the NMDA competitive antagonist, NPC17742. Overall, these data suggest that NMDA glycine-site antagonists may be less likely to produce the undesirable psychotropic side effects seen in clinical trials with many other NMDA antagonists. Nicholson KL, Balster RL. The discriminative stimulus effects of N-methyl-D-aspartate glycine-site ligands in NMDA antagonist-trained rats. Psychopharmacol. 2009; 203:441-451.

Individual Differences in the Incentive Value of Cocaine-associated Cues

Stimuli associated with drugs can motivate drug-seeking and drug-taking behavior and over repeated pairing with drug, come to elicit approach

behavior. In this study, the investigators asked whether individual differences in attention to cocaine-associated cues was correlated with the ability of these stimuli to motivate drug-related behavior. First, they trained rats in a Pavlovian procedure where a lighted lever was presented for 8 seconds and then a food pellet was delivered into a food hopper some distance from the lever. All of the rats learned lever signaled food arrival. However, when the lever appeared, some rats approached and engaged with the lever, moving to the food hopper only when the food came, whereas other rats went to the food hopper as soon as the lever appeared. Rats who exhibit the first pattern of behavior are called "sign trackers" (ST) and the others are called "goal trackers' (GT). They then compared rats with the strongest ST behavior and rats with the strongest GT behavior, on measures of drug self-administration. For the first experiment, they trained the rats to self-administer cocaine using two nose-poke ports. When a rat poked the active port, it received an infusion of cocaine and a light in the port was turned on. After initial training, they conducted a cue removal test for 2 days, in which everything was the same, except that the light was not turned on. Removal of the cue decreased self-administration in the STs, but not the GTs. Responding was restored to baseline with 4 more days of training (with the light present) and then the rats underwent 28 days of extinction training in which no cocaine was delivered, but the light was still turned on after a nose poke. The ST rats were more resistant to extinction: they continued to respond for the light alone much more than the GT rats. A second experiment with a new group of animals examined reinstatement behavior after 7 days of extinction training with no cocaine and no cue, and 30 days of abstinence with no testing. In this experiment also, ST rats responded more robustly than GT rats when the cue was again presented. These results indicate that for the ST animals that attributed the most incentive salience to a food cue, a cocaine cue spurred motivation to take drugs (they responded less when the cue was removed), and were more vulnerable to cue-induced reinstatement. For the GT animals, the cocaine cue had relatively less ability to motivate behavior. The study also suggests that it is possible to determine, using the sign-tracking vs. goal-tracking measure, which individuals will have the most difficulty resisting drug cues even before they have been exposed to drugs. This finding opens up many possibilities for neurobiological and other studies of drug-addiction vulnerability without the confound of drug exposure. Saunders BT, Robinson TE. A cocaine cue acts as an incentive stimulus in some but not others: implications for addiction. Biol Psychiat. 2009 Dec 31. [Epub ahead of print].

Dopaminergic Mechanisms Involved in Amphetamine-induced Impairment of Social Bonding

This study used the prairie vole to investigate drug-induced impairment of social bonding. The prairie vole is a socially monogamous rodent that forms pair bonds after mating. In the first experiment, Zuoxin Wang and his colleagues found that conditioned place preference (CPP) for an amphetamine-associated environment was mediated by D1-like DA receptors and that antagonism of D2-like DA receptors had no effect. Next, they showed that repeated AMPH exposure impaired the formation of mating-induced partner preferences in male voles. Partner preference after mating is a measure of social bonding. Importantly, the animals were tested a day after the final AMPH treatment, so that no drug was present during the behavioral test, and these drug-exposed animals were not impaired in mating behavior itself. Using in situ immunocytochemistry, they found that AMPH exposure increased the number of D1 receptors (D1Rs), but not D2Rs in the nucleus accumbens (NAcc). They had previously shown that, in male prairie voles, activation of D1Rs within the NAcc prevented formation of partner preferences, whereas activation of D2Rs in NAcc promotes this behavior. They tested therefore, the effect of blocking D1Rs in the NAcc during the AMPH exposure sessions and found that this D1R blockade did eliminate the impairment of partner preference formation. The

finding indicates that distinct dopaminergic mechanisms in NAcc regulate AMPH- and partner-motivated behaviors. Their working model is that, under normal circumstances, a relatively low amount of DA is released in the NAcc during mating, which preferentially stimulates high-affinity D2Rs and promotes pair bonding. However, AMPH exposure releases a large amount of DA, which stimulates the lower affinity D1Rs and increases their number. After this treatment, DA released during mating is sufficient to stimulate D1Rs and block pair bonding. These studies, along with other research on drug impairment of maternal behavior and social play, are beginning to provide an understanding of the interactions between social behavior and drug use. Liu Y, Aragona BJ, Young KA, Dietz DM, Kabbaj M, Mazei-Robison M, Nestler EJ, Wang Z. Nucleus accumbens dopamine mediates amphetamine-induced impairment of social bonding in a monogamous rodent species. Proc Natl Acad Sci USA. 2009 Dec 29. [Epub ahead of print].

Environmental Enrichment Prevents Relapse in a Rat Model

Animal models have been used to study environmental stimulation effects on initiation, maintenance and relapse to drug-taking. Environmental stimulation is studied in experiments that rear some animals in "enriched" conditions (EC), consisting of social, physical and sensory stimulation, while control rats are raised in single-cage isolation. Previous studies have demonstrated that enriched conditions protect against the acquisition of i.v. drug self-administration; or, conversely, that isolation conditions (the typical laboratory housing condition) predispose animals to acquire this behavior. EC, imposed after conditioning, blocks the expression of cocaine-associated place preference and cue-elicited sucrose-seeking behavior. As drug-seeking can be triggered by exposure to drug paired cues, or by reintroducing the drug after drug-taking has extinguished, Dr. Janet Neisewander sought to determine if EC might also attenuate the ability of these experiences to produce relapse in the reinstatement paradigm. Using reinstatement, drug-seeking behavior (pressing a lever which previously delivered i.v. drug infusions) is measured in an attempt to mimic human relapse. In this study, rats were exposed to EC or isolation during a forced abstinence period, after previously acquiring steady i.v. self-administration of cocaine. EC conditions grouped five rats per cage, for 21 days, in a large plastic tub with running wheels and novel "toys". Extinction and reinstatement testing revealed that EC and isolated rats took equal amounts of drug prior to abstinence, but drug seeking was significantly reduced in the EC group during both extinction and cue-induced reinstatement. However, when given a 10 mg/kg i.p. priming injection of cocaine, both groups exhibited similar reinstatement of lever pressing behavior. A second experiment examined cocaine-seeking during an extinction phase in groups that were housed in isolation, in EC, or in pairs during abstinence. This study demonstrated that isolate rats had significantly higher rates of drug-seeking when returned to the drug-taking environment, compared to both pair-housed and EC groups. Thus, the ability of EC conditions to reduce drug-seeking in this model of relapse can be attributed to the EC complex of influences (e.g., not only social, but also sensory and motor). These findings are important in that they extend previous studies of EC in drug abuse to models of relapse and suggest that enrichment may be a part of the treatment strategy for relapse prevention. Thiel KJ, Sanabria F, Pentkowski NS, Neisewander JL. Anti-craving effects of environmental enrichment. Int J Neuropsychopharmacol. 2009; 12: 1151-1156.

Anxiolytic Effects of Nicotine Demonstrated with an Approach-avoidance Conflict Procedure

Smoking is generally believed to be driven by positive reinforcing or pleasurable subjective effects of nicotine. However, many reasons are cited for smoking, including relief from negative states such as stress. Thus, nicotine

may also have anxiolytic effects that contribute to its continued use. Dr. Aaron Ettenberg developed an animal behavioral assay for separating a drug's positive subjective effects from those which are aversive. Using a runway procedure, he has demonstrated that cocaine induces both positive and aversive subjective effects. He has also used this paradigm to investigate drug interactions that may explain the concurrent use of different substances by human abusers. Lastly, by separating positive and aversive effects, the paradigm lends itself to study of treatment mechanisms of action (i.e., whether an addiction treatment attenuates hedonic impact, or perhaps increases unpleasant drug effects). In a recent study he investigated nicotine's putative anxiolytic properties by testing the drug's effect on retreat responses (indicating escape or avoidance of an unpleasant state) by measuring nicotine effects on approach-avoidance conflict in rats running down the alley to receive food reward that was paired with mild electric shock. During training, food-deprived animals learned to leave a start box and run down an alley to a goal box, where food was delivered. On day 11 of training, mild shock was delivered in the goal box, following the food, and animals continued to be tested every day until demonstrating at least three retreats per day. In the third phase of the study, rats were tested with a random order of five nicotine doses, administered i.v. by the experimenter, 10-min before runway testing. Separate groups of animals were tested to assess locomotor effects of representative nicotine doses and to collect a different measure of nicotine effects on anxiety using an open-field test. Results revealed anti-conflict effects (significant reductions in mean retreat frequencies) with the two highest doses tested: 0.06 and 0.075 mg/kg. While the nicotine doses tested did not elevate general locomotor activity, testing with 0.06mg/kg also showed that this dose significantly reduced entries into the center of an open field test box, providing additional evidence of nicotine's anxiolytic effects. Cohen A, Young RW, Velazquez MA, Groysman M, Noorbehesht K, Ben-Shahar OM, Ettenberg A. Anxiolytic effects of nicotine in a rodent test of approach-avoidance conflict. Psychopharmacol. 2009; 204: 541-549.

Extended Access to D-amphetamine Increases Impulsive Choice Behavior

Impulsivity has been associated with human drug abuse, but it is not known if highly impulsive individuals are more likely to become addicted, or if drugs of abuse increase impulsivity. Animal behavior studies of impulsivity are useful for studying the direct effects of drugs of abuse on this behavioral characteristic. While a number of different behavioral tests have been used to measure impulsive behavior, measures of impulsive choice, or the preference for immediate over delayed rewards, may best mimic the impulsivity seen on delay discounting tasks conducted with drug abusers. Studies in rat models have yielded inconsistent effects with oral psychostimulant administration, on delay discounting functions. However, as these earlier studies failed to employ a drug exposure regimen that mimics human patterns of compulsive drug abuse, Dr. Michael Bardo recently compared animals treated with extended access to d-amphetamine (amp), for 6 h/day, versus those that continue to self-administer i.v. drug for only 1 h/day. Before being allowed to self-administer amp, animals were first trained on a delay discounting (DD) task. Under this procedure animals could choose between responding on a lever that delivered one sucrose pellet immediately after a lever press or responding on another lever that rrsulted in the delivery of three sucrose pellets following a delay. The animals were given many choices for immediate and delayed pellets in a single session. Over the session, the delay to receiving the three food pellets varied depending on how frequently the animal chose this option. That is, if animals chose the three pellet option more over the course of the session, the delay for the three pellet choice increased. If they chose the three pellets less often, the delay decreased. This procedure resulted in a derived dependent variable "mean adjusted delay" or MAD score, was computed based on the proportion of

delayed 3-pellet to choices to immediate 1-pellet choices. The Higher MAD score the less "impulsive" the animal is considered to be. After this phase of the experiment, i.v. catheters were implanted and rats were trained for i.v. self administration of (0.03 or 0.10 mg/kg infusion) amp for 1 h/day, while continuing DD trials each day prior to self administration. In the next phase, animals were split into two groups that either were allowed to self administer amp for 1 h/day and or 6 h/day extended access to amp. After 21 days, seven days of extinction with no drug were imposed, and DD testing was again conducted. Results show that prior to 6 h availability, animals had similar MAD scores to those assigned to the 1h/day self-administration group. However following access to amp, animals that self-administered amp for 6 h/day had significantly lower MAD scores (became more impulsive) over 21 days of self-administration and also had significantly lower MAD scores during the first three withdrawal sessions. When examining the pattern of drug intake over 21 days of access, the experimenter noted a typical escalation pattern in this 6h/day group- increasing drug intake over days - for the 0.03 dose only. Interestingly, both doses lowered the MMAD score in the DD procedure when drug was available for extended access periods over 21 days, whether or not a pattern of compulsive drug intake developed. Gipson CD, Bardo MT. Extended access to amphetamine self-administration increases impulsive choice in a delay discounting task in rats. Psychopharmacol. 2009; 207: 391-400.

Stress and Cue-induced Relapse Induce Additive Effects in Animal Reinstatement

Drug abusers relapse under conditions of stress and also may relapse when exposed to cues previously associated with drug use. Investigators have examined the neuroanatomical substrate for these relapse effects in animal studies, and identified unique but overlapping neural substrates for these two effects. As it is likely that human addicts are exposed to both stress and drug-related cues, simultaneously, in the natural environment, Dr. Ronald See sought to determine if exposures to both these factors would induce synergistic or additive effects. In his study, rats were trained to self administer i.v. cocaine to a criterion of 10 sessions with at least 10 drug infusions per session. Then they underwent extinction, during which time drug was not delivered for lever presses. Extinction sessions were followed by seven reinstatement tests, where rats were given either 15 min of intermittent foot shock followed by lever availability, or lever availability alone (without prior shock). On half of the sessions, pressing the active lever resulted in presentation of cues previously paired with i.v. cocaine infusion (cue only versus shock + cue conditions). Results revealed that all rats reached the self-administration criterion and decreased responding during extinction when drug and cues were not available. The ability of shock to enhance cue-induced relapse was evident by comparing the mean number of active lever responses during extinction, cue presentation alone, footshock alone, and the cue+shock condition: Cue presentation resulted in more than double the mean number of lever responses than seen during extinction; footshock also significantly increased responding over the mean seen during extinction. However, when shock at the two highest levels (0.5 and 0.75 mA) was delivered prior to cue presentation, mean active lever presses were approximately double that seen in response to cue alone. In conclusion, the findings reveal the ability of stress, in a dose-dependent manner, to enhance cue-induced relapse. Future studies will examine the neurobiological substrates that are involved in this additive effect. Buffalari DM, See RE. Footshock stress potentiates cue-induced cocaine-seeking in an animal model of relapse. Physiol Behav. 2009; 98:614-617.

Cannabinoid CB1 Receptors May Modulate Stress-induced Overeating

Exogenous and endogenous cannabinoid agonists increase food intake in

humans and animals, and these effects are mediated through CB1 receptors. Conversely, CB1 antagonists, such as rimonabant, lower the motivation for food and may be useful for the treatment of obesity. Two hypotheses have been proposed to account for anorexigenic properties attributed to CB1 activation: Modification of the hedonic effects of food, or modification of the incentive motivation for food. As overeating may be related to stress, NIDA researchers recently investigated the effects of THC (a CB1 agonist) on stress-induced disruptions of operant responding for food in a mouse model. Food deprived mice were trained to respond for three kinds of food: Standard laboratory pellets, chocolate flavored pellets and high-fat pellets. Then footshock was introduced to reduce the rate of responding for food on the active lever, and animals increased their rate of response on the non-contingent lever. Rats responding for three different types of pellets were pretreated with either the CB1 agonist THC or an appropriate vehicle. The effects of associating footshock with food delivery resulted in similar rates of responses on the reinforced and the non-reinforced levers. At the end of training for food, mice responding for the chocolate pellets made significantly more responses than animals in the other two groups. Comparisons between THC treated and vehicle treated groups revealed that THC had no effect on operant responding for normal or high-fat pellets associated with the delivery of foot-shock. However, in mice responding to receive highly palatable chocolate flavored pellets + footshock, THC significantly improved the discrimination between active and inactive levers; thus, THC treatment returned response rates to the pattern seen before footshock was introduced. With THC treatment, mice responding for chocolate pellets made very few responses on the inactive lever. This effect may be due to the ability of CB1 activation to increase the incentive value of food, or to attenuate the stress induced by footshock. Pending further studies to separate these alternate explanations, CB1 receptors may be therapeutic targets for reducing stress-induced overeating. Barbano MF, Castane A, Martin-Garcia E, Maldonado R. Delta-9-tetrahydrocannabinol enhances food reinforcement in a mouse operant conflict test. Psychopharmacol. 2009; 205:475-487.

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Research Findings - Brain and Behavioral Development Research

Prenatal Exposure to Methamphetamine and Brain Volume: Differentiating Alcohol Effects

Dr. Elizabeth Sowell and her colleagues at UCLA investigated the effects of prenatal exposure to methamphetamine (MA) on local brain volume using magnetic resonance imaging. Because many women who use MA during pregnancy also use alcohol, a known teratogen, the team examined whether local brain volumes differed among 61 children (ages 5-15 years), 21 with prenatal MA exposure, 18 with concomitant prenatal alcohol exposure (the MAA group), 13 with heavy prenatal alcohol but not MA exposure (ALC group), and 27 unexposed controls. Volume reductions were observed in both exposure groups relative to controls in striatal and thalamic regions bilaterally and in right prefrontal and left occipitoparietal cortices. Striatal volume reductions were more severe in the MAA group than in the ALC group, and, within the MAA group, a negative correlation between full-scale intelligence quotient (FSIQ) scores and caudate volume was observed. Limbic structures, including the anterior and posterior cingulate, the inferior frontal gyrus (IFG), and ventral and lateral temporal lobes bilaterally, were increased in volume in both exposure groups. Cingulate and right IFG volume increases were more pronounced in the MAA than ALC group. Discriminant function analyses using local volume measurements and FSIQ were used to predict group membership, yielding factor scores that correctly classified 72% of participants in jackknife analyses. These findings suggest that striatal and limbic structures, known to be sites of neurotoxicity in adult MA abusers, may be more vulnerable to prenatal MA exposure than alcohol exposure and that more severe striatal damage is associated with more severe cognitive deficit. Sowell ES, Leow AD, Bookheimer SY, Smith LM, O'Connor MJ, Kan E, Rosso C, Houston S, Dinov ID, Thompson PM. Differentiating prenatal exposure to methamphetamine and alcohol versus alcohol and not methamphetamine using tensor-based brain morphometry and discriminant analysis. J Neurosci. 2010 Mar 17; 30(11): 3876-3885.

Prenatal Methadone Exposure and Neonatal Neurobehavioral Functioning

Opioid-exposed infants display a wide and variable range of dysregulated neurobehavioral functioning, but the regulatory difficulties experienced by these infants outside the defined clusters of neonatal abstinence syndrome (NAS) have not been well described and may have implications for the infant's developmental course. This study by Dr. Lauren Jansson and her colleagues at Johns Hopkins University describes the neurobehavioral functioning of neonates prenatally exposed to methadone, using the NICU Network Neurobehavioral

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Scale (NNNS), and explores the relationships between maternal factors and infant functioning. The relationship between NNNS measures, NAS severity, and need for pharmacotherapy for NAS was also evaluated. Infants who required pharmacologic treatment for NAS showed more dysregulated behavior and signs of stress and abstinence as indicated by NNNS scores, but NNNS scores were not significantly correlated with maternal methadone dose. The determination of the range of the methadone-exposed infant's neurobehavioral repertoire could guide the optimal treatment of all such infants, particularly those requiring only nonpharmacologic care. Velez ML, Jansson LM, Schroeder J, Williams E. Prenatal methadone exposure and neonatal neurobehavioral functioning. Pediatr Res. 2009 Dec; 66(6): 704-709.

Effects of Prenatal Cocaine Exposure on School-aged Children

Studies through 6 years have shown no long-term direct effects of prenatal cocaine exposure (PCE) on children's physical growth, developmental test scores, or language outcomes. Little is known about the effects of PCE among school-aged children aged 6 years and older. Dr. Maureen Black and her colleagues reviewed articles from studies that examined the effects of PCE on growth, cognitive ability, academic functioning, and brain structure and function among school-aged children. Articles were obtained by searching PubMed, Medline, TOXNET, and PsycInfo databases from January 1980 to December 2008 with the terms "prenatal cocaine exposure," "cocaine," "drug exposure," "substance exposure," "maternal drug use," "polysubstance," "children," "adolescent," "in utero," "pregnancy," "development," and "behavior." Criteria for inclusion were (1) empirical research on children aged 6 years and older prenatally exposed to cocaine, (2) peer-reviewed English-language journal, (3) comparison group, (4) longitudinal follow-up or historical prospective design, (5) masked assessment, (6) exclusion of subjects with serious medical disabilities, and (7) studies that reported nonredundant findings for samples used in multiple investigations. Thirty-two unique studies met the criteria. Each article was independently abstracted by 2 authors to obtain sample composition, methods of PCE assessment, study design, comparison groups, dependent variables, covariates, and results. Associations between PCE and growth, cognitive ability, academic achievement, and language functioning were small and attenuated by environmental variables. PCE had significant negative associations with sustained attention and behavioral self-regulation, even with covariate control. Although emerging evidence suggests PCE-related alterations in brain structure and function, interpretation is limited by methodologic inconsistencies. Consistent with findings among preschool-aged children, environmental variables play a key role in moderating and explaining the effects of PCE on school-aged children's functioning. After controlling for these effects, PCE-related impairments are reliably reported in sustained attention and behavioral self-regulation among school-aged children. Ackerman JP, Riggins T, Black MM. A review of the effects of prenatal cocaine exposure among school-aged children. Pediatrics. 2010 Mar; 125(3): 554-565.

Structured Parenting of Toddlers at High versus Low Genetic Risk: Two Pathways to Child Problems

Little is known about how parenting might offset genetic risk to prevent the onset of child problems during toddlerhood. Dr. Jenae Neiderhiser and her colleagues used a prospective adoption design to separate genetic and environmental influences and test whether associations between structured parenting and toddler behavior problems were conditioned by genetic risk for psychopathology. The sample included 290 linked sets of adoptive families and birth mothers and 95 linked birth fathers. Genetic risk was assessed via birth mother and birth father psychopathology (anxiety, depression, antisociality, and drug use). Structured parenting was assessed via microsocial coding of

adoptive mothers' behavior during a cleanup task. Toddler behavior problems were assessed with the Child Behavior Checklist. Controlling for temperamental risk at 9 months, there was an interaction between birth mother psychopathology and adoptive mothers' parenting on toddler behavior problems at 18 months. The interaction indicated two pathways to child problems: Structured parenting was beneficial for toddlers at high genetic risk but was related to behavior problems for toddlers at low genetic risk. This crossover interaction pattern was replicated with birth father psychopathology as the index of genetic risk. The effects of structured parenting on toddler behavior problems varied as a function of genetic risk. Children at genetic risk might benefit from parenting interventions during toddlerhood that enhance structured parenting. Such interventions may impact adolescent vulnerability to substance abuse. Leve LD, Harold GT, Ge X, Neiderhiser JM, Shaw D, Scaramella LV, Reiss D. Structured parenting of toddlers at high versus low genetic risk: Two pathways to child problems. J Am Acad Child Adolesc Psychiatry. 2009 Nov; 48(11): 1102-1109.

Cocaine Addiction in Mothers: Potential Effects on Maternal Care and Infant Development

Maternal cocaine addiction is a significant public health issue particularly affecting children, with high rates of reported abuse, neglect, and foster care placement. This paper by Dr. Linda Mayes and her colleague Dr. Lane Strathearn reviews both preclinical and clinical evidence for how cocaine abuse may affect maternal care and infant development, exploring brain, behavioral, and neuroendocrine mechanisms. There is evidence that cocaine affects infant development both directly, via in utero exposure, and indirectly via alterations in maternal care. Two neural systems known to play an important role in both maternal care and cocaine addiction are the oxytocin and dopamine systems, mediating social and reward-related behaviors and stress reactivity. These same neural mechanisms may also be involved in the infant's development of vulnerability to addiction. Understanding the neuroendocrine pathways involved in maternal behavior and addiction may help facilitate earlier, more effective interventions to help substance-abusing mothers provide adequate care for their infant and perhaps prevent the intergenerational transmission of risk. Strathearn L, Mayes LC. Cocaine addiction in mothers: Potential effects on maternal care and infant development. Ann N Y Acad Sci. 2010 Feb; 1187: 172-183.

Marijuana Use and Adherence to Doctor's Appointments among HIV-infected Female Youth

This project conducted in the Adolescent Trials Network for HIV/AIDS Interventions (ATN) identified factors associated with medical appointment-keeping among HIV-infected adolescents and young adults in five U.S. cities. Youth were followed for 18 months to examine adherence to scheduled clinic visits with their HIV care provider. Psychosocial and behavioral factors shown in other populations to influence appointment adherence (mood disorder, depressive symptoms, social network support, healthcare satisfaction, disease acceptance, HIV stigma, alcohol use, and marijuana use) were measured at baseline and follow-up visits using an audio computer-assisted self-interview questionnaire. CD4 count and prescription of antiretroviral therapy medication were also monitored to understand the influence of health status on appointment- keeping. Participants included 178 youth with a mean age of 20.6 years. Forty-two percent had clinically significant depressive symptoms, 10% had a diagnosable mood disorder, 37% reported marijuana use in the last 90 days, and 47% reported alcohol use. Overall, participants attended 67.3% of their scheduled visits. Controlling for age and health status, marijuana use was the only variable that was associated with appointment-keeping behavior. Considering the importance of appointment-keeping for maintaining personal

health and preventing further transmission, screening HIV-infected adolescents for marijuana use could help alert providers of this specific barrier to visit compliance. Dietz E, Clum GA, Chung SE, Leonard L, Murphy DA, Perez LV, Harper GW, Ellen JM. Adherence to scheduled appointments among HIV-infected female youth in five U.S. cities. J Adolesc Health. 2010 Mar; 46(3): 278-283.

Recruiting and Retaining Mobile Young Injection Drug Users in a Longitudinal Study

Longitudinal studies that research homeless persons or transient drug users face particular challenges in retaining subjects. This paper reports on research methods that resulted in successful recruitment and retention of young ketamine injection drug users (IDUs), a population not previously tracked longitudinally. Between 2005 and 2006, 101 mobile young ketamine IDUs were recruited in Los Angeles into a 2-year longitudinal study. Several features of ethnographic methodology, including fieldwork and qualitative interviews, and modifications to the original design, such as toll-free calls routed directly to ethnographer cell phones and wiring incentive payments, resulted in retention of 78% of subjects for the first follow-up interview. Longitudinal studies that are flexible and based upon qualitative methodologies are more likely to retain mobile subjects while also uncovering emergent research findings. Lankenau SE, Sander B, Hathazi D, Bloom JJ. Recruiting and retaining mobile young injection drug users in a longitudinal study. Subst Use Misuse. 2010 Apr; 45(5): 684-699. Co-occurring Anxiety and Externalizing Disorders in Offspring of Mothers with Substance Abuse and/or Psychiatric Disorders This study used data from a study of 340 mothers with substance use and/or psychiatric disorders and their children to examine characteristics of children with co-occurring diagnoses of anxiety and externalizing disorders and compare them with children with a sole diagnosis or no diagnosis. Comparisons were made using 4 child-diagnostic groups: anxiety-only, externalizing-only, co-occurrence, and no-problem groups. Most mothers were characterized by low income and histories of substance use and/or affective/anxiety and/or antisocial personality disorder diagnoses during the child's lifetime. Analyses using multinomial logistic regressions found the incidence of co-occurring childhood disorders to be significantly linked with maternal affective/anxiety disorders during the child's lifetime. In exploring implications for developmental competence, the study found the co-occurrence group to have the lowest level of adaptive functioning among the 4 groups, faring significantly worse than the no-problem group on both academic achievement and intelligence as assessed by standardized tests. Findings underscore the importance of considering co-occurring behavior problems as a distinct phenomenon when examining children's developmental outcomes. Yoo JP, Brown PJ, Luthar SS. Children with co-occurring anxiety and externalizing disorders: Family risks and implications for competence. Am J Orthopsychiatry. 2009 Oct; 79(4): 532-540.

Neural Mechanisms of the Influence of Popularity on Adolescent Ratings of Music

It is well-known that social influences affect consumption decisions. Dr. Berns and his colleagues at Emory University School of Medicine used functional magnetic resonance imaging (fMRI) to elucidate the neural mechanisms associated with social influence with regard to music. The study population consisted of adolescents, age 12-17. Music is a common purchase in this age group, and it is widely believed that adolescent behavior is influenced by perceptions of popularity in their reference group. Using 15-s clips of songs from MySpace.com, behavioral measures of preferences and neurobiological responses to the songs were obtained. The data were gathered with, and without, the overall popularity of the song revealed. Song popularity had a significant effect on the participants' likability ratings of the songs. Imaging

results showed a strong correlation between the participants' rating and activity in the caudate nucleus, a region previously implicated in reward-driven actions. The tendency to change one's evaluation of a song was positively correlated with activation in the anterior insula and anterior cingulate, two regions that are associated with physiological arousal and negative affective states. Sensitivity to popularity was linked to lower activation levels in the middle temporal gyrus, suggesting a lower depth of musical semantic processing. The results suggest that a principal mechanism whereby popularity ratings affect consumer choice is through the anxiety generated by the mismatch between one's own preferences and others'. This mismatch anxiety motivates people to switch their choices in the direction of the consensus. The data suggest that this is a major force behind the conformity observed in music tastes in some teenagers. Berns G, Capra C, Moore S, Noussair C. Neural mechanisms of the influence of popularity on adolescent ratings of music. NeuroImage 2010 49:2687-2696.

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Research Findings - Clinical Neuroscience Research

Mesolimbic Dopamine Reward System Hypersensitivity in Individuals with Psychopathic Traits

Zald and colleagues at Vanderbilt University used a combination of PET ligand imaging and BOLD fMRI to determine whether brain responses to reward are modulated by impulsive-antisocial psychopathic traits that are linked to criminal behavior and substance abuse. Using [(18)F]fallypride PET and BOLD fMRI, they found that impulsive-antisocial psychopathic traits selectively predicted nucleus accumbens dopamine release and reward anticipation-related neural activity in response to pharmacological and monetary reinforcers, respectively. These findings suggest that neurochemical and neurophysiological hyper-reactivity of the dopaminergic reward system may comprise a neural substrate for impulsive-antisocial behavior and substance abuse in psychopathy. Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Benning SD, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Shelby ES, Smith CE, Cole D, Kessler RM, Zald DH. Mesolimbic dopamine reward system hypersensitivity in individuals with psychopathic traits. Nature Neurosci 2010 April; 13(4): 419-421.

Brain Reactivity to Smoking Cues Prior to Smoking Cessation Predicts Ability to Maintain Tobacco Abstinence

Janes and colleagues from McLean Hospital sought to identify nicotine-dependent women at high risk for relapse to aid in prevention therapy. After baseline fMRI, using smoking-related and neutral images, and an Emotional Stroop (ES) test, using smoking-related words, smokers then made an attempt to quit. Subjects who "slipped" (smoked one or more cigarettes after abstinence) had heightened fMRI reactivity to smoking-related images in brain regions implicated in emotion, introspective awareness, and motor planning and execution. Insula and dorsal anterior cingulate cortex (dACC) reactivity induced by smoking images correlated with an attentional bias to smoking-related words. Additionally, smokers who slipped had decreased fMRI functional connectivity between an insula-containing network and brain regions involved in cognitive control, including the dACC and dorsal lateral prefrontal cortex, possibly reflecting reduced top-down control of cue-induced emotions. These findings suggest that the insula and dACC are important substrates of smoking relapse vulnerability. The data also suggest that relapse-vulnerable smokers can be identified before quit attempts with implications for tailoring interventions to the needs of these individuals. Janes AC, Pizzagalli DA, Richard S, Frederick BD, Chuzi S, Pachas G, Culhane MA, Holmes AJ, Fava M, Evins AE, Kaufman MJ. Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. Biol Psychiatry. 2010 February. [Epub ahead of print].

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Toward Discovery Science of Human Brain Function

Kelly of New York University School of Medicine and colleagues from 35 international centers gathered resting-state functional MRI (R-fMRI) data from 1,414 subjects. R-fMRI constitutes a candidate approach to develop common paradigms for interrogating the myriad functional systems in the brain without the constraints of a priori hypotheses. Comprehensive mapping of the "functional connectome," and its subsequent utility for genetics and brain-behavior relationships, will require such multicenter collaborative datasets. A universal architecture of positive and negative functional connections, as well as consistent loci of inter-individual variability, was demonstrated. Age and sex emerged as significant determinants. These results demonstrate that independent R-fMRI datasets can be aggregated and shared. High-throughput R-fMRI can provide quantitative phenotypes for molecular genetic studies and biomarkers of developmental and pathological processes in the brain. To initiate discovery science of brain function, the 1000 Functional Connectomes Project dataset is freely accessible at www.nitrc.org/projects/fcon_1000/. Biswal BB, Mennes M, Zuo XN, Gohel S, Kelly C, Smith SM, Beckmann CF, Adelstein JS, Buckner RL, Colcombe S, Dogonowski AM, Ernst M, Fair D, Hampson M, Hoptman MJ, Hyde JS, Kiviniemi VJ, Kšter R, Li SJ, Lin CP, Lowe MJ, Mackay C, Madden DJ, Madsen KH, Margulies DS, Mayberg HS, McMahon K, Monk CS, Mostofsky SH, Nagel BJ, Pekar JJ, Peltier SJ, Petersen SE, Riedl V, Rombouts SA, Rypma B, Schlaggar BL, Schmidt S, Seidler RD, Siegle GJ, Sorg C, Teng GJ, Veijola J, Villringer A, Walter M, Wang L, Weng XC, Whitfield-Gabrieli S, Williamson P, Windischberger C, Zang YF, Zhang HY, Castellanos FX, Milham MP. Toward discovery science of human brain function. PNAS USA. 2010 Mar 9; 107(10): 4734-4739.

Modafinil Normalizes Sleep in Abstaining Chronic Cocaine Users

Morgan and Malison at Yale and colleagues at Harvard assessed sleep quality after morning doses of modafinil in chronic cocaine users. The subjects were assessed over a three week period of (in-patient) abstinence. Normalization of slow-wave sleep time, total sleep time, and sleep latency improved over the period. These results suggest that modafinil may be relevant in the treatment of cocaine dependence. Morgan PT, Pace-Schott E, Pittman B, Stickgold R, Malison RT. Normalizing effects of modafinil on sleep in chronic cocaine users. Am J Psychiat. 2010; 167(3): 331-340.

Amphetamine Increased Ratings of Stimulation in Individuals with One Gene Variant of the Dopamine Transporter

Hamidovic, de Wit and colleagues at the University of Chicago assessed ratings of d-amphetamine in healthy volunteers divided according to specific gene variants of the dopamine transporter, SLC6A3. Four SNPs were chosen for comparison but only individuals with the C/C allele compared to the A/A/+A/C allele of the rs460000 SNP reported approximately two-fold higher ratings of stimulation and euphoria at both 10 and 20 mg of d-amphetamine administration. This SNP is in linkage disequilibrium with another SNP that is associated with ADHD. These results suggest that this polymorphic locus may have a pleiotropic effect for both ADHD and amphetamine sensitivity. Hamidovic A, Dlugos A, Palmer AA, de Wit H. Polymorphisms in dopamine transporter (SLC6A3) are associated with stimulant effects of d-amphetamine: an exploratory pharmacogenetic study using healthy volunteers. Behav Genet. 2010; 40(2): 255-261.

Sleep Deprivation Differentially Affects Methadone Maintenance Patients Compared to Healthy Controls

Lukas and colleagues at McLean Hospital studied methadone-maintained (MM) participants during recovery from 40 hours of sleep deprivation. The study was motivated by the observation of sleep disturbances in individuals using chronic opiates. Both sleep architecture and brain metabolic activity was assessedÑthe former with polysomnography (PSG), the latter with magnetic resonance spectroscopy (MRS). Results indicated that increases in total sleep time and sleep efficiency commonly associated with recovery sleep were not apparent in the methadone-maintained individuals. These differences were especially apparent for MM individuals who have been in therapy less than a year compared to those whose treatment was much longer. PSG also showed that MM participants had greater power in the delta, theta, and alpha spectral bands. Finally, MRS revealed greater elevations of beta-NTPÑa direct measure of adenosine tri-phosphate following recovery sleep. These results of differences of both sleep architecture and brain chemistry during recovery sleep in MM participants suggest a disruption in homeostatic sleep function. Trksak GH, Jensen JE, Plante DT, Penetar DM, Tartarini WL, Maywalt MA, Brendel M, Dorsey CM, Renshaw PF, Lukas SE. Effects of sleep deprivation on sleep homeostasis and restoration during methadone-maintenance: A [31]P MRS brain imaging study. Drug Alcohol Depend. 2010; 106(2-3): 79-91.

Long Term Neurocognitive and Affective Improvement among Methamphetamine Users Exhibiting Stable Abstinence

Dr. Igor Grant and colleagues found that the neuropsychological disorder and affective distress in methamphetamine-dependent participants continued to recover in those who were able to maintain abstinence at the one-year follow-up. A significantly and disproportionately greater improvement in processing speed and slightly greater improvement in motor abilities were evident in comparison to those who continued to use methamphetamine. Functional recovery to a level comparable to healthy subjects was observed in some long-term abstainers. These results suggest recovery of neuropsychological functioning and improvement in affective distress upon sustained abstinence from methamphetamine may extend beyond a year or more. Iudicello JE, Woods SP, Vigil O, Cobb SJ, Cherner M, Heaton RK, Hampton AJ, Grant I. Longer term improvement in neurocognitive functioning and affective distress among methamphetamine users who achieve stable abstinence. J Clin Exp Neuropsychol. 2010 March. [Epub ahead of print].

Early Detection of Compromised Neurocognitive Dysfunction in Patients Living with HIV

Grant and colleagues reported evidence of a significant interaction between HIV serostatus and performance on mental rotationÑa task widely used to detect the ability to manipulate three-dimensional objects in space that demand neurally complex coordination of spatial cognition. HIV+ individuals committed a greater number of errors than demographically similar seronegative persons on Luria's hand rotation task, but not on the corresponding parallelogram rotation task. Hand rotation errors were associated with worse performance on measures of executive function and working memory, but not with measures of visuoperception. Considered in the context of the preferential frontostriatal neuropathology of HIV-associated neurocognitive disorders, these preliminary findings suggest that the observed deficit in the mental rotation of hands may arise from a disrupted fronto-striato-parietal network. The tasks can be very useful tools for the early detection of compromised neurocognitive capacity in medically stable and clinically asymptomatic HIV+ patients. Weber E, Woods SP, Cameron MV, Gibson SA, Grant I; HIV Neurobehavioral Research Center Group. Mental rotation of hands in HIV infection: Neuropsychological evidence of dysfunction in fronto-striato-parietal networks. J Neuropsychiatry Clin Neurosci. 2010; 22(1): 115-122.

Dissociation of Procedural Learning with Deficit in HIV+ Individuals during Iowa Gambling Decision-making

Martin and colleagues found HIV+ individuals performed poorly in the Iowa Gambling Task (IGT), a complex measure of "decision-making." However, IGT performance was not associated with three measures of procedure learning: The Rotary Pursuit, Mirror Star Tracing, and Weather Prediction tasks. Although other nondeclarative processes (e.g., somatic markers) were found important for IGT performance, it was concluded that differences in the procedural learning performance do not account for the decision-making deficits or variability in the observed performances among HIV+ individuals with a history of substance dependence. Gonzalez R, Wardle M, Jacobus J, Vassileva J, Martin-Thormeyer EM. Influence of procedural learning on Iowa Gambling Task performance among HIV+ individuals with history of substance dependence. Arch Clin Neuropsychol. 2010; 25(1): 28-38.

Relation of Dopamine Type 2/3 Receptor Availability in the Striatum to Social Status in Humans

Martinez and colleagues at Columbia University used PET ligand imaging in humans to extend previous findings in monkeys that striatal dopamine type 2/3 (D-2/3) receptors correlate with social hierarchy and that dominant animals exhibit higher levels of D-2/3 receptor binding. Social status, assessed by the Barratt Simplified Measure of Social Status, was positively correlated with dopamine D-2/3 receptors as was the perceived level of social support, assessed by the Multidimensional Scale of Perceived Social Support; higher [C-11]raclopride binding potential correlated with higher scores. The results of this study support the hypothesis that social status and social support are correlated with D-2/3 receptor binding. Martinez D, Orlowska D, Narendran R, Slifstein M, Liu F, Kumar D, Broft A, Van Heertum R, Kleber HD. Dopamine type 2/3 receptor availability in the striatum and social status in human volunteers. Biol Psychiatry 2010; 67(3): 275-278.

Financial and Psychological Risk Attitudes Associated with Two Single Nucleotide Polymorphisms in the Nicotine Receptor (CHRNA4) Gene

Beversdorf and colleagues at Ohio State University conducted an exploratory study of the genetic basis of risk-taking using constructs from both psychology and economics. Analysis of the genotyping data identified two single nucleotide polymorphisms (SNPs) in the gene encoding the alpha 4 nicotine receptor (CHRNA4, rs4603829 and rs4522666) that were significantly associated with harm avoidance. Novelty seeking was associated with several COMT (catechol-O-methyl transferase) SNPs. Economic risk attitude measures were marginally associated with several VMAT2 (vesicular monoamine transporter) SNPs. These exploratory results provide a starting point for understanding the genetic basis of risk attitudes by considering the range of methods available for measuring risk attitudes and by searching beyond the traditional direct focus on dopamine and serotonin receptor and transporter genes. Roe BE, Tilley MR, Gu HH, Beversdorf DQ, Sadee W, Haab TC, Papp AC. Financial and psychological risk attitudes associated with two single nucleotide polymorphisms in the nicotine receptor (CHRNA4) gene. PLoS ONE 2009; 4(8): e6704.

Gene Polymorphisms in Enzymes that Degrade Endogenous Cannabinoids Influence Acute Response to Amphetamine

DeWit and colleagues at University of Chicago examined whether amphetamine's effects in humans are known to be modulated by genetic

differences in the degradation of endogenous cannabinoids. Two single nucleotide polymorphisms (SNPs) in the gene for the enzyme fatty acid amide hydrolase (FAAH) were significantly associated with increased ratings of arousal and fatigue, assessed by the Profile of Mood States, after administration of a10-mg dose of d-amphetamine. Fatigue levels were also found to be associated with two haplotypes, CCC and TAT. These data suggest that the endocannabinoid system influences variation in subjective response to amphetamine. These data suggest a role of endogenous cannabinoids in response to amphetamine which help to understand the genetic determinants of inter-individual differences in stimulant effects. Dlugos AM, Hamidovic A, Hodgkinson CA, Goldman D, Palmer AA, de Wit H. More aroused, less fatigued: fatty acid amide hydrolase gene polymorphisms influence acute response to amphetamine. Neuropsychopharmacology 2010; 35(3): 613-622.

Functional Imaging of Moral Deliberation and Moral Intuition

Kiehl and colleagues at the MIND Institute at the University of New Mexico used BOLD fMRI to determine whether the same brain systems process different types of moral decisions. Prior studies of moral processing have utilized "explicit" moral tasks that involve moral deliberation (e.g., reading statements such as "he shot the victim" and rating the moral appropriateness of the behavior) or "implicit" moral tasks that involve moral intuition (e.g., reading similar statements and memorizing them for a test but not rating their moral appropriateness). Half of the participants performed the explicit task; half performed the implicit task. Participants performing the explicit, but not the implicit task showed increased ventromedial prefrontal activity while viewing moral pictures. Both groups showed increased temporo-parietal junction activity while viewing moral pictures. These results suggest that the ventromedial prefrontal cortex may contribute more to moral deliberation than moral intuition, whereas the temporo-parietal junction may contribute more to moral intuition than moral deliberation. Harenski CL, Antonenko O, Shane MS, Kiehl KA. A functional imaging investigation of moral deliberation and moral intuition. NeuroImage 2010; 49(3): 2707-2716.

Reversal of Error Effects in Anterior Cingulate Cortex with High Error Likelihood

Brown and colleagues at Indiana University used BOLD fMRI to test competing hypotheses about the neural basis of error-related activity in the anterior cingulate cortex and adjacent medial prefrontal cortex (mPFC). Most studies to date use tasks that generate relatively low error rates, confounding the expectedness and the desirability of an error. The present study found that when losses are more frequent than wins, the mPFC error effect disappears, and moreover, exhibits the opposite pattern by responding more strongly to unexpected wins than losses. These findings provide perspective on recent electrophysiological evoked potential studies and suggest that mPFC error effects result from a comparison between actual and expected outcomes. Jessup RK, Busemeyer JR, Brown JW. Error effects in anterior cingulate cortex reverse when error likelihood is high. Journal of Neuroscience 2010; 30(9): 3467-3472.

The Effect of Motivation on Cingulate and Ventral Striatum Activity Related to Executive Function and Error Detection

Garavan and colleagues used BOLD fMRI to determine how motivation modulates brain activity related to error detection in a GO/NOGO task where a financial punishment was introduced for errors. The dorsal anterior cingulate cortex (ACC) had equal trial-specific activity for errors in the neutral and punishment conditions but had greater tonic activity throughout the

punishment condition where there were slower responses and fewer commission errors. A region of interest analysis revealed different activation patterns between the dorsal and the rostral parts of the ACC with the rostral ACC having only trial-specific activity for errors in the punishment condition, an activity profile similar to one observed in the nucleus accumbens. This study suggests that there is a motivational influence on cognitive processes in the ACC and nucleus accumbens and hints at a dissociation between tonic proactive activity and phasic reactive error-related activity. Sim›es-Franklin C, Hester R, Shpaner M, Foxe JJ, Garavan H. Executive function and error detection: The effect of motivation on cingulate and ventral striatum activity. Human Brain Mapping 2010; 31(3): 458-469.

Learned Reward and Error Outcome Predictions Compete in the Anterior Cingulate Cortex

Brown and colleagues at Indiana University used fMRI to test a specific hypothesis of anterior cingulate cortex (ACC) function. The fMRI results ruled out a modulatory effect of expected reward on error likelihood effects in favor of a competition effect between expected reward and error likelihood. Dynamic causal modeling showed that error likelihood and expected reward signals are intrinsic to the ACC rather than received from elsewhere. These findings agree with interpretations of ACC activity as signaling both perceptions of risk and predicted reward. Alexander WH, Brown JW. Competition between learned reward and error outcome predictions in anterior cingulate cortex. Neuroimage 2010 February; 49(4): 3210-3218.

Available Alternative Incentives Modulate Anticipatory Nucleus Accumbens Activation

Knutson and colleagues at Stanford used event-related fMRI to investigate how neural representations of an anticipated incentive might be influenced in the context of other available alternatives of a monetary incentive delay task with uncertain or certain gains and losses. The availability of certain gains and losses increased NAcc activation for uncertain losses and decreased the difference between uncertain gains and losses. The results suggest that this pattern of activation can result from reference point changes across blocks, and that the worst available loss may serve as an important anchor for NAcc activation. These findings imply that NAcc activation represents anticipated incentive value relative to the current context of available alternative gains and losses. Cooper JC, Hollon NG, Wimmer GE, Knutson B. Available alternative incentives modulate anticipatory nucleus accumbens activation. Social Cognitive and Affective Neuroscience 2009; 4(4): 409-416.

Primary and Secondary Rewards Differentially Modulate Neural Activity Dynamics during Working Memory

Braver and colleagues at Washington University used fMRI to examine whether brain activity to a reinforcer is different if a secondary (monetary) or primary (liquid) reward was used as an outcome during a working memory task. Performance was dramatically and equivalently enhanced in each incentive condition, where the monetary reward condition was associated with a tonic activation increase in primarily right-lateralized cognitive control regions including anterior prefrontal cortex (PFC), dorsolateral PFC, and parietal cortex. In the liquid reward condition, the identical regions instead showed a shift in transient activation from a reactive control pattern (primary probe-based activation) during no-incentive trials to proactive control (primary cue-based activation) during rewarded trials. Additionally, liquid-specific tonic activation increases were found in subcortical regions (amygdala, dorsal striatum, nucleus accumbens), indicating an anatomical double dissociation in the locus of

sustained activation. These different activation patterns suggest that primary and secondary rewards may produce similar behavioral changes through distinct neural mechanisms of reinforcement. Beck SM, Locke HS, Savine AC, Jimura K, Braver TS. Primary and secondary rewards differentially modulate neural activity dynamics during working memory. PLoS ONE 2010; 5(2): e9251.

The Amygdala is Distinctly Responsive to Novel Unusual Stimuli

Zald and colleagues at Vanderbilt University used fMRI to determine whether the amygdala and hippocampus are differentially activated by two types of novelty: Stimuli that are ordinary, but novel in the current context, and stimuli that are unusual. When presented with the novel common stimuli, the BOLD signal increased significantly in both the amygdala and hippocampus. However, for the novel unusual stimuli, only the amygdala showed an increased response compared to the novel common stimuli. These findings suggest that the amygdala is distinctly responsive to novel unusual stimuli, making a unique contribution to the novelty detection circuit. Blackford JU, Buckholtz JW, Avery SN, Zald DH. A unique role for the human amygdala in novelty detection. NeuroImage 2010; 50(3): 1188-1193.

Sex-Related Differences in Amygdala Activity Influences Immediate Memory

Krystal and colleagues at Yale used fMRI to determine whether amygdala responses to emotional pictures would predict performance on an immediate recognition memory test. They found that increased right amygdala activation during unpleasant picture viewing was related to lower false-positive rates (i.e., commission errors) for men and higher false-positive rates for women. Their results indicate that increased amygdala activation while viewing unpleasant pictures may preferentially facilitate immediate recognition memory in men relative to women. Aikins DE, Anticevic A, Kiehl KA, Krystal JH. Sex-related differences in amygdala activity influences immediate memory. NeuroReport 2010; 21(4): 273-276.

Brain Activation during Memory of Emotionally Salient Events Depends on Individual Perspective

LaBar and colleagues at Duke capitalized on the high personal fan investment and rivalry of a Duke-UNC basketball game to examine the neural correlates of emotional memory retrieval of similar events from different perspectives. Male fans watched a video of a past game in a social setting. During a subsequent functional magnetic resonance imaging session, participants viewed video clips depicting individual plays of the game that ended with the ball being released toward the basket. For each play, participants recalled whether or not the shot went into the basket. BOLD fMRI signals time-locked to correct memory decisions were analyzed as a function of emotional intensity and valence, according to the fan's perspective. Intensity-modulated retrieval activity was observed in midline cortical structures, sensorimotor cortex, the striatum, and the medial temporal lobe, including the amygdala. Positively valent memories specifically recruited processing in dorsal frontoparietal regions, and additional activity in the insula and medial temporal lobe for positively valent shots recalled with high confidence. This novel paradigm reveals how brain regions implicated in emotion, memory retrieval, visuomotor imagery, and social cognition contribute to the recollection of specific plays in the mind of a sports fan. Botzung A, Rubin DC, Miles A, Cabeza R, LaBar KS. Mental hoop diaries: Emotional memories of a college basketball game in rival fans. J Neuroscience 2010; 30(6): 2130-2137.

Practiced Visual Characterization Results in Changes in Functional Connectivity Patterns

D'Esposito and colleagues at University of California, Berkeley used fMRI to examine how brain processes related to visual categorization during the transition from initially-learned to well-practiced categorization, i.e., during habit formation. Brain activation with fMRI and functional connectivity scans were obtained when subjects performed an initially learned categorization task (100 trials of training) and during a well-practiced task (4250 trials of training). Connectivity analyses revealed an increased coordination among inferior temporal cortex, medial temporal lobe premotor cortex when making category judgments during the well-practiced task. These results suggest that category learning involves an increased coordination between a distributed network of regions supporting retrieval and representation of categories. DeGutis J, D'Esposito M. Network changes in the transition from initial learning to well-practiced visual categorization. Front Hum Neurosci. 2009; 3: 44-48.

Chronic Cocaine Users Exhibit Loss of Laterality of Motor-Cortical Recruitment

Hanlon and colleagues from Wake Forest used fMRI to investigate whether chronic cocaine abusers exhibit alterations in brain activity related to movement disturbances. BOLD fMRI scans were obtained from 14 chronic cocaine users and 15 age- and gender-matched controls while they performed a sequential finger-tapping task with their dominant, right hand interleaved with blocks of rest. Cocaine users had significantly longer reaction times and higher error rates than controls. Whereas the controls used a left-sided network of motor-related brain areas to perform the task, cocaine users activated a less lateralized pattern of brain activity. Users had significantly more activity in the ipsilateral (right) motor and premotor cortical areas, anterior cingulate cortex and the putamen than controls. These data demonstrate that there are pronounced alterations in sensorimotor control in these individuals, which are associated with functional alterations throughout movement-related neural networks. Hanlon CA, Wesley MJ, Roth AJ, Miller MD, Porrino LJ. Loss of laterality in chronic cocaine users: An fMRI investigation of sensorimotor control. Psychiatry Research: Neuroimaging 2010; 181(1): 15-23.

Smoking Reduces Pain-Related Evoked Potentials

Domino and colleagues at University of Michigan, together with colleagues at the National Institute for Physiological Sciences, Myodaiji-cho (Okazaki, Japan) used evoked potential recordings to investigate the effects of human tobacco smoking and nicotine on pain-related brain activities. EEG responses evoked by a painful laser beam (laser evoked potentials; LEPs), and the plasma nicotine concentration (PNC) were measured. The amplitude of P2 was significantly smaller in the smoking session than in the no-smoking session. A significant negative correlation was found between PNC and the amplitude of N2 as well as P2. The results were consistent with the hypothesis that smoking and/or nicotine have an antinociceptive effect, which supports most non-human studies and some human studies. Smoking of a single tobacco cigarette did not show a subjectively perceivable extent of reduction in the intensity of evoked pain. Miyazaki T, Wang X, Inui K, Domino EF, Kakigi R. The effect of smoking on pain-related evoked potentials. Brain Res 2010; 1313: 185-191.

Assessing Liking and Wanting of Drug and Non-Drug Rewards in Active Cocaine Users

Goldstein and colleagues at Brookhaven National Laboratories developed and

tested a questionnaire (STRAP-R) that can assess "liking" and "wanting" of expected "drug" rewards as compared to natural rewards (e.g., "food" and "sex"). In all, 20 cocaine-addicted individuals (mean abstinence = 2 days) and 20 healthy control subjects were administered the questionnaire after receiving an oral dose of the dopamine agonist methylphenidate (20 mg) or placebo. The reinforcers' relative values changed within the addicted sample when reporting about the "under drug influence" situation (drug > food; otherwise, drug < food). This change was highest in the youngest age of onset of cocaine use. Moreover, "drug wanting" exceeded "drug liking" in the addicted subjects when reporting about this situation during methylphenidate. Thus, cocaine-addicted individuals assign the highest subjective valence to "drug" rewards but only when recalling cue-related situations. When recalling this situation, they also report higher drug "wanting" than hedonic "liking," a motivational shift that was only significant during methylphenidate. Together, these valence shifts may underlie compulsive stimulant abuse upon pharmacological or behavioral cue exposure in addicted individuals. Additional studies are required to assess the reliability of the STRAP-R in larger samples and to examine its validity in measuring the subjective value attributed to experienced reinforcers or in predicting behavior. Goldstein R, Woicik P, Moeller S, Telang F, Jayne M, Wong C, Wang G, Fowler J, Volkow N. Liking and wanting of drug and non-drug rewards in active cocaine users: the STRAP-R questionnaire. J Psychopharm 2010; 24(2): 257-266.

Tracking Changes in Control over Smoking during Addiction and Recovery Processes

DiFranza and colleagues at University of Massachusetts created a questionnaire to study how smokers lose autonomy over smoking and regain it after quitting. The Autonomy Over Smoking Scale (AOSS) was developed iteratively through a process involving item generation, focus-group evaluation, testing in adults to winnow items, field testing with adults and adolescents, and head-to-head comparisons with other measures. The final 12-item scale showed excellent reliability (alpha s = .91-97), with a one-factor solution explaining 59% of the variance in adults and 61%-74% of the variance in adolescents. Concurrent validity was supported by associations with age of smoking initiation, lifetime use, smoking frequency, daily cigarette consumption, history of failed cessation, Hooked on Nicotine Checklist scores, and Diagnostic and Statistical Manual of Mental Disorder (4th ed., text rev.; American Psychiatric Association, 2000) nicotine dependence criteria. Potentially useful features of this new instrument include (a) it assesses tobacco withdrawal, cue-induced craving, and psychological dependence on cigarettes; (b) it measures symptom intensity; and (c) it asks about current symptoms only, so it could be administered to quitting smokers to track the resolution of symptoms. DiFranza JR, Wellman RJ, Ursprung WWSA, Sabiston C. The Autonomy Over Smoking Scale. Psychology of Addictive Behaviors 2009; 23(4): 656-665.

Questionnaire for Methamphetamine-Related Paranoia

Salo and colleagues at University of California, Davis developed a questionnaire to characterize paranoia in methamphetamine (MA) users. The Methamphetamine Experience Questionnaire (MEQ), was administered to 274 MA-dependent subjects. Of the total subjects, 45% (123) first experienced paranoia with MA use; 55% did not. Obtaining or using a weapon while paranoid was common (37% and 11% of subjects with MA-induced paranoia, respectively). Test-retest and inter-rater reliability for MA-induced paranoia showed substantial agreement (kappa = .77, $p < .05$ and kappa = .80, $p < .05$, respectively). First episodes of paranoia occurred more often with intravenous use of MA, and subsequent episodes at higher doses. There was modest correlation between paranoia on the MEQ and the Brief Symptom Inventory (BSI) paranoid ideation scale (rho = .27, $p < .05$). As expected,

there was a poor correlation between paranoia on the MEQ and the BSI depression scale (rho = .14, p = .07). The MEQ provides useful information on drug use variables that contribute to paranoia commonly associated with MA use. Leamon MH, Flower K, Salo RE, Nordahl TE, Kranzler HR, Galloway GP. Methamphetamine and Paranoia: The Methamphetamine Experience Questionnaire. Am J Addictions 2010; 19(2): 155-168.

Quantitative Analysis of the Serotonin 5-HT1B Receptor Radioligand [11C]P943 in Humans

Ding and colleagues at Yale examined several methods for quantitative analysis of new radioligand [C-11]P943, for imaging serotonin 5-Hydroxytryptamine (5-HT1B) receptors in humans with positron emission tomography (PET). Positron emission tomography data and arterial input function measurements were acquired 32 human subjects. Using arterial input functions, compartmental modeling, the Logan graphical analysis, and the multilinear method MA1 were tested. Both the two tissue-compartment model and MA1 provided good fits of the PET data and reliable distribution volume estimates. Using the cerebellum as a reference region, BPND binding potential estimates were computed. [C-11]P943 BPND estimates were significantly correlated with in vitro measurements of the density of 5-HT1B receptors, with highest values in the occipital cortex and pallidum. To evaluate noninvasive methods, two-and three-parameter graphical analyses, Simplified Reference Tissue Models (SRTM and SRTM2), and Multilinear Reference Tissue Models (MRTM and MRTM2) were tested. The MRTM2 model provided the best correlation with MA1 binding-potential estimates. Parametric images of the volume of distribution or binding potential of [C-11]P943 could be computed using both MA1 and MRTM2. The results show that [C-11]P943 provides quantitative measurements of 5-HT1B binding potential. Gallezot J, Nabulsi N, Neumeister A, Planeta-Wilson B, Williams WA, Singhal T, Kim S, Maguire RP, McCarthy T, Frost JJ, Huang Y, Ding Y, Carson RE. Kinetic modeling of the serotonin 5-HT1B receptor radioligand [11C]P943 in humans. J Cereb Blood Flow Metab 2009; 30(1): 196-210.

Simplified Quantification of 5-HT2A Receptors in the Human Brain

Bhagwagar and colleagues at Yale in collaboration with University Hospital, Freiburg developed simple methods for quantitative analysis of the 5-HT2A PET ligand, [C-11]MDL100,907 using the cerebellum as reference region. Five healthy volunteers underwent two PET scanning sessions; baseline and after pre-treatment with mirtazapine, a drug that binds with high affinity at the serotonin 5-HT2B receptors. Regional time-activity curves of 10 regions of interest (ROI) were analyzed for binding potential (BPND) and mirtazapine receptor occupancy (Occ) using 5 approaches: 1) simplified reference tissue model (SRTM), 2) multi-linear reference tissue model (MRTM), 3) their two-parameter versions (SRTM2/MRTM2), 4) non-invasive graphical analysis (NIGA) and 5) a tissue activity concentration ratio. NIGA was also applied voxel-wise to generate BPND maps. These methods were compared with a two-tissue compartment model with arterial input function (2TCM). SRTM and MRTM frequently failed to yield reliable results. NIGA was found to be well suited for analysis of [C-11]MDL100,907 PET studies, yielding estimates of 5-HT2A receptor availability and changes that are highly correlated with results from invasive 2TCM with arterial input function analyses. Use of NIGA should greatly enhance the applicability of 5-HT2A receptor PET studies. Meyer PT, Bhagwagar Z, Cowen PJ, Cunningham VJ, Grasby PM, Hinz R. Simplified quantification of 5-HT2A receptors in the human brain with [11C]MDL 100,907 PET and non-invasive kinetic analyses. NeuroImage 2010; 50(3): 984-993.

Does D2 Receptor Internalization Alter Binding Affinity of

Neuroimaging Ligands?

Abi-Dargham and colleagues at Columbia used an in vitro assay to address whether agonist-induced D2 receptor internalization may contribute to the sustained decrease in D2 receptor-binding potential seen following a DA surge in PET ligand imaging. In PET ligand imaging studies, D2 radiotracer binding is generally thought to be due to competition between endogenous DA and the radioligands for D2 receptors. However, there is a temporal discrepancy between amphetamine-induced increases in DA as measured by microdialysis, which last on the order of 2 h, and the prolonged decrease in ligand binding, which lasts up to a day. To test whether this discrepancy is due to D2 receptor internalization, an in vitro system was developed that exhibits robust agonist-induced D2 receptor internalization following treatment with the agonist quinpirole. All the imaging ligands bound with high affinity to both surface and internalized D2 receptors. Affinity of most of the ligands to internalized receptors was modestly lower, indicating that internalization would reduce the binding potential measured in imaging studies carried out with these ligands. However, between-ligand differences in the magnitude of the internalization-associated affinity shift only partly accounted for the data obtained in neuroimaging experiments, suggesting the involvement of mechanisms beyond competition and internalization. Guo N, Guo W, Kralikova M, Jiang M, Schieren I, Narendran R, Slifstein M, Abi-Dargham A, Laruelle M, Javitch JA, Rayport S. Impact of D2 receptor internalization on binding affinity of neuroimaging radiotracers. Neuropsychopharm 2009; 35(3): 806-817.

MDMA (Ecstasy) Use is Associated with Reduced BOLD Signal Change during Semantic Recognition in Abstinent Human Polydrug Users

Cowan and colleagues at Vanderbilt tested whether MDMA users would show altered brain activation during performance of a functional magnetic resonance imaging (fMRI) task that probed semantic verbal memory. During semantic recognition, lifetime MDMA use was associated with decreased activation in left BA 9, 18 and 21/22 but not 45. This was partly influenced by contributions from cannabis and cocaine use. MDMA exposure was not associated with accuracy or response time during the semantic recognition task. During semantic recognition, MDMA exposure was associated with reduced regional brain activation in regions mediating verbal memory. These findings partially overlap with previous structural evidence for reduced grey matter in MDMA users and may, in part, explain the consistent verbal memory impairments observed in other studies of MDMA users. Raj V, Liang H, Woodward N, Bauernfeind A, Lee J, Dietrich M, Park S, Cowan R. MDMA (ecstasy) use is associated with reduced BOLD signal change during semantic recognition in abstinent human polydrug users: a preliminary fMRI study. J Psychopharm 2009; 24(2): 187-201.

Evidence of Dysregulated Serotonergic Transmission in HIV-Associated Depression

Using [(11)C]DASB positron emission tomography (PET), Nath and colleagues evaluated the association between serotonergic transmission and HIV-associated depression. The serotonin transporter (5-HTT) binding potential was lower in HIV+ individuals than in healthy subjects. A significant change was detected in the insula. There was no correlation between duration of illness and binding potentials. The diminished serotonergic transmission was regarded as a consequence of serotonergic neuronal dysfunction associated with HIV neurodegeneration. Among HIV+ individuals, those comorbid with depression had a higher mean regional biding potential than non-depressed subjects. The observation is consistent with reports of higher transmission and clearance of

serotonin in patients with depression. Hammoud DA, Endres CJ, Hammond E, Uzuner O, Brown A, Nath A, Kaplin AI, Pomper MG. Imaging serotonergic transmission with [11C]DASB-PET in depressed and non-depressed patients infected with HIV. NeuroImage. 2010; 49(3): 2588-2595.

Nicotine Reduced ADHD Symptoms and Negative Moods Independent of Smoking Status

Gehricke evaluated the self-medication hypothesis by examining the effects of nicotine in the everyday lives of abstinent smokers and nonsmokers with attention-deficit/hyperactivity disorder (ADHD). Participants were administered one nicotine patch condition and one placebo patch condition in counterbalanced order on two consecutive mornings. The use of nicotine patch reduced reports of ADHD symptoms by 8% and negative moods by 9%, independent of smoking status. In addition, nicotine increased cardiovascular activity during the first 3 to 6 hours after nicotine patch administration. The results support the self-medication hypothesis for nicotine in adults with ADHD and suggest that smoking cessation and prevention efforts for individuals with ADHD will need to address both the symptom reducing and mood enhancing effects of nicotine. Gehricke JG, Hong N, Whalen CK, Steinhoff K, Wigal TL. Effects of transdermal nicotine on symptoms, moods, and cardiovascular activity in the everyday lives of smokers and nonsmokers with attention-deficit/hyperactivity disorder. Psychol Addict Behav. 2009 December; 23(4): 644-655.

Negative Affect and Pain in Children

Tsao and colleagues examined the relationships among anxiety sensitivity, catastrophizing, somatization and pain in children. Children with pain problems reported greater anxiety sensitivity and catastrophizing relative to those without pain problems. Anxiety sensitivity, but not catastrophizing, was significantly associated with current pain while both anxiety sensitivity and catastrophizing were significantly associated with somatization. These findings suggest that anxiety sensitivity and catastrophizing represent related but partially distinct cognitive constructs that may be targeted by interventions aimed at alleviating pain and somatization in children. Tsao JC, Allen LB, Evans S, Lu Q, Myers CD, Zeltzer LK. Anxiety sensitivity and catastrophizing: Associations with pain and somatization in non-clinical children. J Health Psychol. 2009 Nov; 14(8): 1085-1094.

White Matter Architecture Aberrations in Methamphetamine Dependence are Apparent in Early Withdrawal

London and colleagues at UCLA compared brain white matter characteristics in 23 methamphetamine-dependent subjects abstinent from methamphetamine for 7-13 days and 18 healthy comparison subjects. Using diffusion tensor imaging at 1.5 T, they measured fractional anisotropy (FA) in prefrontal and corpus callosum. The methamphetamine group exhibited lower FA in right prefrontal white matter above the AC-PC plane (11.9% lower; $p = 0.007$), in midline genu corpus callosum (3.9%; $p = 0.019$), in left and right midcaudal superior corona radiata (11.0% in both hemispheres, p's = 0.020 and 0.016, respectively), and in right perforant fibers (7.3%; $p = 0.025$). FA in left midcaudal superior corona radiata was correlated with depressive and generalized psychiatric symptoms within the methamphetamine group. These findings support the idea that methamphetamine abuse produces microstructural abnormalities in white matter underlying and interconnecting prefrontal cortices and hippocampal formation. These effects are already present during the first weeks of abstinence from methamphetamine and are linked to psychiatric symptoms assessed during this period. Tobias MC, O'Neill

J, Hudkins M, Bartzokis G, Dean AC, London ED. White-matter abnormalities in brain during early abstinence from methamphetamine abuse. Psychopharm (Berl). 2010; 209(1): 13-24.

Stress-induced Changes in Mood Predict Mood Effects of Amphetamine

Hamidovic and de Wit compared responses to a stress-inducing behavior test (Trier Social Stress Test, TSST) to responses after double-blind administration of d-amphetamine. Based on animal model and previous studies in humans, the hypothesis was that individual differences in sensitivity to acute stress may underlie some of the individual differences in vulnerability to addiction. The results substantiated the hypothesis whereby it was found that negative mood states induced by stress were positively related to stimulant and euphoric mood states after d-amphetamine. The highest correlation was between the rating of anxiety after stress and rating of "liking" (from a drug effects questionnaire) after amphetamine. The results suggest that similar neural pathways may underlie both types of responses which may explain the reason that individual differences in stress responsivity are related to vulnerability to taking drugs. Hamidovic A., Childs E., Conrad M., King, A., de Wit H. Stress-induced changes in mood and cortisol release predict mood effects of amphetamine. Drug Alcohol Depend. 2010 February [Epub ahead of print].

Altered Neural Cholinergic Receptor Systems in Cocaine-Addicted Subjects

Adinoff and collaborators at University of Texas SW assessed alterations in cholinergic receptor systems in limbic regions of abstinent cocaine-addicted subjects compared with healthy controls. Cocaine-addicted subjects and control subjects were administered the muscarinic and nicotinic cholinergic agonist physostigmine, the muscarinic antagonist scopolamine, and saline. Regional cerebral blood flow (rCBF) after each infusion was determined using single photon emission-computed tomography. Both cholinergic probes induced rCBF changes ($p<.005$) in relatively distinct, cholinergic-rich, limbic brain regions. After physostigmine, cocaine-addicted subjects showed altered rCBF, relative to controls, in limbic regions, including the left hippocampus, left amygdala, and right insula. Group differences in the right dorsolateral prefrontal cortex, posterior cingulate, and middle temporal gyrus were also evident. Scopolamine also revealed group differences in the left hippocampus and right insula as well as the posterior cingulate and middle temporal gyrus. Cocaine addicted and controls differed in their subcortical, limbic, and cortical response to cholinergic probes in areas relevant to craving, learning, and memory. Cholinergic systems may offer a pharmacologic target for cocaine addiction treatment. Adinoff B, Devous Sr MD, Williams MJ, Best SE, Harris TS, Minhajuddin A, Zielinski T, Cullum M. Altered neural cholinergic receptor systems in cocaine-addicted subjects. Neuropsychopharm. 2010 March. [Epub ahead of print].

Neurochemistry of Drug Action

Licata, at McLean Hospital, and her colleague compiled a comprehensive review of the use of proton magnetic resonance spectroscopy ((1)H MRS) as a technique that complements other brain imaging techniques in the field of substance abuse research. Drug abuse studies using (1)H MRS have identified several biochemical changes in the brain. The most consistent alterations across drug class were reductions in N-acetylaspartate and elevations in myo-inositol; changes in choline, creatine, and amino acid transmitters also were abundant. Together, the studies provide evidence that drugs of abuse may have a profound effect on neuronal health, energy metabolism and maintenance, inflammatory processes, cell membrane turnover, and

neurotransmission, and these biochemical changes may underlie the neuropathology that subsequently gives rise to the cognitive and behavioral impairments associated with drug addiction. Licata SC, Renshaw PF. Neurochemistry of drug action: Insights from proton magnetic resonance spectroscopic imaging and their relevance to addiction. Ann N Y Acad Sci. 2010 Feb; 1187: 148-171.

Impulsive Choice and Response in Dopamine Agonist-Related Impulse Control Behaviors

Potenza and colleagues at Yale investigated impulsive choice in Parkinson's Disease (PD) patients with impulse control disorders (ICDs). PD patients with impulse control disorders (IDC), PD controls without ICDs, and medication-free matched normal controls were tested on the Experiential Discounting Task (EDT), a feedback-based inter-temporal choice task, spatial working memory, and attentional set shifting. PDI patients and PD controls were tested on and off dopamine agonist. On the EDT, there was a group by medication interaction effect with pair-wise analyses demonstrating that DA status was associated with increased impulsive choice in PDI patients but not in PD controls. PDI patients also had faster RT compared to PD controls. DA status was associated with shorter RT and decision conflict RT in PDI patients but not in PD controls. There were no correlations between different measures of impulsivity. PDI patients on DA had greater spatial working memory impairments compared to PD controls on DA. Greater impulsive choice, faster RT, faster decision conflict RT, and executive dysfunction may contribute to ICDs in PD. Understanding the role of impulsivity may contribute to the identification of risk factors and the optimization of treatment modalities. Voon V, Reynolds B, Brezing C, Gallea C, Skaljic M, Ekanayake V, Fernandez H, Potenza MN, Dolan RJ, Hallett M. Impulsive choice and response in dopamine agonist-related impulse control behaviors. Psychopharm (Berl). 2010 January; 207(4): 645-659.

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Research Findings - Epidemiology and Etiology Research

Racial and Sex Disparities in Life Expectancy Losses among HIV-infected Persons in the U.S.: Impact of Risk Behavior, Late Initiation, and Early Discontinuation of Antiretroviral Therapy

Researchers sought to evaluate sex and racial/ethnic disparities in life-years lost as a result of HIV risk behavior, late presentation for HIV care, and early discontinuation of HIV care. Using a state-transition model of HIV disease (i.e., the Cost Effectiveness of Preventing AIDS Complications or CEPAC model), they simulated cohorts of HIV-infected persons and compared them with uninfected individuals with similar demographic characteristics in the general population. They estimated non-HIV-related mortality with use of risk-adjusted standardized mortality ratios as well as years of life lost due to late presentation of care and early discontinuation of therapy for HIV infection. Cohort data (N=8091) for these analyses were from the HIV Research Network, an ongoing consortium of primary care sites for HIV-infected patients in 4 regions of the U.S., stratified by sex (75% male) and race/ethnicity (50% African American, 27% White, 21% Hispanic). The analyses indicated that, for HIV-uninfected persons who have risk profiles (i.e., substance abuse and other high risk behaviors) similar to individuals with HIV infection, the projected life expectancy starting at 33 years of age was 34.58 years, compared with 42.91 years for the general US population (i.e., an average of 8.33 years of life lost, even in the absence of HIV infection). Persons with HIV infection lost an additional 11.92 years of life if they received HIV care concordant with current guidelines and an additional 3.30 years due to late presentation for HIV care and early discontinuation of therapy. Survival disparities resulting from late initiation and early discontinuation of therapy were most pronounced for Hispanic HIV-infected men and women (3.90 years). The high-risk behavioral profile of HIV-infected persons, HIV infection itself, late initiation of care, and early discontinuation and inadequate retention in care all lead to substantial decreases in life expectancy. These findings underscore the importance of interventions that address HIV risk behaviors and facilitate earlier linkage and retention in HIV care to improve survival for HIV-infected persons in the U.S. Losina E, Schackman B, Sadownik S, Gebo K, Walensky R, Chiosi J, Weinstein M, Hicks P, Aaronson W, Moore R, Paltiel A, Freedberg K. Racial and sex disparities in life expectancy losses among HIV-infected persons in the United States: Impact of risk behavior, late initiation, and early discontinuation of antiretroviral therapy. Clin Infect Dis. 2009; 49 (10): 1570-1578.

Neighborhood Poverty and Injection Cessation in a Sample of Injection Drug Users

Researchers examined the relationship between neighborhood socioeconomic environment and injection drug use cessation using data from the ALIVE (AIDS

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Linked to the Intravenous Experience), a prospective cohort study of injection drug users in Baltimore, MD. The analysis was based on 1,875 IDU followed from 1990 to 2006, who contributed a total of 19,054 study assessment visits. Respondent address information at each visit was geocoded to the 174 the census tracts that serve as proxies for the City's neighborhoods, and data from the 1990 U.S. Census were used to estimate the percentage of residents living in poverty per census tract. After adjustment for potential time-fixed and time-varying confounders, exposure, and outcome, the analysis found a strong inverse association between neighborhood poverty and injection drug use cessation: Living in a neighborhood with fewer than 10%, compared with more than 30%, of residents in poverty was associated with a 44% increased odds of not injecting in the 6 months prior to the current visit (odds ratio = 1.44, 95% confidence interval: 1.14, 1.82). Socioeconomic deprivation and environmental disorder in a neighborhood have been linked to the presence of drug use networks and drug trafficking. This study suggests that such conditions also have important determinative effects on drug injection behaviors, independent of individual-level characteristics. Nandi A, Glass TA, Cole SR, Chu H, Galea S, Celentano DD, Kirk GD, Vlahov D, Latimer WW, Mehta SH. Neighborhood poverty and injection cessation in a sample of injection drug users. Am J Epidemiol. 2010; 171(4): 391-398.

Early Mortality and Cause of Deaths in Patients Using HAART in Brazil and the United States

Researchers from the U.S. and Brazil collaborated in the analysis of patterns of mortality and causes of death among patients in their HIV clinical cohorts who initiated HAART. The collaboration was made possible because both cohort studies used similar data collection methods over approximately the same time periods. Cohort data were combined from the Johns Hopkins HIV/AIDS Clinical Cohort in Baltimore and by the Evandro Chagas Clinical Research Institute AIDS Clinic in Rio de Janeiro, Brazil for all participants who entered either cohort between 1999 and 2007 as antiretroviral naïve and, at their first one-year follow-up assessment, had initiated HAART. Cox proportional hazards regression analysis was used to assess the role of the city on the risk of death. A total of 859 and 915 participants from Baltimore and Rio de Janeiro, respectively, were included in the analysis. There were significant differences between Rio de Janeiro and Baltimore in terms of patient age [median 41 years in Rio; 39 years in Baltimore] and HIV risk group [51.2% heterosexual and 29.1% MSM in Rio; 36.2% IDU and 38.5% heterosexual in Baltimore]. There were 34 (3.7%) deaths in Rio and 45 (5.2%) deaths in Baltimore within the first year after initiation of HAART. In Rio de Janeiro, 64.7% of deaths occurred within 90 days of HAART initiation; in Baltimore, 48.9% occurred between 180 and 365 days. AIDS-defining illness (61.8%) and non-AIDS-defining illness (55.6%) predominated as causes of death in Rio de Janeiro and Baltimore, respectively. Risk of death was similar in both cities after adjusting for CD4 T cell count, age, sex, HIV risk group, prior AIDS-defining illness, and opportunistic infections; patients with a CD4 T cell count less than or equal to 50 cells/microl (hazard ratio 4.36; P = 0.001) or older (hazard ratio, 1.03; P = 0.03) were more likely to die. These results indicate that late HIV diagnosis is a problem in both developed and developing countries, although differences in timing and in causes of deaths suggest that, besides interventions for early HIV diagnosis, different strategies to curb early mortality need to be tailored in each country. Grinsztejn B, Veloso V, Friedman R, Moreira R, Luz P, Campos D, Pilotto J, Cardoso S, Keruly J, Moore R. Early mortality and cause of deaths in patients using HAART in Brazil and the United States. AIDS. 2009; 23 (16): 2107-2114.

Social and Behavioral Correlates of Sexually Transmitted Infection- and HIV-discordant Sexual Partnerships in Bushwick, Brooklyn, New York

Researchers analyzed data collected during a social network study conducted from 2002 to 2005 in Bushwick, a Brooklyn, NY, neighborhood, that sought to examine linkages between high risk and low risk individuals that may influence patterns of drug use and HIV. The analysis focused on identifying social and behavioral characteristics of respondents (N = 343) involved in HIV-discordant, herpes simplex virus-2- discordant, and chlamydia-discordant partnerships. Just over half the 343 participants were male (53%), the mean age was 33 for men and 27 for women, and the sample was 70% Latino and 21% African American. Nearly 75% reported they had used crack, cocaine, or heroin by non-injection; 38% had ever injected, and all had used non-injection drugs. Almost half (48%) were HSV-2-infected, 10% HIV-infected, and 6% were infected with chlamydia. HIV partnership discordance was associated with injection drug use, but was generally not associated with sexual behaviors including multiple partnerships and sex trade. Herpes simplex virus-2 and chlamydia partnership discordance were associated with multiple partnerships, sex trade, and same-sex partnership history. Additional correlates of sexually transmitted infection (STI)/HIV-discordant partnerships included older age (>or=25 years), noninjection drug use, and incarceration history. The analyses also examined the sensitivity and specificity of CDC's screening tools composed of recommended sexual risk and injection drug indicators for identifying priority risk groups and found that, by adding the social and behavioral indicators correlated with STI/HIV discordance, there was a significant improvement in STI/HIV case-finding effectiveness. Khan MR, Bolyard M, Sandoval M, Mateu-Gelabert P, Krauss B, Aral SO, Friedman SR J AIDS. 2009; 51(4): 470-485.

Emergency Department Utilization among HIV-infected Patients in a Multisite Multistate Study

The aim of this study was to examine Emergency Department (ED) utilization and clinical and sociodemographic correlates of ED use among HIV-infected patients. During 2003, 951 patients participated in face-to-face interviews at 14 HIV clinics in the U.S. multisite, multistate HIV Research Network. Gender, age, race/ethnicity, the reported means of becoming HIV-infected, CD4 cell count in 2003, and the proportion with an undetectable viral load were similar between respondents and in the larger population of patients at these clinics. Using logistic regression, researchers identified factors associated with visiting the ED in the last 6 months and admission to the hospital from the ED. Thirty-two per cent of respondents reported at least one ED visit in the last 6 months. In multivariate analysis, any ED use was associated with Medicaid insurance, high levels of pain (the third or fourth quartile), more than seven primary care visits in the last 6 months, current or former illicit drug use, social alcohol use and female gender. Of those who used ED services, 39% reported at least one admission to the hospital. Patients with pain in the highest quartile reported increased admission rates from the ED as did those who made six or seven primary care visits, or more than seven primary care visits vs. three or fewer. These findings indicate that the likelihood of visiting the ED has not diminished since the advent of highly active antiretroviral therapy (HAART). More ED visits were for treatment of illnesses not related to HIV or injuries than to treat direct sequelae of HIV infection. The findings suggest that, with the growing prevalence of people living with HIV infection in the U.S., the numbers of HIV-infected patients visiting the ED may increase. ED providers will also need to identify and understand the potential complications associated with HIV disease. Josephs J, Fleishman J, Korthuis P, Moore R, Gebo K, Gebo K. Emergency department utilization among HIV-infected patients in a multisite multistate study. HIV Med. 2010; 11(1): 74-84.

Smoking of Crack Cocaine as a Risk Factor for HIV Infection among People who Use Injection Drugs

Little is known about the possible role that smoking crack cocaine has on the incidence of HIV infection. Given the increasing use of crack cocaine, researchers sought to examine whether use of this illicit drug has become a risk factor for HIV infection. They analyzed data from 1048 participants in the Vancouver Injection Drug Users Study who reported injecting illicit drugs at least once in the month before enrollment, lived in the greater Vancouver area, were HIV-negative at enrollment and completed at least 1 follow-up study visit. To determine whether the risk of HIV seroconversion among daily smokers of crack cocaine changed over time, they used Cox proportional hazards regression and divided the study into 3 periods: May 1, 1996-Nov. 30, 1999 (period 1), Dec. 1, 1999-Nov. 30, 2002 (period 2), and Dec. 1, 2002-Dec. 30, 2005 (period 3). Of the 1048 participants, 137 acquired HIV infection during follow-up. The mean proportion who reported daily smoking of crack cocaine increased from 11.6% in period 1 to 39.7% in period 3. After adjusting for potential confounders, researchers found that the risk of HIV seroconversion among participants who were daily smokers of crack cocaine increased over time (period 1: hazard ratio [HR] 1.03, 95% confidence interval [CI] 0.57-1.85; period 2: HR 1.68, 95% CI 1.01-2.80; and period 3: HR 2.74, 95% CI 1.06-7.11). These results indicate that smoking of crack cocaine is an independent risk factor for HIV seroconversion among people who inject drugs, underscoring the need for evidence-based public health initiatives targeted at people who smoke crack cocaine. DeBeck K, Kerr T, Li K, Fischer B, Buxton J, Montaner J, Wood E. Smoking of crack cocaine as a risk factor for HIV infection among people who use injection drugs. CMAJ. 2009; 181(9): 585-589.

Unstable Housing and Hepatitis C Incidence among Injection Drug Users in a Canadian Setting

There has been a growing recognition of the link between housing and health, and in Vancouver, Canada, there have been increasing concerns about homelessness brought about by urban renewal in the lead-up to the 2010 Winter Olympic Games. Researchers sought to evaluate hepatitis C virus (HCV) incidence among injection drug users (IDU) with and without stable housing in Vancouver. Data were derived from two prospective cohort studies of IDU in Vancouver, Canada. Cox Proportional Hazards regression was used to compare HCV incidence among participants with and without stable housing, and to determine independent predictors of HCV incidence. Overall, 3074 individuals were recruited between May 1996 and July 2007, among whom 2541 (82.7%) were baseline HCV-infected. Among the 533 (17.3%) individuals who were not HCV-infected at baseline, 147 tested HCV antibody-positive during follow-up, for an incidence density of 16.89 (95% confidence interval: 14.76 - 19.32) per 100 person-years. In a multivariate Cox regression model, unstable housing remained independently associated with HCV infection (relative hazard = 1.47 (1.02 - 2.13). These findings indicate that HCV prevalence and incidence are high in this setting and are associated with unstable housing. Efforts to protect existing low-income housing and improve access to housing may help to reduce HCV incidence. Kim C, Kerr T, Li K, Zhang R, Tyndall M, Montaner J, Wood E. Unstable housing and hepatitis C incidence among injection drug users in a Canadian setting. BMC Public Health. 2009; 9: 270-276.

Multistage Genomewide Association Study Identifies a Locus at 1q41 Associated with Rate of HIV-1 Disease Progression to Clinical AIDS

A mean of 9-10 years of HIV-1 infection elapses before clinical AIDS develops in untreated persons, but this rate of disease progression varies substantially among individuals. To investigate host genetic determinants of the rate of progression to clinical AIDS, researchers performed a multistage genomewide association study. The discovery stage comprised 156 individuals from the Multicenter AIDS Cohort Study, enriched with rapid and long-term

nonprogressors to increase statistical power. This was followed by replication tests of putatively associated genotypes in an independent population of 590 HIV-1-infected seroconverters from five natural history cohorts of persons with HIV/AIDS (including the ALIVE and MACS). Significant associations with delayed AIDS progression were observed in a haplotype located at 1q41, 36 kb upstream of PROX1 on chromosome 1 (relative hazard ratio, 0.69; Fisher's combined P = 6.23 X 10(-7)). This association was replicated further in an analysis stratified by transmission mode, with the effect consistent in sexual or mucosal and parenteral transmission (relative hazard ratios, 0.72 and 0.63, respectively; combined P = 1.63 X 10(-6)). This study identified and replicated a locus upstream of PROX1 that is associated with delayed progression to clinical AIDS. PROX1 is a negative regulator of interferon-gamma expression in T cells and also mitigates the advancement of vascular neoplasms, such as Kaposi sarcoma, a common AIDS-defining malignancy. This study adds to information about the cumulative polygenic host component that effectively regulates the progression to clinical AIDS among HIV-1-infected individuals, raising prospects for potential new avenues for therapy and improvements in AIDS prognosis. Herbeck J, Gottlieb G, Winkler C, Nelson G, An P, Maust B, Wong K, Troyer J, Goedert J, Kessing B, Detels R, Wolinsky S, Martinson J, Buchbinder S, Kirk G, Jacobson L, Margolick J, Kaslow R, O 'Brien S, Mullins J. Multistage genomewide association study identifies a locus at 1q41 associated with rate of HIV-1 disease progression to clinical AIDS. J Infect Dis. 2010; 201(4): 618-626.

Characterization of the Emerging HIV Type 1 and HCV Epidemics among Injecting Drug Users in Dushanbe, Tajikistan

This study sought to determine HIV, HCV, and syphilis prevalence and correlates, and to characterize the molecular epidemiology of HIV-1 among IDUs in Dushanbe, Tajikistan. A cross-sectional study was conducted to assess risk factors for HIV and HCV using an interview survey. A total of 491 active adult IDUs were recruited from May to November 2004 in Dushanbe, Tajikistan. HIV-1 antibody status was determined with rapid testing and confirmed with ELISA. HCV antibody testing was conducted using a BIOELISA HCV kit. HIV-1 subtyping was completed on a subset with full-length sequencing. Correlates of HIV and HCV infection were assessed using logistic regression. Overall prevalence of HIV was 12.1%, HCV was 61.3%, and syphilis was 15.7%. In a multivariate logistic regression model controlling for gender and ethnicity, daily injection of narcotics [odds ratio (OR) OR 3.22] and Tajik nationality (OR 7.06) were significantly associated with HIV status. Tajik nationality (OR 1.91), history of arrest (OR 2.37), living/working outside Tajikistan in the past 10 years (OR 2.43), and daily injection of narcotics (OR 3.26) were significantly associated with HCV infection whereas being female (OR 0.53) and always using a sterile needle (OR 0.47) were inversely associated with HCV infection. Among 20 HIV-1-positive IDU with specimens available for typing, 10 were subtype A, 9 were CRF02_AG, and one was an A-CRF02_AG recombinant. Epidemics of HIV-1, HCV, and drug use are underway in Dushanbe. The molecular epidemiology is distinctive, with West African variants accounting for roughly 50% of prevalent infections. These findings underscore the need for targeted prevention programs that offer both needle exchange programs and opiate substitution therapies to prevent further epidemic spread of HIV and HCV in Tajikistan. Beyrer C, Patel Z, Stachowiak J, Tishkova F, Stibich M, Eyzaguirre L, Carr J, Mogilnii V, Peryshkina A, Latypov A, Strathdee S. Characterization of the emerging HIV type 1 and HCV epidemics among injecting drug users in Dushanbe, Tajikistan. AIDS Res Hum Retroviruses. 2009; 25(9): 853-860.

Temporal Trends in Spatial Access to Pharmacies that Sell Over-the-Counter Syringes in New York City Health Districts: Relationship to Local Racial/Ethnic Composition and Need

Pharmacies that sell over-the-counter (OTC) syringes are a major source of sterile syringes for injection drug users in cities and states where such sales are legal. In these cities and states, however, black injectors are markedly less likely to acquire syringes from pharmacies than white injectors. This analysis documents spatial and temporal trends in OTC pharmacy access in New York City health districts over time (2001-2006) and investigates whether these trends are related to district racial/ethnic composition and to local need for OTC pharmacies. For each year, researchers estimated spatial access to OTC pharmacies within each health district, with higher values indicating better access to the pharmacies. "Need" was computed using two the indices, the number of newly diagnosed injection-related AIDS cases per 10,000 residents (averaged across 1999-2001) and the number of drug-related hospital discharges per 10,000 residents (averaged across 1999-2001). District sociodemographic characteristics were assessed using 2000 US decennial census data. Hierarchical linear models (HLM) were used for descriptive and inferential analyses of whether the relationship between need and temporal trajectories in accessing the Expanded Syringe Access Demonstration Program varied by district racial/ethnic composition after controlling for district poverty rates. The analyses indicated that mean spatial access to OTC pharmacies across NYC health districts was 12.71 in 2001 and increased linearly by 1.32 units annually thereafter. Temporal trajectories in spatial access to OTC pharmacies depended on both need and racial/ethnic composition. Within high-need districts, OTC pharmacy access was twice as high in 2001 and increased three times faster annually in districts with higher proportions of non-Hispanic white residents versus districts with low proportions of these residents. In low-need districts, "whiter" districts had substantially greater baseline access to OTC pharmacies than districts with low proportions of non-Hispanic white residents. Access remained stable thereafter in low-need districts, regardless of racial/ethnic composition. The results show that in both high- and low-need districts, spatial access to OTC pharmacies was greater in "Whiter" districts in 2001; in high-need districts, access increased more rapidly over the time period in "whiter" districts. These findings highlight the importance of equitable spatial access to OTC pharmacies to help reduce injection-related HIV transmission overall, and to reduce racial/ethnic disparities in HIV incidence among injectors. Cooper H, Bossak B, Tempalski B, Friedman S, Des Jarlais D. Temporal trends in spatial access to pharmacies that sell over-the-counter syringes in New York City health districts: Relationship to local racial/ethnic composition and need. J Urban Health. 2009; 86(6): 929-945.

Factors Associated with Initiation of Ecstasy Use Among US Adolescents: Findings from a National Survey

This study investigated adolescent pathways to ecstasy use by (1) examining how early onsets of smoking, drinking, and marijuana use are related to a child's risk of initiation of ecstasy use and (2) assessing the influence of other individual and parental factors on ecstasy use initiation. Data on 6426 adolescents (12-17 years old at baseline) from the National Survey of Parents and Youth (NSPY), a longitudinal, nationally representative household survey of youth and their parents, were used in the analyses. Information on youth substance use, including ecstasy use, as well as familial and parental characteristics, was available. Findings show that initiation of ecstasy use is predicted by an adolescent's early initiation of smoking, drinking, or marijuana use. In particular, early initiation either of marijuana use, or of both smoking and drinking, increases a child's risk for ecstasy use initiation. Among the familial and parental variables, parent drug use emerged as significantly predictive of child initiation of ecstasy use; living with both parents and close parental monitoring, on the other hand, are negatively associated with ecstasy use initiation, and may be protective against it. At the individual level, sensation seeking tendencies and positive attitudes towards substance use, as

well as close associations with deviant peers, are predictive of adolescent initiation of ecstasy use. These findings on the risk and protective factors for initiation of ecstasy use, especially with regard to factors that are modifiable, will be useful for prevention programs targeting youth use not only of ecstasy, but also of other drugs. Wu P, Liu X, Fan B. Factors associated with initiation of ecstasy use among US adolescents: findings from a national survey. Drug Alcohol Depend. 2010; 106(2-3): 193-198.

Syringe Exchange, Injecting and Intranasal Drug Use

Researchers sought to assess trends in injecting and non-injecting drug use after implementation of large-scale syringe exchange in New York City. They were particularly interested in examining the belief that implementation of syringe exchange will lead to increased drug injecting, which has been a persistent argument against syringe exchange. They analyzed administrative records on route of administration for primary drug of abuse among drug users enrolling in the Beth Israel methadone maintenance program from 1995 to 2007. Approximately 2000 participants enter the program each year. The researchers found that during and after the period of large-scale implementation of syringe exchange, the numbers of methadone program entrants reporting injecting drug use decreased while the numbers of entrants reporting intranasal drug use increased ($P < 0.001$). Although it is difficult to assess the possible effects of syringe exchange on trends in injecting drug use, these results may be the strongest to date showing no increase in drug injecting following the implementation of syringe exchange. Des Jarlais D, Arasteh K, McKnight C, Ringer M, Friedman S. Syringe exchange, injecting and intranasal drug use. Addiction. 2010; 105(1): 155-158.

Syphilis in Drug Users in Low and Middle Income Countries

Genital ulcer disease (GUD), including syphilis, is an important cause of morbidity in low and middle income (LMI) countries and syphilis transmission is associated with HIV transmission. Researchers conducted a literature review to evaluate syphilis infection among drug users in LMI countries for the period 1995-2007. Countries were categorized using the World Bank Atlas method according to 2006 gross national income per capita. Thirty-two studies were included (N=13,848 subjects), mostly from Southeast Asia with some from Latin America, Eastern Europe, Central and East Asia, North Africa and the Middle East but none from regions such as Sub-Saharan Africa. The median prevalence of overall lifetime syphilis (N= 32 studies) was 11.1% (interquartile range: 6.3-15.3%) and of HIV (N=31 studies) was 1.1% (interquartile range: 0.22-5.50%). There was a modest relationship (r=0.27) between HIV and syphilis prevalence. Median syphilis prevalence by gender was 4.0% (interquartile range: 3.4-6.6%) among males (N=11 studies) and 19.9% (interquartile range: 11.4-36.0%) among females (N=6 studies). There was a strong relationship (r=0.68) between syphilis prevalence and female gender that may be related to female sex work. Drug users in LMI countries have a high prevalence of syphilis but data are limited and, in some regions, entirely lacking. Further data are needed on the risks among women, for example, to develop effective interventions that promote safer sex, HIV and STD testing, counseling and education and prevent new syphilis infections and reduce HIV transmission among drug users and their partners in LMI countries. Coffin LS, Newberry A, Hagan H, Cleland CM, Des Jarlais DC, Perlman DC. Int J Drug Policy. 2010; 21(1): 20-27.

Survival Sex Work Involvement as a Primary Risk Factor for Hepatitis C Virus Acquisition in Drug-Using Youths in a Canadian Setting

This study examined whether there were differential rates of hepatitis C virus (HCV) incidence in injecting drug-using youths who did and did not report involvement in survival sex work. Data were derived from two prospective cohort studies of injecting drug users (May 1, 1996, to July 31, 2007) in Vancouver, British Columbia, Canada. Analyses were restricted to HCV antibody-negative youths who completed baseline and at least 1 follow-up assessment. Of 3074 injecting drug users, 364 (11.8%) were youths (aged 14-24 years) with a median age of 21.3 years and a duration of injecting drug use of 3 years. The main exposure variable of interest was survival sex work involvement. The Kaplan-Meier method and Cox proportional hazards regression were used to compare HCV incidence among youths who did and did not report survival sex work. Baseline HCV prevalence was 51%, with youths involved in survival sex work significantly more likely to be HCV antibody positive (60% vs 44%; P = .002). In baseline HCV antibody-negative youths, the cumulative HCV incidence at 36 months was significantly higher in those involved in survival sex work (68.4% vs 38.8%; P < .001). The HCV incidence density was 36.8 (95% confidence interval [CI], 24.2-53.5) per 100 person-years in youths reporting survival sex work involvement at baseline compared with 14.1 (9.4-20.3) per 100 person-years in youths not reporting survival sex work. In multivariate Cox proportional hazards analyses, survival sex work was the strongest predictor of elevated HCV incidence (adjusted relative hazard, 2.30; 95% CI, 1.27-4.15). This study calls attention to the role of unsafe sex among youth who also use injecting drugs as a factor in the acquisition of HCV and potentially of other serious infectious diseases including HIV. There is a critical need for evidence-based social and structural HCV prevention efforts that target youths who use injecting drugs and engage in survival sex work. Shannon K, Kerr T, Marshall B, Li K, Zhang R, Strathdee S, Tyndall M, Montaner J, Wood E. Survival sex work involvement as a primary risk factor for hepatitis C virus acquisition in drug-using youths in a Canadian setting. Arch Pediatr Adolesc Med. 2010; 164(1): 61-65.

Binge Use and Sex and Drug Use Behaviors among HIV(-), Heterosexual Methamphetamine Users in San Diego

This study identified sociodemographic factors, drug using practices, sexual behaviors, and motivational factors associated with binge (a period of uninterrupted) methamphetamine (MA) use among heterosexual MA users. The FASTLANE study provided cross-sectional data collected by audio computer-assisted self-interview (ACASI) between June 2001 and August 2004 from 451 HIV-negative MA users in San Diego, California, who had engaged in unprotected sex and used MA in the previous two months. The study sample was 67.8% male, 49.4% Caucasian, 26.8% African-American, and 12.8% Hispanic with a mean age of 36.6 years; 183 (40.5%) reported binge use in the past 2 months. Compared with non-binge users, binge users of MA were more likely to report risky drug use and sex behaviors and differed in motivations to initiate and currently use MA. The final logistic regression model for binge use included more days of MA use in the last month, ever treated for MA use, injection drug use, higher Beck Depression Inventory score, "experimentation" as a motivation for initiating MA use, and engaging in sex marathons while high on MA. HIV prevention efforts should differentiate and address these differences in motivations for MA use and the associated HIV-risk sex and drug use behaviors as key targets for effective intervention. Cheng W, Garfein R, Semple S, Strathdee S, Zians J, Patterson T. Binge use and sex and drug use behaviors among HIV(-), heterosexual methamphetamine users in San Diego. Subst Use Misuse. 2010; 45(1-2): 116-133.

Evaluating the Use of Respondent-Driven Sampling in a Major Metropolitan Area

This study sought to empirically evaluate respondent-driven sampling (RDS)

recruitment methods, which have been proposed as an advantageous means of surveying hidden populations. The National HIV Behavioral Surveillance system used RDS to recruit 370 injection drug users (IDU) in the Seattle area in 2005 (NHBS-IDU1). Researchers compared the NHBS-IDU estimates of participants' area of residence, age, race, sex, and drug most frequently injected to corresponding data from two previous surveys, the RAVEN and Kiwi Studies, and to persons newly diagnosed with HIV/AIDS and reported from 2001 through 2005. The NHBS-IDU population was estimated to be more likely to reside in downtown Seattle (52%) than participants in the other data sources (22%-25%), to be older than 50 years of age (29% vs. 5%-10%), and to report multiple races (12% vs. 3%-5%). The NHBS-IDU population resembled persons using the downtown needle exchange in age and race distribution. An examination of cross-group recruitment frequencies in NHBS-IDU suggested barriers to recruitment across different areas of residence, races, and drugs most frequently injected. These results indicate that substantial differences in age and area of residence between NHBS-IDU and the other data sources suggest that RDS may not have accessed the full universe of Seattle area injection networks. Further empirical data are needed to guide the evaluation of RDS-generated samples. Burt RD, Hagan H, Sabin K, Thiede H. Evaluating respondent-driven sampling in a major metropolitan area: Comparing injection drug users in the 2005 Seattle area national HIV behavioral surveillance system survey with participants in the RAVEN and Kiwi studies. Ann Epidemiol. 2010; 20(2): 159-167.

Health Outcomes and Costs of Community Mitigation Strategies for an Influenza Pandemic in the United States

The optimal community-level approach to control pandemic influenza is unknown. Researchers estimated the health outcomes and costs of combinations of 4 social distancing strategies and 2 antiviral medication strategies to mitigate an influenza pandemic for a demographically typical US community. They used a social network, agent-based model to estimate strategy effectiveness and an economic model to estimate health resource use and costs and data from the literature to estimate clinical outcomes and health care utilization. They found that, at 1% influenza mortality, moderate infectivity (R(o) of 2.1 or greater), and 60% population compliance, the preferred strategy is adult and child social distancing, school closure, and antiviral treatment and prophylaxis. This strategy reduces the prevalence of cases in the population from 35% to 10%, averts 2480 cases per 10,000 population, costs $2700 per case averted, and costs $31,300 per quality-adjusted life-year gained, compared with the same strategy without school closure. The addition of school closure to adult and child social distancing and antiviral treatment and prophylaxis, if available, is not cost-effective for viral strains with low infectivity (R(o) of 1.6 and below) and low case fatality rates (below 1%). High population compliance lowers costs to society substantially when the pandemic strain is severe (R(o) of 2.1 or greater). The findings show that multilayered mitigation strategies that include adult and child social distancing, use of antivirals, and school closure are cost-effective for a moderate to severe pandemic. Choice of strategy should be driven by the severity of the pandemic, as defined by the case fatality rate and infectivity. Perlroth DJ, Glass RJ, Davey VJ, Cannon D, Garber AM, Owens DK. Health outcomes and costs of community mitigation strategies for an influenza pandemic in the United States. Clin Infect Dis. 2010; 50(2):165-174.

Effectiveness and Cost-Effectiveness of Expanded Antiviral Prophylaxis and Adjuvanted Vaccination Strategies for an Influenza A (H5N1) Pandemic

The pandemic potential of influenza A (H5N1) virus is a prominent public health concern of the 21st century. This study estimated the effectiveness and cost-

effectiveness of alternative pandemic (H5N1) mitigation and response strategies. A compartmental epidemic model was used in conjunction with a Markov model of disease progression, drawing data from the literature and expert opinion. Residents of a U.S. metropolitan city with a population of 8.3 million were the target population, over the lifetime. The interventions involved 3 scenarios: 1) vaccination and antiviral pharmacotherapy in quantities similar to those currently available in the U.S. stockpile (stockpiled strategy), 2) stockpiled strategy but with expanded distribution of antiviral agents (expanded prophylaxis strategy), and 3) stockpiled strategy but with adjuvanted vaccine (expanded vaccination strategy). All scenarios assumed standard non-pharmaceutical interventions. The outcome measures were infections and deaths averted, costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness. The base-case analysis showed that expanded vaccination was the most effective and cost-effective of the 3 strategies, averting 68% of infections and deaths and gaining 404 030 QALYs at $10,844 per QALY gained relative to the stockpiled strategy. Expanded vaccination remained incrementally cost-effective over a wide range of assumptions. The model assumed homogenous mixing of cases and contacts; heterogeneous mixing would result in faster initial spread, followed by slower spread, and interventions were not modeled for children or older adults; the model is not designed to target interventions to specific groups. Results indicate that expanded adjuvanted vaccination is an effective and cost-effective mitigation strategy for an influenza A (H5N1) pandemic. Expanded antiviral prophylaxis can help delay the pandemic while additional strategies are implemented. Khazeni N, Hutton DW, Garber AM, Owens DK. Effectiveness and cost-effectiveness of expanded antiviral prophylaxis and adjuvanted vaccination strategies for an influenza A (H5N1) pandemic. Ann Intern Med. 2009; 151(12): 840-853.

Parsing Social Network Survey Data from Hidden Populations Using Stochastic Context-Free Grammars

Human populations are structured by social networks in which individuals tend to form relationships based on shared attributes. Certain attributes that are ambiguous, stigmatized or illegal can create a hidden population, so-called because its members are difficult to identify. Many hidden populations are also at an elevated risk of exposure to HIV and other infectious diseases. Consequently, public health agencies are adopting modern survey techniques that traverse social networks in hidden populations by soliciting individuals to recruit their peers, e.g., respondent-driven sampling (RDS). The concomitant accumulation of network-based epidemiological data, however, is rapidly outpacing the development of computational methods for analysis. Moreover, current analytical models rely on unrealistic assumptions, such as that the traversal of social networks can be modeled by a Markov chain rather than a branching process. In this analysis, researchers developed a new methodology based on stochastic context-free grammars (SCFGs) that are well-suited to modeling tree-like structure of the RDS recruitment process. They applied this methodology to an RDS case study of injection drug users (IDUs) in Tijuana, MŽxico, a hidden population at high risk of blood-borne and sexually-transmitted infections (i.e., HIV, hepatitis C virus, syphilis). Survey data were encoded as text strings that were parsed using a customized implementation of the inside-outside algorithm in a publicly-available software package (HyPhy), which uses either expectation maximization or direct optimization methods and permits constraints on model parameters for hypothesis testing. The researchers identified significant latent variability in the recruitment process that violates assumptions of Markov chain-based methods for RDS analysis: firstly, IDUs tended to emulate the recruitment behavior of their own recruiter; and secondly, the recruitment of like peers (homophily) was dependent on the number of recruits. These findings indicate that SCFGs provide a rich probabilistic language that can articulate complex latent structure in survey

data derived from the traversal of social networks. Such structure—that has no representation in Markov chain-based models—can interfere with the estimation of the composition of hidden populations if left unaccounted for, raising critical implications for the prevention and control of infectious disease epidemics. Poon A, Brouwer K, Strathdee S, Firestone-Cruz M, Lozada R, Pond S, Heckathorn D, Frost S. Parsing social network survey data from hidden populations using stochastic context-free grammars. PLoS One. 2009; 4(9): 6777-6786.

The Reliability and Validity of Drug Users' Self Reports of Amphetamine Use among Primarily Heroin and Cocaine Users

Relatively few studies have addressed the psychometric properties of self-report measures of amphetamine use. This study examines the reliability and validity of the Risk Behavior Assessment's (RBA) lifetime and recent amphetamine-use questions. To evaluate validity, 4027 out-of-treatment primarily cocaine and heroin users provided urine samples that were compared to self-report data; to evaluate reliability, 218 completed the RBA at two time points, 48h apart. In the overall sample, self-reports demonstrated moderately high validity, with a 95% accuracy rate (kappa=.54). When analysis was restricted to recent amphetamine users validity was lower (71.5% accuracy; kappa=.41). Test-retest data indicated good reliability for self-reports of ever having used amphetamine (kappa=.79), and amphetamine use in the past 30 days (.75<r (.75<r<.91). Out-of-treatment drug users provided accurate self-reports of amphetamine use. Reliable and valid measures are essential for describing and predicting trends in amphetamine use, evaluating the effectiveness of interventions, and developing policies and programs. Napper L, Fisher DG, Johnson ME, Wood M. The reliability and validity of drug users' self reports of amphetamine use among primarily heroin and cocaine users. Addict Behav. 2010; 35(4): 350-354.

Examining Factorial Structure and Measurement Invariance of the Brief Symptom Inventory (BSI)-18 among Drug Users

The purpose of this study was to examine the factorial structure of the Brief Symptom Inventory 18 (BSI-18) and test its measurement invariance among different drug using populations. A total sample of 710 drug users was recruited using respondent-drive sampling (RDS) from three states: Ohio (n=248), Arkansas (n=237), and Kentucky (n=225). The results of confirmatory factor analysis (CFA) showed: 1) the BSI-18 has a three-factor structure (somatization, depression, and anxiety) with an underlying second-order factor (global severity index of distress); and 2) its factorial structure and metric (factor loadings) are invariant across populations under study. However, the scalars (intercepts) of the BSI-18 items are not invariant, and the means of the latent factors also varied across populations. The findings provide evidence of a valid factorial structure of the BSI-18 that can be readily applied to studying drug using populations. Wang J, Kelly BC, Booth BM, Falck RS, Leukefeld C, Carlson RG. Examining factorial structure and measurement invariance of the Brief Symptom Inventory (BSI)-18 among drug users. Addict Behav. 2010; 35(1): 23-29.

Opt-out Testing for Stigmatized Diseases: A Social Psychological Approach to Understanding the Potential Effect of Recommendations for Routine HIV Testing

Few studies have examined experimentally whether an opt-out policy will increase testing rates or whether this strategy is especially effective in the case of stigmatized diseases such as HIV. In this research, one study using a 2 x 2 factorial design asked 118 participants (63 men, 55 women, average age 23

years) to make moral judgments about a person's decision to test for stigmatized diseases under an opt-in versus an opt-out policy. In another study, a 2 x 2 factorial design measuring testing rates explored whether opt-out methods reduce stigma and increase testing for stigmatized diseases in a group of 79 undergraduates (32 men, 47 women, average age 19.8 years). The first study found that getting HIV tested draws suspicion regarding moral conduct in an opt-in system, whereas not getting tested draws suspicion in an opt-out system. The second study found that an opt-out policy may increase testing rates for stigmatized diseases and lessen the effects of stigma in people's reluctance to test. These findings suggest that a social psychological approach to health services can be used to show how HIV testing policies can influence both the stigmatization associated with testing and participation rates. An understanding of how HIV testing policies may affect patient decision making and behavior is imperative for creating effective testing policies. Young SD, Monin B, Owens DK. Opt-out testing for stigmatized diseases: a social psychological approach to understanding the potential effect of recommendations for routine HIV testing. Health Psychol. 2009; 28(6): 675-681.

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Research Findings - Prevention Research

Multidimensional Treatment Foster Care for Preschoolers Reduces Permanent Placement Failures

The aims of the present study were to examine the effects of a therapeutic intervention for foster preschoolers with histories of placement instability on permanency outcomes and to determine whether the intervention's effectiveness on these outcomes varied based on prior maltreatment experiences. Permanency outcomes for 52 children who had experienced 4 or more placements prior to study entry (n = 29 intervention condition (MTFC-P); n = 23 regular foster care condition (RFC)) were examined through 24 months post-study entry. Data for the present study came from a subset of children in a randomized clinical trial to evaluate the MTFC-P program. The sample for the larger study consisted of 117 3- to 5-year-old foster children entering new foster placements and 60 nonmaltreated community children from low-income families. The authors operationalized the concept of prior placement instability in the present study as a child having experienced four or more placements prior to study entry. This produced a sample of 52 children (27 boys and 25 girls; 23 RFC and 29 MTFC-P) for the present study. On average across the two study conditions, the children had experienced approximately six transitions (M = 5.79, SD = 1.66), and 12 children (23%) had experienced seven or more transitions prior to entering the study. Age at first placement ranged from birth to 5 years with a mean of 2.42 years (SD = 1.32). There was no significant difference in age at first placement between groups. The children were predominantly European Americans (90.4%), which was representative of the geographical region in which the study was conducted. There was no significant group difference in terms of child ethnicity. The results indicated no group differences in permanency attempt rates but more than double the rate of successful permanency attempts for the intervention condition. The findings indicated that systematic interventions have the potential to impact permanency outcomes among children with prior instability. Fisher PA, Kim HK, Pears KC. Effects of multidimensional treatment foster care for preschoolers (MTFC-P) on reducing permanent placement failures among children with placement instability. Children and Youth Services Review. 2009; 31: 541-546.

Two-year Follow-up of Computer Delivered Program for Preventing Substance Use among Adolescent Girls

This study examined the two-year follow-up impact of a computer-delivered program for preventing substance use among adolescent girls. Nine hundred and sixteen girls aged 12.76 +/- 1.0 years and their mothers were assigned to an intervention arm or to a test-only control arm. Intervention-arm dyads engaged in exercises to improve the mother-daughter relationship, build girls' substance use prevention skills, and reduce associated risk factors. Study

Planned Meetings

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outcomes were girls' and mothers' substance use and mediator variables related to girls' substance use risk and protective factors. The study was conducted between September 2006 and February 2009 with participants from greater New York City, including southern Connecticut and eastern New Jersey. At 2-year follow-up and relative to control-arm girls, intervention-arm girls reported lower relevant risk factors and higher protective factors as well as less past 30-day use of alcohol ($p < 0.006$), marijuana ($p < 0.016$), illicit prescription drugs ($p < 0.03$), and inhalants ($p < 0.024$). Intervention-arm mothers showed more positive 2-year outcomes than control-arm mothers on variables linked with reduced risks of substance use among their daughters (e.g., communication with their daughters, observance of family rituals, monitoring of their daughters' out-of-home activities) and mothers reported lower rates of weekly alcohol consumption ($p < 0.0001$). This computer-delivered prevention program for adolescent girls and their mothers was effective in changing girls' risk and protective factors in a positive direction, as well as in impacting both girls' and mothers' substance use behavior in desired ways. These findings lend support to the potential of gender-specific, parent-involvement, and computerized approaches to preventing substance use among early adolescent girls. Schinke S, Fang L, Cole K. Computer-delivered, parent-involvement intervention to prevent substance use among adolescent girls. Prev Med. 2009; 49(5): 429-435.

Effectiveness of the BRAVE Intervention

This article examines the effectiveness of a career-oriented intervention for preventing involvement with alcohol, tobacco, and other drugs (ATODs) and violence and for promoting resilient behavior among eighth-grade, African American middle school students (N = 178) through the implementation of the Building Resiliency and Vocational Excellence (BRAVE) Program. Students were randomly assigned to either the intervention or control group. Students in the intervention condition participated in the school-based BRAVE Program and the standard public school curriculum. Comparison students participated only in the standard curriculum. Alcohol, tobacco, and other drug use and violent behavior were assessed for students at baseline, post-test, and one-year follow up (one year after baseline). Results revealed a beneficial effect of the intervention on participants frequency of use of alcohol ($p < .04$) and marijuana ($p < .05$), but no effect for violent behavior. Griffin J, Holliday R, Frazier E, Braithwaite R. The BRAVE (Building Resiliency and Vocational Excellence) Program: Evaluation Findings for a career-oriented substance abuse and violence preventive intervention. J Health Care Poor Underserved. 2009; 20(3): 798-816.

Brief Multiple Behavior Intervention for College Students has Sustained Effects on 12-month Follow-up

This study examined whether 3-month outcomes of a brief image-based multiple behavior intervention on health habits and health-related quality of life for college students were sustained at 12-month follow-up without further intervention. A randomized control trial was conducted with 303 undergraduates attending a public university in southeastern US (average age 19.2). Participants were randomized to receive either a brief intervention (a brief tailored consultation and fitness goal plan) or usual care control (print materials from a trained fitness specialist). Baseline, 3-month, and 12-month data were collected during fall of 2007. Repeated-measures MANOVAs were used to evaluate baseline and 12-month data to test whether positive outcomes at 3 months were maintained at the 12-month follow-up. A significant omnibus MANOVA interaction effect was found for health-related quality of life, $p = 0.01$, with univariate interaction effects showing fewer days of poor spiritual health, social health, and restricted recent activity, p's < 0.05, for those receiving the brief intervention. Significant group by time interaction effects were found for driving after drinking, $p = 0.04$, and moderate exercise,

p = 0.04, in favor of the brief intervention. Effect sizes typically increased over time and were small except for moderate size effects for social health-related quality of life. This study found that 3-month outcomes from a brief image-based multiple behavior intervention for college students were partially sustained at 12-month follow-up. Health-related quality of life effects, moderate exercise and driving after drinking effects were maintained. However, effects on alcohol use, marijuana use, and amount of sleep were not sustained over time. The findings from this study are critical to understanding the degree to which short-term brief intervention outcomes are sustained, and whether or not boosters may be needed to bolster specific behavioral degradations over time. Werch C, Moore M, Bian H, DiClemente C, Huang I, Ames S, Thombs D, Weiler R, Pokorny S. Are effects from a brief multiple behavior intervention for college students sustained over time? Prev Med. 2010; 50(1-2): 30-34.

Protective Families are Less Protective for Youth in High-risk Environment

This study used data from a sample of 6th to 12th grade students (N = 48,641, 51% female), nested in 192 Pennsylvania schools, to determine if the influence of family-based protective factors varied across different school contexts. Hierarchical logistic regression models were used to examine the effects of individual-level family protective factors, relative to school-level aggregates of the same factors, on recent (past 30 days) use of cigarettes, alcohol, and marijuana. Cross-level interactions indicated that the effect of the student's level of family protection, relative to other students in their school, differed depending on the aggregated school level of family protection. The results suggested that the benefit of belonging to a well-functioning family was more influential for students attending schools characterized by higher-than-average aggregated levels of protection compared to students attending schools of lower-than-average protection. Thus, family-level factors offered less protection for students in relatively high-risk school contexts. These results were consistent with a protective-reactive interaction and suggest that a thorough understanding of adolescent substance use must consider the complex interplay among adolescents, their families, and their social environments. Cleveland MJ, Feinberg ME, Greenberg MT. Protective families in high- and low-risk environments: implications for adolescent substance use. J Youth Adolesc. 2010; 39(2): 114-126.

Marijuana Use Among Teens Can Be Reduced with Parental Monitoring

Parental monitoring is commonly recognized as an important protective factor against risky adolescent behaviors. In this meta-analytic review, associations of adolescents' perceptions of parental monitoring with adolescent marijuana use were collected and quantified across 25 independent samples from 17 empirical studies involving 35,367 unique participants. Applying a random-effects model, the average magnitude of effect was r = -.21. The association was significantly stronger in female-only samples and when parental monitoring was defined purely in terms of parental knowledge of the child's whereabouts, activities, and relations. Cross-sectional (r = -.23) and longitudinal studies (r = -.10) disclosed significant effect sizes. To assess publication bias, a file-drawer analysis indicated that 7,358 studies of nil effect size would be necessary to render the association of parental monitoring and reduced marijuana usage nonsignificant. This review suggests that parents are far from irrelevant, even when it comes to an illegal and often secretive behavior on the part of their adolescent children. Information derived from this quantitative synthesis may prove useful in marijuana-based prevention programs and campaigns targeting parents, and might offer insight on how to alleviate a risky behavior that is all too common at an important transitional stage between childhood and

adulthood. Lac A, Crano WD. Meta-analytic review reveals the reliable linkage of parental monitoring with adolescent marijuana Use. Perspect Psychol Sci. 2009; 4(6): 578-586.

Perceptions of Parents' Alcohol Use and Permissibility of Teen Alcohol Use Predicts College Students' Drinking Behaviors

This study examined the impact of parental modeled behavior and permissibility of alcohol use in late high school on the alcohol use and experienced negative drinking consequences of college students. Two-hundred ninety college freshmen at a large university were assessed for perceptions of their parents' permissibility of alcohol use, parents' alcohol-related behavior, and own experienced negative consequences associated with alcohol use. Results indicate that parental permissibility of alcohol use is a consistent predictor of teen drinking behaviors, which was strongly associated with experienced negative consequences. Parental modeled use of alcohol was also found to be a risk factor, with significant differences across the gender of the parents and teens. For example, the effect of paternal acceptability differed by gender, such that high levels of paternal acceptability appeared to function as a weak protective factor for male students and as a moderate risk factor for female students. The effect of maternal modeled drinking behavior also differed by gender, such that maternal drinking was riskier for women. Preventive efforts for college students' drinking should consider the impact of parents on student behavior. Abar C, Abar B, Turrisi R. The impact of parental modeling and permissibility on alcohol use and experienced negative drinking consequences in college. Addict Behav. 2009; 34(6-7): 542-547.

Intermediate Effects of a Community Preventive Intervention to Reduce Adolescent Use of Harmful Legal Products

This study describes preliminary results from a preventive intervention to reduce the use of Harmful Legal Products (HLPs) such as inhalants and over the counter drugs, among 5th through 7th grade students in three Alaskan rural communities. The intervention had two primary components, an environmental strategy (ES) to reduce access to HLPs at home, in schools, and from retail outlets and a school-based curriculum intended to enhance knowledge about HLP use and problems and improve refusal skills and assertiveness (ThinkSmart). Pretest surveys were given in classrooms in each school, the ES and ThinkSmart interventions were fielded, then a posttest was given one year later. Data were collected from 5th, 6th and 7th grade students in all schools in all three communities assessing knowledge of HLP risks, use of refusal skills, assertiveness, peer attitudes and use of HLPs, perceived availability of HLPs, and intent to use and avoid use of HLPs in the future. The student survey was administered to 336 students in wave 1 and 286 students in wave 2. Of those students who had parental consent to participate in the survey, approximately 90% completed the survey at each wave. A simple pretest - post-test no control design enabled preliminary tests of program effects on intermediate variables related to HLP use. Evidence was found for significant increases in knowledge about HLP use and risks and decreases in perceived availability of HLP products in the home and at school. The results of this study provide encouragement to pursue mixed environmental and school-based strategies for the reduction of HLP use among young people in these Alaskan rural communities. The absence of a control group by which to assess preliminary effects on intermediate variables should lend some skepticism to these observed program effects. Gruenwald P, Johnson K, Shamblem S, Ogilvie K, Collins D. Reducing adolescent use of harmful legal products: intermediate effects of a community prevention intervention. Subst Use Misuse. 2009; 44 (14): 2080-2098.

A Model for Mindfulness-based Parenting Interventions

This paper introduces a model of mindful parenting as a framework whereby parents intentionally bring moment-to-moment awareness to the parent-child relationship. This is done by developing the qualities of listening with full attention when interacting with their children, cultivating emotional awareness and self-regulation in parenting, and bringing compassion and nonjudgmental acceptance to their parenting interactions. First, the theoretical and empirical literature on mindfulness and mindfulness-based interventions are outlined. Next, an operational definition of mindful parenting as an extension of mindfulness to the social context of parent-child relationships is presented. Implications of mindful parenting for the quality of parent-child relationships, particularly across the transition to adolescence are discussed, along with the literature on the application of mindfulness in parenting interventions. Finally, an example of the integration of mindful parenting into a well-established, evidence-based family prevention program is presented, with recommendations for future research on mindful parenting interventions. Duncan L, Coatsworth J, Greenberg M. A model of mindful parenting: implications for parent-child relationships and prevention research. Clin Child Fam Psychol Rev. 2009; 12(3): 255-270.

Development Process for a Mindfulness-based Parenting Intervention

The purpose of the present study was to conduct a small pilot study to test the acceptability of a new model for family-focused drug prevention programs for families of early adolescents. An existing evidence-based behavioral intervention, the Strengthening Families Program: For Parents and Youth 10-14 (SFP), was adapted to include concepts and activities related to mindfulness and mindful parenting (an extension of mindfulness to the interpersonal domain of parent-child relationships). The foundation for this innovative intervention approach stems from research on the effects of mind-body treatments involving mindfulness meditation and the function of stress and coping in relation to parenting and parent well-being. One group of families (n=5 families; 9 adult participants), recruited through a local school district, participated in a seven-week pilot of this mindfulness-enhanced version of SFP. Results of a mixed-method implementation evaluation suggest that the new intervention activities were generally feasible to deliver, acceptable to participants, and perceived to yield positive benefits for family functioning and parent psychological well-being. The next phase of this research will involve curriculum refinement based upon results of this initial study, and a larger pilot efficacy trial. Duncan L, Coatsworth J, Greenberg M. Pilot study to gauge acceptability of a mindfulness-based, family-focused preventive intervention. J Prim Prev. 2009; 30(5): 605-618.

Indiscriminate Friendliness among Foster Children

The willingness to approach and interact with unfamiliar adults in a familiar fashion (e.g., making personal comments to, initiating physical contact with, and being willing to leave with the adult) is a pattern of behavior that has been noted in children who have had early adverse care experiences such as maltreatment and the absence of a consistent caregiver. This behavior has been variously called indiscriminate friendliness. Indiscriminate friendliness is well documented in children adopted internationally following institutional rearing but is less studied in maltreated foster children. Precursors and correlates of indiscriminate friendliness were examined in 93 preschool-aged maltreated children residing in foster care and 60 age-matched, nonmaltreated children living with their biological parents. All children were between 3 and 6 years of age. The foster care (FC) and community control (CC) groups did not

differ on mean child age, gender, or ethnicity. Mean age at baseline assessment was 4.45 years in the FC group and 4.33 years in the CC group. Boys made up 52% of the FC group and 53% of the CC group. Measures included parent reports, official case record data, and standardized laboratory assessments. Foster children exhibited higher levels of indiscriminate friendliness than nonmaltreated children. Inhibitory control was negatively associated with indiscriminate friendliness even after controlling for age and general cognitive ability. Additionally, the foster children who had experienced a greater number of foster caregivers had poorer inhibitory control, which was in turn associated with greater indiscriminate friendliness. The results indicate a greater prevalence of indiscriminate friendliness among foster children and suggest that indiscriminate friendliness is part of a larger pattern of dysregulation associated with inconsistency in caregiving. Pears KC, Bruce J, Fisher PA, Kim, HK. Indiscriminate friendliness in maltreated foster children. Child Maltreat. 2010; 15(1): 64-75.

Distribution of Risk Exposure among High Risk Young Children

This descriptive study examined the distribution of risk factors in a sample that was selected on the basis of existing potential for difficult child behaviors. Specifically, the study focused on whether exposure to risk factors was distributed equally across different contexts of ethnicity, locality, and child gender. Participants included 731 mother-child dyads, with a 2-year-old child, recruited from WIC Programs in rural, suburban, and urban localities, who were participating in a randomized prevention trial of a brief family-based intervention for toddler-age children at risk for behavior problems linked to later drug use. Cumulative risk indices were constructed using neighborhood, family, and individual risk factors. The findings generally revealed that African American children and children in urban localities were exposed to higher numbers of risk factors and cumulative risk in relation to other ethnic children and localities. On the other hand, Caucasian children expressed higher levels of vulnerabilities to risk for internalizing behaviors than did other children. The results highlight the importance to prevention research of understanding differences in context-specific rates of risk exposure and vulnerability. Wilson M, Hurtt C, Shaw D, Dishion T, Gardner F. Analysis and influence of demographic and risk factors on difficult child behaviors. Prev Sci. 2009; 10(4): 353-365.

Early Predictors of Adolescent Depression

This study examined the longitudinal relationship of childhood predictors to adolescent depression 7 years later. The sample consisted of 938 students who were involved in a larger study that started in 1993. Data collected from parents, teachers, and youth self-reports on early risk factors when students were in 1st and 2nd grade were compared to adolescent self-reported depression. Regression analyses were conducted with each risk factor separately and combined, while also examining gender and the gender x risk factor interaction. Results showed that individual level characteristics such as depression, anxiety, and antisocial behavior were predictive of later depression. Gender differences were found among the longitudinal risk factors for depression. Mazza JJ, Abbott RD, Fleming CB, Harachi TW, Cortes RC, Park J, Haggerty KP, Catalano RF. Early predictors of adolescent depression: a 7-year longitudinal study. The Journal of Early Adolescence. 2009; 29(5): 664-692.

Comparing Self Report and Biological Assessment of Drug Use in Young Adults Attending Electronic Music Dance Events

Most information on the prevalence of drug use comes from self-report surveys. The sensitivity of such information is cause for concern about the

accuracy of self-report measures. In this study, self-reported drug use in the last 48 hr is compared to results from biological assays of saliva samples from 371 young adults entering clubs in both east coast and west coast locations. The relationship between self-reports and drug presence in oral fluid was determined for cocaine, marijuana, and amphetamine. For approximately 85% of participants, self-report responses regarding 48 hour drug use matched the results of the biological assay. Among those whose reports did not match their assays, there were twice as many who said they did not use drugs recently but tested positive as those who said they did use drugs but tested negative. Notably, forty-one percent of the participants with drugs detected in their oral fluids reported no use in the last 48 hr. The underreporting was greatest for cocaine (67%) and amphetamines (52%). This research suggests that a substantial portion of drug users will deny use. Johnson M, Voas R, Miller B, Holder H. Predicting drug use at electronic music dance events: self-reports and biological measurement. Eval Rev. 2009; 33(3): 211-225.

The Power of Drugs, the Nature of Support, and their Impact on Homeless Youth

The purpose of this study was to explore homeless youths' perspectives on the power of drugs in their lives, the preferred type of drugs used, barriers to treatment, and strategies to prevent drug initiation and abuse. This was a descriptive, qualitative study using focus groups with a purposeful sample of 24 drug-using homeless youth, aged 17-25. The results provided insight into the lives of these youth. The most commonly used drugs were marijuana and alcohol. Reported reasons for drug use were parental drug use, low self-esteem, and harsh living conditions on the streets. Barriers to treatment were pleasure/enjoyment of the drug, physical dependence, and non-empathetic mental health providers. Suggested strategies to prevent initiation and abuse of drugs were creative activities, such as art, sports, and music. This inquiry provides useful insight into understanding the motivation of homeless youth for using drugs and strategies that may be helpful for intervention and prevention. Hudson A, Nyamathi A, Slagle A, Greengold B, Griffin D, Khalilifard F, Gedzoff D, Reid C. The power of the drug, nature of support, and their impact on homeless youth. J Addict Dis. 2009; 28(4): 356-365.

Review of Truancy Intervention Programs: Challenges and Innovations to Implementation

School truancy, particularly in primary and secondary schools, represents a serious issue deserving attention in communities across the nation. Unfortunately, with few exceptions, truancy has not received significant attention by criminologists. The authors provide a general review of the key issues learned from implementation of various truancy reduction programs in the United States. Highlighted are several model truancy programs in various settings, their effectiveness, and the challenges they faced during the implementation process. The programs highlighted include school-based, community-based and school- and community-based, court-based programs, and programs offered in other settings. The authors summarize challenges that present obstacles to implementing successful truancy programs. These challenges included program barriers related to funding and staffing. Additional challenges identified include family mobility, which makes it difficult to maintain contact information on students and parents and continued engagement of families; ineffective communication and/or cooperation among program staff, parents, and school or community officials; different definitions of truancy used by programs; and, lack of a continuum of care. Finally, the authors describe efforts that are underway in Hillsborough County, Florida, in implementing an effective continuum of service for truant youth and their families. The authors discuss enhancements to the Hillsborough County Juvenile Assessment Center (JAC) Truancy Intake Center (TIC), which include

an increased number of truant youth being brought to the truancy center, where their psychosocial problems, including school issues, can be identified; follow-up involvement in in-home intervention services; and for youth attending schools with neighborhood accountability boards (NABs), longer-term case management and referral services. Descriptive data on 883 truant youth processed at the TIC during the 2007-2008 school year are presented. The youth averaged younger than 14 years of age and most were in grades seven through nine (77%). Nearly 30% of the youth had an arrest record including at least one felony arrest, and of the youth who completed the Personal Experience Screening Questionnaire (PESQ), 23% reported moderate to higher level of drug involvement in the past year. Dembo R, Gulledge LM. Truancy intervention programs: challenges and innovations to implementation. Crim Justice Policy Rev. 2009; 20(4): 437-456.

Influence of Alcohol Use Expectancies on Risky Sex Outcomes

Higher levels of alcohol use have consistently been related to higher rates of sexual risk taking; however, it is not clear whether this relationship is causal. This study examined the concurrent and predictive associations among alcohol use-related sexual enhancement expectancies, drinking alcohol before engaging in sex, and casual sex during the transition into emerging adulthood and whether these associations differed for men and women. Data came from 590 men and women who were interviewed 3 times at 6-month intervals after high school. Growth curve analyses indicated that alcohol-related sexual enhancement expectancies were related to casual sex indirectly through drinking before sex but did not predict change in either of these behaviors. However, increases in drinking before sex predicted increases in casual sex over time. The findings provide some support for prevention programs that focus on alcohol-related sexual expectancies to reduce sexually transmitted illnesses among emerging adults. White H, Fleming C, Catalano R, Bailey J. Prospective associations among alcohol use-related sexual enhancement expectancies, sex after alcohol use, and casual sex. Psychol Addict Behav. 2009; 23(4): 702-707.

Adolescent Alcohol Expectancies Predict Adult Alcohol Use

Alcohol expectancies are strong concurrent predictors of alcohol use and problems. The current study addressed their unique power to predict from adolescence to midlife. Longitudinal data from the ongoing national British Cohort Study 1970 (N = 2146, 59.8% female) were used to predict alcohol use and misuse in the mid-30s by alcohol expectancies reported in adolescence. Individuals born in 1 week in April 1970 were assessed at birth with a 96.7% response rate and in ongoing follow-ups using a multi-method, multi-informant approach. Hierarchical ordinary least-squares (OLS) regression analyses were used to predict concurrent (age 16) and future (ages 26 and 35) alcohol use, and hierarchical logistic regression analyses predicted lifetime and past year alcohol misuse (assessed at age 35). Cohort members with more positive alcohol expectancies at age 16 reported greater alcohol quantity concurrently, increases in alcohol quantity relative to their peers between ages 16 and 35, and a higher likelihood of lifetime and previous year alcohol misuse at age 35, independent of gender, social class in family of origin, age of alcohol use onset, adolescent delinquent behavior and age 16 exam scores. Alcohol expectancies were strong proximal predictors of alcohol use and predicted relative change in alcohol use and misuse across two decades into middle adulthood. The findings are important for understanding early determinants of adult drinking patterns and for identifying potential opportunities for intervention. Patrick M, Wray-Lake L, Finlay A, Maggs J. The long arm of expectancies: adolescent alcohol expectancies predict adult alcohol use. Alcohol. 2010; 45(1): 17-24.

Trends in Adolescent Environmental Attitudes, Beliefs, and

Behaviors across Three Decades

Since the Environmental Movement began, adolescents' views have been largely ignored in studies of public opinion. This article presents findings from a descriptive analysis of trends in the environmental attitudes, beliefs, and behaviors of high school seniors from 1976 to 2005. The authors used data from the Monitoring the Future (MTF) study, a national survey of high school seniors conducted annually since 1976 (Johnston, Bachman, & O'Malley, 2006; see also www.monitoringthefuture.org). The sample is selected using a multistage random sampling from public and private high schools across the nation. The datasets contain sample weights which were used to ensure that results are representative of American high school seniors. The sample size of nearly 100,000 provided sufficient statistical power for detecting even weak relationships. Time trends for all items considered readily reached statistical significance in ordinal logistic models treating year as a categorical variable and controlling for respondents' sex, race, parental education, and educational aspirations ($_x2 > 500$, $df = 29$, $p < .001$). Across a range of indicators, environmental concerns of adolescents show increases during the early 1990s and declines across the remainder of the three decades. Declining trends in reports of personal responsibility for the environment, conservation behaviors, and the belief that resources are scarce are particularly noteworthy. Across all years, findings reveal that youth tended to assign responsibility for the environment to the government and consumers rather than accepting personal responsibility. Recent declines in environmental concerns for this nationally representative sample of youth signal the need for a renewed focus on young people's views and call for better environmental education and governmental leadership. Wray-Lake L, Flanagan CA, Osgood DW. Examining trends in adolescent environmental attitudes, beliefs, and behaviors across three decades. Environ Behav. 2010; 42(1): 61-85.

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Research Findings - Research on Behavioral and Combined Treatments for Drug Abuse

Psychometric Properties of the Contingency Management Competence Scale

Contingency management interventions have been found to be particularly efficacious for treating drug addiction. However, most therapists in clinical trials of contingency management have been highly trained and well supervised. Moreover, implementation experts agree that transfer of evidence based treatments to community settings requires training as well as reliable and valid measurement of training effects and feedback about progress to ensure successful implementation. As part of a clinical trial on therapist training in prize-based contingency management, a Contingency Management Competence Scale was developed and its reliability and validity were examined. Initial scale items were drawn from tapes of sessions from past trials and manuals on contingency management. Factor analysis showed the final items loaded on two factors. The first factor concerned general session skillfulness, especially conveying confidence in the participants' abilities and praising their attempts. The second factor was specific to contingency management prize drawing tasks. Coders used the scale to rate therapy tapes from the trial and inter-rater reliability was established. Concurrent validity was measured by correlating therapeutic alliance and competence scores on the general skillfulness subscale. Predictive validity was examined by correlating each factor with duration of continuous abstinence. The general factor, but not the CM drawing factor, predicted duration of continuous abstinence. This is significant because it suggests that therapist attention to client efforts and praise are important for achieving optimal outcomes. Overall this study is important because it is the first to establish a tool for provider training to facilitate clinic implementation of a brief CM intervention. It is also important because it shows concrete therapist behaviors beyond rewarding abstinence including praising participants' efforts and conveying confidence in the participants' abilities make a measurable difference in outcome. Petry NM, Alessi SM, Ledgerwood DM, Sierra S. Psychometric properties of the Contingency Management Competence Scale. Drug Alcohol Depend. 2010 Feb 9. [Epub ahead of print].

Group-Based Contingency Management Reduces HIV Viral Loads

This study examined how a group-based contingency management (CM) intervention that focused on reinforcing health behaviors in HIV positive cocaine or opioid users compared with 12-step facilitation therapy (TS) groups over 24 weeks. To mitigate potential effects of incentives on participation, both groups received $10 per session and about $2 per urine sample and $25 for follow-up assessment participation. During the treatment period, patients in

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the CM group also received chances to win prizes contingent upon completing health activities and submitting substance-free specimens for which they earned $260 on average. Although CM participants and TS did not submit different proportions of negative samples, CM participants on average achieved a higher number of consecutive weeks drug free. Additionally, from pre- to post treatment, CM participants showed greater reductions in viral loads and HIV-risk behaviors than did TS participants, but these effects were not maintained throughout the follow-up period. This study suggests group-based CM can have positive effects in HIV-positive substance abusers with respect to viral load. However more research is needed to determine how to stretch the intervention effects beyond the active intervention timeframe. Petry NM, Weinstock J, Alessi SM, Lewis MW, Dieckhaus K. Group-based randomized trial of contingencies for health and abstinence in HIV patients. J Consult Clin Psychol. 2010 Feb; 78(1): 89-97.

Randomized Controlled Trial of Behavioral Activation Smoking Cessation Treatment for Smokers with Elevated Depressive Symptoms

Investigators at the University of Maryland conducted this pilot study to examine whether a behavioral activation treatment for smoking (BATS) can enhance cessation outcomes. A sample of 68 adult smokers with mildly elevated depressive symptoms (M = 43.8 years of age; 48.5% were women; 72.7% were African American) seeking smoking cessation treatment were randomized to receive either BATS paired with standard treatment (ST) smoking cessation strategies including nicotine replacement therapy (n = 35) or ST alone including nicotine replacement therapy (n = 33). BATS and ST were matched for contact time and included 8 sessions of group-based treatment. Quit date was assigned to occur at Session 4 for each treatment condition. Across the follow-ups over 26 weeks, participants in BATS reported greater smoking abstinence (adjusted odds ratio = 3.59, 95% CI [1.22, 10.53], p = .02) than did those in ST. Participants in BATS also reported a greater reduction in depressive symptoms (B = -1.99, SE = 0.86, p = .02) than did those in ST. Results suggest BATS is a promising intervention that may promote smoking cessation and improve depressive symptoms among underserved smokers of diverse backgrounds. Macpherson L, Tull MT, Matusiewicz AK, Rodman S, Strong DR, Kahler CW, Honko DR, Zvolensky MJ, Brown RA, Lejuez CW. Randomized controlled trial of behavioral activation smoking cessation treatment for smokers with elevated depressive symptoms. J Consult Clin Psychol. 2010 Feb; 78(1): 55-61.

Mechanisms of Change in Extended Cognitive Behavioral Treatment for Tobacco Dependence

Dr. Hendricks and colleagues at the University of California, San Francisco conducted this study to evaluate potential mediators of an extended cognitive behavioral smoking cessation intervention. Data were analyzed from a randomized clinical trial of smoking cessation among older smokers (³50 years old) receiving Standard Treatment (N=100) or extended cognitive behavioral treatment (N=99). Analyses revealed that extended CBT increased abstinence self-efficacy over the first 52 weeks post cessation. This effect, in turn, was positively associated with 7-day point prevalence abstinence at week 64 while controlling for treatment condition, and eliminated the independent effect of treatment condition on abstinence. The test of mediation indicated a significant effect, and abstinence self-efficacy accounted for 61% to 83% of the total effect of treatment condition on smoking abstinence. Results failed to support a meditational role of negative affect, abstinence-specific social support, or motivation to quit. The results of the present study are consistent with theories of relapse and studies of more time-limited interventions, and underscore the importance of abstinence self-efficacy in achieving long-term abstinence from

cigarettes. Hendricks PS, Delucchi KL, Hall SM. Mechanisms of change in extended cognitive behavioral treatment for tobacco dependence. Drug Alcohol Depend. 2010 Jan 20. [Epub ahead of print].

The Day-to-Day Process of Stopping or Reducing Smoking: A Prospective Study of Self-Changers

Investigators at the University of Vermont conducted the current study to examine the day-to-day process preceding a quit or reduction attempt in addition to the daily process after a failure to quit or reduce. Participants were 220 adult daily cigarette smokers who planned to quit abruptly, to quit gradually, to reduce only, or to not change on their own. Participants called a voice mail system each night for 28 days to report cigarette use for that day and their intentions for smoking for the next day. No treatment was provided. Three main findings emerged: (a) The large majority of participants did not show a simple pattern of change but rather showed a pattern of multiple transitions among smoking, abstinence, and reduction over a short period of time; (b) most of those who reported an initial goal to quit abruptly actually reduced; and (c) daily intentions to quit strongly predicted abstinence, while daily intentions to reduce weakly predicted reduction. Investigators concluded that the day-to-day process of attempts to change smoking among nontreatment seekers is much more dynamic than previously thought. This suggests that extended treatment beyond initial lapses and relapses and during post cessation reduction may be helpful. Peters EN, Hughes JR. The day-to-day process of stopping or reducing smoking: A prospective study of self-changers. Nicotine Tob Res. 2009, Sep; 11(9): 1083-1092.

Shaping Smoking Cessation in Hard-to-Treat Smokers

Dr. Lamb and colleagues conducted this study to examine if shaping can improve contingency management (CM) outcomes in hard-to-treat (HTT) individuals. Shaping sets intermediate criteria for incentive delivery between the present behavior and total abstinence. This should result in HTT individuals having improving, rather than poor, outcomes. Smokers were stratified into HTT (n = 96) and easier-to-treat (ETT [abstinent at least once during baseline]; n = 50) and randomly assigned to either CM or CM with shaping (CMS). CM provided incentives for breath carbon monoxide (CO) levels <4 ppm (approximately 1 day of abstinence). CMS shaped abstinence by providing incentives for COs lower than the 7th lowest of the participant's last 9 samples or <4 ppm. Interventions lasted for 60 successive weekday visits. Cluster analysis identified 4 groups of participants: stable successes, improving, deteriorating, and poor outcomes. In comparison with ETT, HTT participants were more likely to belong to 1 of the 2 unsuccessful clusters. This difference was greater with CM than with CMS, in which the difference between HTT and ETT participants was not significant. Assignment to CMS predicted membership in the improving ($p = .002$) as compared with the poor outcomes cluster. The authors concluded that shaping can increase CM's effectiveness for HTT smokers. Lamb RJ, Kirby KC, Morral AR, Galbicka G, Iguchi MY. Shaping smoking cessation in hard-to-treat smokers. Journal of Consulting and Clinical Psychology. 2010 Feb; 78(1): 62-71.

Feasibility of a Tobacco Cessation Intervention for Pregnant Alaska Native Women

Dr. Patten and colleagues conducted this pilot study to assess the feasibility and acceptability of a targeted cessation intervention for Alaska Native pregnant women, where about 79% of women smoke cigarettes or use smokeless tobacco during pregnancy. Enrolled participants were randomly assigned to the control group (n = 18; brief face-to-face counseling at the first

visit and written materials) or to the intervention group (n = 17) consisting of face-to-face counseling at the first visit, four telephone calls, a video highlighting personal stories, and a cessation guide. Interview-based assessments were conducted at baseline and follow-up during pregnancy (³ 60 days post randomization). Feasibility was determined by the recruitment and retention rates. The participation rate was very low with only 12% of eligible women (35/293) enrolled. Among enrolled participants, the study retention rates were high in both the intervention (71%) and control (94%) groups. The biochemically confirmed abstinence rates at follow-up were 0% and 6% for the intervention and control groups, respectively. The low enrollment rate suggests that the program was not feasible or acceptable. Alternative approaches are needed to improve the reach and efficacy of cessation interventions for Alaska Native women. Patten CA, Windsor RA, Renner CC, Enoch C, Hochreiter A, Nevak C, Smith CA, Decker PA, Bonnema S, Hughes CA, Brockman T. Feasibility of a tobacco cessation intervention for pregnant Alaska Native women. Nicotine Tob Res. 2010 Feb; 12(2): 79-87.

Public Health Clinical Demonstration Project for Smoking Cessation in Veterans with Posttraumatic Stress Disorder

Investigators at the Durham VA designed this clinical demonstration project to provide a low-cost, feasibly implemented smoking cessation intervention that would maximize the number of smokers who accessed the intervention. Five hundred eighty-four veteran smokers were contacted by invitational letters. Interested veterans received follow-up telephone calls using standardized scripts offering three intervention resources: 1) a referral to the National Cancer Institute's Smoking Quitline, 2) web-based counseling, and 3) local Veteran Affairs pharmacologic treatment for smoking cessation. Twenty-three percent of survey recipients participated in the clinical program. Two months after these resources were offered by phone, follow-up phone calls indicated that 25% of participants providing follow-up information reported maintaining smoking abstinence. This clinical demonstration project was associated with a 2.6% impact (i.e., reach [31.1% of smokers accessed intervention] by efficacy [8.4% of those accessing intervention quit]), meaning that 2.6% of the total number of targeted smokers reported 8 week abstinence. Results suggested that this brief, low-cost intervention was feasible and promoted smoking cessation in veterans with Posttraumatic Stress Disorder. Dedert EA, Wilson SM, Calhoun PS, Moore SD, Hamlett-Berry KW, Beckham JC. Public health clinical demonstration project for smoking cessation in veterans with posttraumatic stress disorder. Addict Behav. 2010 Jan; 35(1): 19-22.

Severity of Withdrawal Symptomatology in Follicular versus Luteal Quitters: The Combined Effects of Menstrual Phase and Withdrawal on Smoking Cessation Outcome

Women are at an increased risk of relapse after a smoking cessation attempt. While the reasons for this phenomenon are not fully understood, recent research indicates that both the menstrual cycle and negative symptomatology may play a role. The goal of this study was to describe the association between withdrawal symptoms during attempted smoking cessation, and to investigate the impact of these symptoms on smoking cessation outcomes as defined by 7-day point prevalence at 14 and 30 days. Negative symptoms associated with the premenstrual period were also assessed. Participants (n=202) were 29.8 (SD+/-6.6) years old and smoked 16.6 (SD+/-5.6) cigarettes per day. They were randomly assigned to quit smoking in the follicular (n=106) or luteal (n=96) menstrual phase. Several significantly more severe premenstrual and withdrawal symptoms were observed in the luteal phase. Regardless of quit phase, most withdrawal symptoms were associated with an increased risk of relapse at 14 and 30 days post quit date. Participants attempting to quit smoking in the follicular phase who had higher levels of Anger and Craving

were more likely to relapse to smoking at 14-days (OR=2.00, p-value=0.026; OR=2.63, p-value=0.006; respectively). These data suggest that the menstrual cycle may play a role in smoking cessation outcome, as well as in the symptomatology experienced during a cessation attempt. Allen AM, Allen SS, Lunos S, Pomerleau CS. Severity of withdrawal symptomatology in follicular versus luteal quitters: The combined effects of menstrual phase and withdrawal on smoking cessation outcome. Addict Behav. 2010 Jan 29. [Epub ahead of print].

The Relationship between Self-Efficacy and Reductions in Smoking in a Contingency Management Procedure

Investigators at the University of Texas Health Science Center conducted this study to examine the relationship between smoking cessation self-efficacy and reductions in smoking. Social-cognitive and behavioral theories of change disagree on what the relevant controlling variables for initiating behavior change are. Correlations between baseline smoking cessation self-efficacy and the changes in breath carbon monoxide (CO) and the reduction in breath CO and increases in smoking cessation self-efficacy from baseline were obtained from a contingency management smoking cessation procedure. A test of the difference between the cross-lag correlations suggested a nonspurious causal relationship between smoking cessation self-efficacy and changes in breath CO. Path analyses showed that decreases in breath CO (reductions in smoking) predicted later increases in smoking cessation self-efficacy. Baseline self-reports of smoking cessation self-efficacy were not significantly correlated with subsequent changes in breath CO. Rather, significant correlations were found between reductions in breath CO and later increases in smoking cessation self-efficacy. These results suggest that self-efficacy may be a cognitive response to one's own behavior, and are inconsistent with a social-cognitive view of self-efficacy's role in behavior change. This study has implications for the development of smoking cessation programs and health-promoting behavior changes in general. Romanowich P, Mintz J, Lamb RJ. The relationship between self-efficacy and reductions in smoking in a contingency management procedure. Exp Clin Psychopharmacol. 2009 Jun; 17(3): 139-145.

Effects of an Intensive Depression-Focused Intervention for Smoking Cessation in Pregnancy

Dr. Cinciripini and colleagues at the University of Texas M.D. Anderson Cancer Center conducted this study to evaluate a depression-focused treatment for smoking cessation in pregnant women versus a time and contact health education control. They hypothesized that the depression-focused treatment would lead to improved abstinence and reduced depressive symptoms among women with high levels of depressive symptomatology. No significant main effects of treatment were hypothesized. Pregnant smokers (N = 257) were randomly assigned to a 10-week, intensive, depression-focused intervention (cognitive behavioral analysis system of psychotherapy; CBASP) or to a time and contact control focused on health and wellness (HW); both included equivalent amounts of behavioral and motivational smoking cessation counseling. Of the sample, 54% were African American, and 37% met criteria for major depression. At 6 months post treatment, women with higher levels of baseline depressive symptoms treated with CBASP were abstinent significantly more often, $F(1, 253) = 5.61$, $p = .02$, and had less depression, $F(1, 2620) = 10.49$, $p = .001$, than those treated with HW; those with low baseline depression fared better in HW. Differences in abstinence were not retained at 6 months postpartum. The results suggest that pregnant women with high levels of depressive symptoms may benefit from a depression-focused treatment in terms of improved abstinence and depressive symptoms, both of which could have a combined positive effect on maternal and child health. Cinciripini PM, Blalock JA, Minnix JA, Robinson JD, Brown VL, Lam C, Wetter DW,

Schreindorfer L, McCullough JP Jr, Dolan-Mullen P, Stotts AL, Karam-Hage M. Effects of an intensive depression-focused intervention for smoking cessation in pregnancy. J Consult Clin Psychol. 2010 Feb; 78(1): 44-54.

Smoking Expectancies and Intention to Quit in Smokers with Schizophrenia, Schizoaffective Disorder and Non-Psychiatric Controls

Cigarette smoking expectancies are systematically related to intention to quit smoking in adult smokers without psychiatric illness, but little is known about these relationships in smokers with serious mental illness. In this study, Tidey and Rohsenow compared positive and negative smoking expectancies, and examined relationships between expectancies and intention to quit smoking, in smokers with schizophrenia (n=46), smokers with schizoaffective disorder (n=35), and smokers without psychiatric illness (n=71). In all three groups, reduction of negative affect was rated as the most important smoking expectancy and intention to quit smoking was systematically related to concerns about the health effects and social consequences of smoking. Compared to the other groups of smokers, those with schizoaffective disorder were more concerned with social expectancies and with the immediate negative physical effects of smoking. Results of this study suggest that challenging positive smoking expectancies and providing more tailored information about the negative consequences of smoking might increase motivation to quit smoking in smokers with schizophrenia and schizoaffective disorder, as has been found with non-psychiatric smokers. Tidey JW, Rohsenow DJ. Smoking expectancies and intention to quit in smokers with schizophrenia, schizoaffective disorder and non-psychiatric controls. Schizophr Res. 2009 Dec; 115(2-3): 310-316.

Is Implementation of the 5 A's of Smoking Cessation at Community Mental Health Centers Effective for Reduction of Smoking by Patients with Serious Mental Illness?

Dr. Lisa Dixon and colleagues at the University of Maryland tested whether implementing the "5 A's" (Ask, Advise, Assess, Assist, Arrange) at six mental health centers reduces smoking among persons with serious mental illness. One hundred and fifty-six patients were evaluated just before initiating the 5 A's and after six and 12 months. A delayed control condition evaluated 148 patients six months before 5 A's implementation, just before and then after six months. Six months of the 5 A's produced no effect. Modest cessation and reduction benefits were noted after 12 months. Implementing the 5 A's at community mental health centers may have modest benefit after twelve months. Dixon LB, Medoff D, Goldberg R, Lucksted A, Kreyenbuhl J, DiClemente C, Potts W, Leith J, Brown C, Adams C, Afful J. Is implementation of the 5 A's of smoking cessation at community mental health centers effective for reduction of smoking by patients with serious mental illness? Am J Addict. 2009 Sep-Oct; 18(5): 386-392.

Tobacco Cessation via Doctors of Chiropractic: Results of a Feasibility Study

Because of the association between tobacco use and the health problems that may provoke referral to chiropractic care, this study was conducted to design and refine a brief office-based tobacco intervention for use within chiropractic settings. This study was conducted in 20 private chiropractic practices in 2 phases: (a) intervention development and (b) feasibility, in which the impact of the intervention was evaluated in 210 tobacco-using chiropractic patients. Analyses were conducted on 156 patients who exclusively smoked cigarettes. Using an intent-to-treat approach, assuming all nonresponders to be smokers,

13 (8.3%) reported 7-day abstinence at 6 weeks, 22 (14.1%) at the 6-month follow-up, and 35 (22.4%) at the 12-month assessment. Eleven participants (7.1%) reported prolonged abstinence at the 6-month follow-up, and 15 (9.6%) reported prolonged abstinence at 12 months. The results of this study were promising and will lead to a randomized clinical trial. If found to be effective, this model could be disseminated to chiropractic practitioners throughout the United States. Gordon JS, Istvan J, Haas M. Tobacco cessation via doctors of chiropractic: Results of a feasibility study. Nicotine Tob Res. 2010 Mar; 12(3): 305-308.

A Tailored Intervention to Support Pharmacy-Based Counseling for Smoking Cessation

Investigators conducted this study to develop and test a pharmacy-based smoking cessation intervention that addresses the barriers that pharmacists encounter in providing smoking cessation counseling to their patients (i.e., limited time, reimbursement, and training in counseling techniques.) A computer-driven software system, "Exper_Quit" (EQ), was tested that provided individually tailored interventions to patients who smoke, as well as matching tailored reports for pharmacists to help guide cessation counseling. A two-phase design was used to recruit an observation-only group (OBS; n = 100), followed by participants (n = 200) randomly assigned to receive EQ-assisted pharmacist counseling or EQ plus 8 weeks of nicotine transdermal patch (EQ+). Both treatment groups were scheduled to receive two follow-up counseling calls from pharmacists. The results indicated that most participants in the EQ and EQ+ groups reported receiving counseling from a pharmacist, including follow-up calls, while none of the OBS participants reported speaking with the pharmacist about cessation. At 6 months, fewer OBS participants reported a quit attempt (42%) compared with EQ (76%) or EQ+ (65%) participants ($p < .02$). At 6 months, 7-day point-prevalence abstinence was 28% and 15% among the EQ+ and EQ groups, respectively, compared with 8% among OBS participants ($p < .01$), and EQ+ participants were twice as likely to be quit than were EQ participants ($p < .01$). The authors suggested that a tailored software system can facilitate the delivery of smoking cessation counseling to pharmacy patients. Results suggest that EQ was successful in increasing (a) the delivery of cessation counseling, (b) quit attempts, and (c) quit rates. Pharmacists can play an important role in the effective delivery of smoking cessation counseling. Bock BC, Hudmon KS, Christian J, Graham AL, Bock FR. A tailored intervention to support pharmacy-based counseling for smoking cessation. Nicotine Tob Res. 2010 Mar; 12(3): 217-225.

A Contingency-Management Intervention to Promote Initial Smoking Cessation among Opioid-Maintained

Patients Investigators at the University of Vermont conducted the present study to examine the efficacy of contingency management for promoting initial smoking abstinence among opioid-maintained patients, a population with a prevalence of cigarette smoking more than threefold that of the general population. Forty methadone- or buprenorphine-maintained cigarette smokers were randomly assigned to a contingent (n = 20) or noncontingent (n = 20) experimental group and visited the clinic for 14 consecutive days. Contingent participants received vouchers based on breath carbon monoxide levels during Study Days 1 to 5 and urinary cotinine levels during Days 6 to 14. Voucher earnings began at $9.00 and increased by $1.50 with each subsequent negative sample for maximum possible of $362.50. Noncontingent participants earned vouchers independent of smoking status. Although not a primary focus, participants who were interested and medically eligible could also receive bupropion (Zyban). Contingent participants achieved significantly more initial smoking abstinence, as evidenced by a greater percentage of smoking-negative samples (55% vs. 17%) and longer duration of continuous abstinence

(7.7 vs. 2.4 days) during the 2 week quit attempt than noncontingent participants, respectively. Bupropion did not significantly influence abstinence outcomes. Results from this randomized clinical trial support the efficacy of contingency management interventions in promoting initial smoking abstinence in this challenging population. Dunn KE, Sigmon SC, Reimann EF, Badger GJ, Heil SH, Higgins ST. A contingency-management intervention to promote initial smoking cessation among opioid-maintained patients. Exp Clin Psychopharmacol. 2010 Feb; 18(1): 37-50.

Educational Disadvantage and Cigarette Smoking during Pregnancy

Dr. Higgins and colleagues at the University of Vermont conducted this study to examine the influence of education on smoking status in a cohort (n=316) of pregnant women who were smokers at the time they learned of the current pregnancy. Subjects were participants in clinical trials examining the efficacy of monetary-based incentives for smoking-cessation and relapse prevention. In multivariate analyses, educational achievement was a robust predictor of smoking status upon entering prenatal care, of achieving abstinence antepartum among those still smoking at entry into prenatal care, and of smoking status at 6-month postpartum in the entire cohort and the subsample who received smoking-cessation treatment. In addition to educational attainment, other predictors of smoking status included smoking-related characteristics (e.g., number of cigarettes/day smoked pre-pregnancy), treatment, maternal age, and stress ratings. The authors suggest that strategies to increase educational attainment be included with more conventional tobacco-control policies in efforts to reduce smoking among girls and young women. Higgins ST, Heil SH, Badger GJ, Skelly JM, Solomon LJ, Bernstein IM. Educational disadvantage and cigarette smoking during pregnancy. Drug Alcohol Depend. 2009 Oct 1; 104 Suppl 1: S100-105.

Bupropion and Cognitive Behavioral Therapy for Weight-Concerned Women Smokers

Dr. Levine and colleagues at Western Psychiatric Institute conducted this study to determine if a behavioral therapy for smoking-related weight concerns (CONCERNS) plus bupropion would enhance abstinence for weight-concerned women smokers. In a randomized, double-blind, placebo controlled trial, weight-concerned women (n=349; 86% white) received smoking cessation counseling and were randomized to 1 of 2 adjunctive counseling components: CONCERNS or STANDARD (standard cessation treatment with added discussion of smoking topics but no specific weight focus), and 1 of 2 medication conditions: Bupropion hydrochloride sustained release (B) or placebo (P) for 6 months. Women in the CONCERNS+B group had higher rates of abstinence (34.0%) and longer time to relapse than did those in the STANDARD+B (21%; P=.05) or CONCERNS+P (11.5%; P=.005) groups at 6 months, although rates of prolonged abstinence in the CONCERNS+B and STANDARD+B groups did not differ significantly at 12 months. Abstinence rates and duration did not differ in the STANDARD+B group (21% and 19%) compared with the STANDARD+P group (10% and 7%) at 6 and 12 months, respectively. There were no differences among abstinent women in post cessation weight gain or weight concerns, although STANDARD+B produced greater decreases in nicotine withdrawal and depressive symptoms than did STANDARD+P. Weight-concerned women smokers receiving the combination of CONCERNS+B were most likely to sustain abstinence. This effect was not related to differences in post cessation weight gain or changes in weight concerns. Levine MD, Perkins KA, Kalarchian MA, Cheng Y, Houck PR, Slane JD, Marcus MD. Bupropion and cognitive behavioral therapy for weight-concerned women smokers. Arch Intern Med. 2010; 170(6): 543-550.

Screening Adolescents for Substance Use-Related High-Risk Sexual Behaviors

In this analysis, Dr. Sharon Levy, Dr. Knight and colleagues intended to determine whether adolescents who screened positive for high-risk substance use with the CRAFFT questions were also more likely to engage in risky sexual behaviors than their peers. The second purpose was to determine the test-retest reliability of a substance use-related sexual risk behaviors inventory. Clinic patients 12-18 years old completed a multi-part questionnaire that included eight demographic items, the CRAFFT substance use screen, and a 14-item scale assessing sexual behaviors associated with substance use. Participants were invited to return 1 week later to complete an identical assessment battery. Of the 305 study participants, 49 (16.1%) had a positive CRAFFT screen result (score of 2 or greater, indicating high risk for substance abuse/dependence) and 101 (33.9%) reported sexual contact during the past 90 days. After controlling for gender, age, race/ethnicity, and number of parents in household, adolescents with a positive CRAFFT screen had significantly greater odds of having sexual contact after using alcohol or other drugs, of having a sexual partner who used alcohol or other drugs, of having sex without a condom, and of having multiple sexual partners within the past year, compared to their CRAFFT negative peers. The substance use-related sexual risk behaviors inventory has acceptable test-retest reliability, and the 10 frequency questions have scale-like properties with acceptable internal consistency (standardized Cronbach's alpha=.79). The authors concluded that clinicians should pay special attention to counseling CRAFFT-positive adolescents regarding use of condoms and the risks associated with sexual activity with multiple partners, while intoxicated, or with an intoxicated partner. Levy S, Sherritt L, Gabrielli J, Shrier LA, Knight JR. Screening adolescents for substance use-related high-risk sexual behaviors. J Adolesc Health. 2009 Nov; 45(5): 473-477.

A Qualitative Study of Clinicians' Use of the Cultural Formulation Model in Assessing Posttraumatic Stress Disorder

The Cultural Formulation (CF) of the Diagnostic and Statistical Manual (DSM) provides a potential framework for improving the diagnostic assessment of Posttraumatic Stress Disorder (PTSD) in culturally diverse patients. In this study, Drs. Fortuna and colleagues analyzed data from the Patient-Provider Encounter Study, a multi-site study that examines the process of diagnosis and clinical decision-making during an initial clinical intake session, in order to examine use of CF for PTSD diagnosis. They found that while the CF is generally used inconsistently or underutilized in routine community settings, when employed appropriately it may assist the formulation and interpretation of traumatic experiences. They discuss the implications for improving the assessment of PTSD in the time-limited setting of the clinical intake encounter and across race/ethnicity. Fortuna LR, Porche MV, Alegr'a M. A qualitative study of clinicians' use of the cultural formulation model in assessing posttraumatic stress disorder. Transcult Psychiatry. 2009 Sep; 46(3): 429-450.

Improved HIV and Substance Abuse Treatment Outcomes for Released HIV-Infected Prisoners: The Impact of Buprenorphine Treatment

HIV-infected prisoners fare poorly after release. Though rarely available, opioid agonist therapy (OAT) may be one way to improve HIV and substance abuse treatment outcomes after release. Of the 69 HIV-infected prisoners enrolled in a randomized controlled trial of directly administered antiretroviral therapy, 48 (70%) met DSM-IV criteria for opioid dependence. Of these, 30 (62.5%) selected OAT, either as methadone (N = 7, 14.5%) or buprenorphine/naloxone

(BPN/NLX; N = 23, 48.0%). Twelve-week HIV and substance abuse treatment outcomes are reported as a sub-study for those selecting BPN/NLX. Retention was high: 21 (91%) completed BPN/NLX induction and 17 (74%) remained on BPN/NLX after 12 weeks. Compared with baseline, the proportion with a non-detectable viral load (61% vs 63% log(10) copies/mL) and mean CD4 count (367 vs 344 cells/mL) was unchanged at 12 weeks. Opiate-negative urine testing remained 83% for the 21 who completed induction. Using means from 10-point Likert scales, opioid craving was reduced from 6.0 to 1.8 within 3 days of BPN/NLX induction and satisfaction remained high at 9.5 throughout the 12 weeks. Adverse events were few and mild. BPN/NLX therapy was acceptable, safe and effective for both HIV and opioid treatment outcomes among released HIV-infected prisoners. Future randomized controlled trials are needed to affirm its benefit in this highly vulnerable population. Springer SA, Chen S, Altice FL. Improved HIV and substance abuse treatment outcomes for released HIV-infected prisoners: The impact of buprenorphine treatment. J Urban Health. 2010 Feb 23. [Epub ahead of print].

A Reciprocal Relationship Between Neurocognitive Impairment and HIV Risk Factors

Cognitive impairment among populations at risk for HIV poses a significant barrier to managing risk behaviors. The impact of HIV and several cofactors, including substance abuse and mental illness, on cognitive function is discussed in the context of HIV risk behaviors, medication adherence, and risk-reduction interventions. Literature suggests that cognitive impairment is intertwined in a close, reciprocal relationship with both risk behaviors and medication adherence. Not only do increased risk behaviors and suboptimal adherence exacerbate cognitive impairment, but cognitive impairment also reduces the effectiveness of interventions aimed at optimizing medication adherence and reducing risk. In order to be effective, risk-reduction interventions must therefore take into account the impact of cognitive impairment on learning and behavior. Anand P, Springer SA, Copenhaver MM, Altice FL. Neurocognitive impairment and HIV risk factors: A reciprocal relationship. AIDS and Behavior. 2010 Mar 16. [Epub ahead of print].

Meta-Analytic Review of the Serotonin Transporter Gene and Risk for Alcohol Dependence

Previous studies have implicated a relationship between particular allelic variations of the serotonin transporter gene (5HTTLPR) and alcohol dependence. To provide a current estimate of the strength of this association, particularly in light of inconsistent results for 5HTTLPR, the authors conducted a meta-analytic review of the association between 5HTTLPR and a clinical diagnosis of alcohol dependence. Of 145 studies initially identified, 22 (including 8050 participants) met inclusion criteria. Results indicated that there was a significant albeit modest association between alcohol dependence diagnosis and the presence of at least 1 short allele (OR=1.15, 95% CI=1.01, 1.30, p<.05). Slightly more robust results were observed for participants who were homogeneous for the short allele (OR=1.21, 95% CI=1.02, 1.44, p<.05). These results were unrelated to sex and race/ethnicity of participants; however, the effect size was moderated by study sample size and publication year. Additionally, the fail-safe N analysis indicated potential publication bias. Therefore, although the review indicated a significant association between 5HTTLPR and alcohol dependence diagnosis, this result should be interpreted with caution. McHugh RK, Hofmann SG, Asnaani A, Sawyer AT, Otto MW. The serotonin transporter gene and risk for alcohol dependence: A meta-analytic review. Drug Alcohol Depend. 2010 Apr 1; 108(1-2): 1-6.

Psychopathology in Methamphetamine-Dependent Adults 3 years

After Treatment

Although psychiatric symptoms are frequently observed in methamphetamine (MA) users, little is known about the prevalence of psychiatric disorders in MA-dependent individuals. This is the first study to examine the association of psychiatric disorders with substance use and psychosocial functioning in a large sample of MA users 3 years after treatment. Participants (N = 526) received psychosocial treatment for MA dependence as part of the Methamphetamine Treatment Project and were reassessed for psychosocial functioning and substance use at a mean of 3 years after treatment initiation. DSM-IV psychiatric diagnoses were assessed at follow-up using the Mini-International Neuropsychiatric Interview. Psychosocial functioning was assessed using the Addiction Severity Index. Results indicated that overall, 48.1% of the sample met criteria for a current or past psychiatric disorder other than a substance use disorder. Consistent with prior reports from clinical samples of cocaine users, this rate was largely accounted for by mood disorders, anxiety disorders and antisocial personality. Those with an Axis I psychiatric disorder evidenced increased MA use and greater functional impairment over time relative to those without a psychiatric disorder. In conclusion, this initial investigation of psychiatric diagnoses in MA users after treatment indicates elevated rates of Axis I and II disorders in this population and underscores the need for integrated psychiatric assessment and intervention in drug abuse treatment settings. Glasner-Edwards S, Mooney LJ, Marinelli-Casey P, Hillhouse M, Ang A, Rawson RA; Methamphetamine Treatment Project Corporate Authors. Psychopathology in methamphetamine-dependent adults 3 years after treatment. Drug Alcohol Rev. 2010 Jan; 29(1): 12-20.

The Alliance in Motivational Enhancement Therapy and Counseling as Usual for Substance Use Problems

Data from a community-based multicenter study of motivational enhancement therapy (MET) and counseling as usual (CAU) for outpatient substance users were used to examine questions about the role of the alliance in MET and CAU. Ninety four percent of the sample met diagnostic criteria for abuse or dependence (primarily alcohol and/or cocaine). Sixteen therapists for CAU and 14 for MET participated. No reliable differences in patient ratings (n = 319) on the Helping Alliance Questionnaire-II (HAq-II) were evident for MET compared to CAU, but significant differences between therapists were found within each condition in mean patient-rated HAq-II scores. Overall, average levels of alliance were high. The between-therapists component of the alliance, but not the within-therapist component, was significantly associated with self-reported days of primary substance use during the follow-up period from Week 4 to Week 16. Therapists with either low or very high alliances had relatively poorer average outcomes. For therapists in both MET and CAU, increased use of MET fundamental techniques and MET advanced techniques during treatment sessions was associated with higher levels of alliance. Implications of the findings for conceptualization of the alliance and for training of therapists are discussed. Crits-Christoph P, Gallop R, Temes CM, Woody G, Ball SA, Martino S, Carroll KM. J Consult Clin Psychol. 2009 Dec; 77(6): 1125-1135.

Substance Use, Childhood Sexual Abuse, and Sexual Risk Behavior Among Women In Methadone Treatment

Substance use and a history of childhood sexual abuse (CSA) are risk factors for unprotected sex among women, yet questions remain as to how their combined influence may differentially affect sexual risk. The current study investigated how complex relationships among drug use and CSA may contribute to unprotected sexual occasions (USO). A Generalized Linear Mixed Model was used to examine the interaction between current cocaine/stimulants

and opioid use and CSA on number of USOs in a sample of 214 sexually active women in outpatient methadone maintenance treatment. For women with CSA, an increase in days of cocaine/stimulant use was associated with a significant increase in USOs. In contrast, an increase in days of opiate use was associated with a significant decrease in USOs. For the group of women who did not report CSA, there was a significant increase in USOs with increased opiate use. Findings indicate that CSA is related to unprotected sexual occasions depending on drug type and severity of use. Women with CSA using cocaine are at particularly high risk for having unprotected sex and should be specifically targeted for HIV prevention interventions. Cohen LR, Tross S, Pavlicova M, Hu MC, Campbell AN, Nunes EV. Am J Drug Alcohol Abuse. 2009; 35(5):305-310.

Incentives for Retention of Pregnant Substance Users: A Secondary Analysis

Retention of pregnant substance users in treatment is challenging. In a multisite clinical trial, 200 pregnant substance users entering outpatient treatment at one of four programs were randomized to either three individual sessions of Motivational Enhancement Therapy for Pregnant Substance users or three individual sessions normally provided. Retail scrip from $25 to $30 was provided for attendance of research visits but not treatment visits. A post hoc analysis of the non-methadone-maintained participants (n = 175) evaluated the hypotheses that monetary reinforcement for attendance would result in more consecutive, and overall, weeks of attendance of research versus nonincentivized treatment visits. Findings indicate participants were nearly three times as likely to attend 4 consecutive weeks of research visits versus treatment sessions. There was no effect for income while fewer dependents were associated with more consecutive weeks of attendance. Incentives in the $25-to-$30 range may serve to significantly increase attendance and retention. Brigham G, Winhusen T, Lewis D, Kropp F. J Subst Abuse Treat. 2010 Jan; 38(1):90-95. Epub 2009 Jul 3.

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Research Findings - Research on Pharmacotherapies for Drug Abuse

Maternal Buprenorphine Dose, Placenta Buprenorphine, and Metabolite Concentrations and Neonatal Outcomes

Buprenorphine is approved as pharmacotherapy for opioid dependence in nonpregnant patients in multiple countries and is currently under investigation for pregnant women in the United States and Europe. This research evaluates the disposition of buprenorphine, opiates, cocaine, and metabolites in five term placentas from a US cohort. Placenta and matched meconium concentrations were compared, and relationships among maternal buprenorphine dose, placenta concentrations, and neonatal outcomes after controlled administration during gestation were investigated. Buprenorphine and/or metabolites were detected in all placenta specimens and were uniformly distributed across this tissue, except for buprenorphine in three placentas. Placenta is a potential alternative matrix for detecting in utero buprenorphine exposure, but at lower concentrations than in meconium. Statistically significant correlations were observed for a) mean maternal daily dose from enrollment to delivery, b) placenta buprenorphine-glucuronide concentration, c) norbuprenorphine-glucuronide concentrations, d) time to neonatal abstinence syndrome onset and duration, e) norbuprenorphine/norbuprenorphine-glucuronide ratio f) maximum neonatal abstinence syndrome score and g) newborn length. Analysis of buprenorphine and metabolites in this alternative matrix may be valuable for prediction of neonatal outcomes for clinicians treating newborns of buprenorphine-exposed women. Concheiro M, Jones HE, Johnson RE, Choo R, Shakleya DM, Huestis MA. Maternal buprenorphine dose, placenta buprenorphine, and metabolite, concentrations and neonatal outcomes. Ther Drug Monit. 2010 Mar 4.

Clinical Characteristics of Central European and North American Samples of Pregnant Women Screened for Opioid Agonist Treatment

Little comparable information is available regarding clinical characteristics of opioid-dependent women from different countries. In the present study, women from the USA, Canada and a Central European country, Austria, were screened for participation in the Maternal Opioid Treatment Human Experimental Research (MOTHER) study, were compared with respect to their demographic and addiction histories. Pregnant women (n = 1,074) were screened for study participation using uniformed clinical criteria and instruments. The screening results were compared with regard to exclusion, demographics, drug use, and psychosocial and treatment histories. Compared to the screened US and Canadian women, Austrian women were more likely to be younger ($p < 0.001$), white ($p < 0.001$), had significantly lower levels of

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educational attainment ($p < 0.001$), were less likely to use opioids daily ($p < 0.001$) and more likely to have been prescribed buprenorphine ($p < 0.001$). Compared to both rural and urban US groups, the Austrian group was less likely to have legal issues ($p < 0.001$) and was younger when first prescribed agonist medication ($p < 0.001$). The differences between North American and European groups may offer unique insights concerning treatment and pregnancy outcomes for opioid-dependent pregnant women. Unger AS, Martin PR, Kaltenbach K, Stine SM, Heil SH, Jones, HE, Arria AM, Coyle MG, Selby P, Fischer G. Clinical characteristics of central European and North American samples of pregnant women screened for opioid agonist treatment. Eur Addict Res. 2010 Feb 17; 16(2):99-107.

Concurrent Validation of the Clinical Opiate Withdrawal Scale (COWS) and Single-item Indices Against the Clinical Institute Narcotic Assessment (CINA) Opioid Withdrawal Instrument

The Clinical Opiate Withdrawal Scale (COWS) is an 11-item clinician-administered scale assessing opioid withdrawal. Though commonly used in clinical practice, it has not been systematically evaluated. This study validates the COWS in comparison to the validated Clinical Institute Narcotic Assessment (CINA) scale. Forty-six out-of-treatment opiate-dependent volunteers were enrolled in a residential trial and stabilized on morphine 30 mg given subcutaneously 4 times daily. Subjects then underwent double-blind, randomized challenges of intramuscularly administered placebo and naloxone (0.4 mg) on separate days, during which the COWS, CINA, and visual analog scale (VAS) assessments were concurrently obtained. Correlations between mean peak COWS and CINA scores as well as self-report VAS questions were calculated. Placebo was not associated with any significant elevation of COWS, CINA, or VAS scores. Internal consistency of COWS was high. The COWS and CINA followed comparable trajectories for the time course of opioid withdrawal. The study showed that the COWS is a valid instrument with sufficient sensitivity to detect mild opiate withdrawal; it would therefore be expected to detect moderate to severe withdrawal. Tompkins DA, Bigelow GE, Harrison JA, Johnson RE, Fudula PJ, Strain EC. Concurrent validation of the Clinical Opiate Withdrawal Scale (COWS) and single-item indices against the Clinical Institute Narcotic Assessment (CINA) opioid withdrawal scale. Drug and Alcohol Dep. 2009; 105: 154-159.

Agonist-like Pharmacotherapy for Stimulant Dependence: Preclinical, Human Laboratory, and Clinical Studies

A variety of natural and synthetic agents have long been used for stimulant properties, with nontherapeutic use producing multiple waves of stimulant abuse and dependence. The multitude of effects of stimulants exist on a continuum, and accordingly, this project characterizes stimulant abuse/dependence and candidate pharmacotherapies in this manner. Behavioral therapy and medications have been investigated for treatment of stimulant abuse/dependence. Effectiveness of some behavioral interventions has been demonstrated. Most medications studied have been found to lack efficacy. However, an expanding literature supports use of agonist-like medications to treat stimulant abuse/dependence, a strategy effective for nicotine and opiate dependence. The agonist-like conceptualization for stimulant dependence posits that medications with properties similar to that of the abused drug, but possessing lesser abuse liability, will normalize neurochemistry and stabilize behavior, thus reducing drug use. Data suggest use of a range of medications, from l-dopa/carbidopa to amphetamine preparations, depending on the severity of use. This report reviews preclinical, human laboratory, and clinical trial data supporting the agonist-like approach, including risks and benefits. Future directions for development of agonist-like medications are also discussed. Herin DV, Rush CR, Grabowski J. Agonist-like

pharmacotherapy for stimulant dependence: preclinical, human laboratory, and clinical studies. Ann NY Acad Sci. 2010 Feb; 1187: 76-100.

Randomized, Double-blind, Placebo-controlled Trial of Modafinil for the Treatment of Methamphetamine Dependence

A 12-week, randomized, placebo-controlled Phase II clinical trial comparing the efficacy of 400 mg modafinil (once daily) to placebo was carried out in 71 treatment-seeking methamphetamine dependent participants. There were no statistically significant effects for modafinil on methamphetamine use, retention, depressive symptoms, or craving. In this study, modafinil was no more effective than placebo at 400 mg daily in a general sample of methamphetamine users. Heinzerling KG, Swanson A, Kim S., Cederblon L, Moe A, Ling W, Shoptaw S. Randomized, double-blind, placebo-controlled trial of modafinil for the treatment of methamphetamine dependence. Drug and Alcohol Dep. 2009 (e-publication ahead of print).

The Cardiovascular and Subjective Effects of Methamphetamine Combinded With γ-Vinyl-γ-Aminobutyric Acid (GVG) in Non-treatment Seeking Methamphetamine-dependent Volunteers

γ-Vinyl-γ-aminobutyric acid (GVG) elevates central nervous system γ-aminobutyric acid (GABA) levels by irreversibly inhibiting GABA transaminase. An open-label clinical trial in humans suggested that GVG may reduce cocaine and methamphetamine use. A double-blind, placebo-controlled parallel group study of GVG interaction with the cardiovascular and subjective effects produced by methamphetamine was carried out to test safety and obtain preliminary data on efficacy of GVG for treating methamphetamine dependence in non-treatment seeking methamphetamine dependent volunteers. Subjects received either GVG (n=8) or placebo (n=9) by random assignment. GVG treatment was initiated at 1 g/day and increased to 5 g/day. After reaching the target dose of 5 g/day, participants received methamphetamine (15 + 30 mg iv) and cardiovascular and subjective effects were assessed. No serious adverse events were noted. No significant differences were detected between the groups for systolic or diastolic blood pressure, or heart rate, following methamphetamine exposure. Methamphetamine-induced subjective effects were statistically similar between GVG and placebo treatment groups. The data indicate that GVG treatment is generally well tolerated but not efficacious in attenuating the positive subjective effects of methamphetamine in a human laboratory setting. De La Garza II R, Zorick T, Heinzerling KG, Nusinowitz S, London ED, Shoptaw S, Moody DE, Newton TF. The cardiovascular and subjective effects of methamphetamine combined with γ-vinyl-γ-aminobutyric acid (GVG) in non-treatment seeking methamphetamine-dependent volunteers. Pharmacology, Biochemistry and Behavior. 2009 94: 186-193.

Methamphetamine and Paranoia: the Methamphetamine Experience Questionnaire

Paranoia in methamphetamine (MA) users is not well characterized or understood. To investigate this phenomenon, this project created the Methamphetamine Experience Questionnaire (MEQ), and tested its reliability and validity in assessing MA-induced paranoia. They administered the MEQ to 274 MA-dependent subjects. Of the total subjects, 45% (123) first experienced paranoia with MA use; 55% did not. Obtaining or using a weapon while paranoid was common (37% and 11% of subjects with MA-induced paranoia, respectively). Test-retest and inter-rater reliability for MA-induced paranoia showed substantial agreement (kappa = .77, $p < .05$ and kappa = .80, $p < .05$, respectively). First episodes of paranoia occurred more often with intravenous use of MA, and subsequent episodes at higher doses. There was

modest correlation between paranoia on the MEQ and the Brief Symptom Inventory (BSI) paranoid ideation scale (rho = .27, p < .05). As expected, there was a poor correlation between paranoia on the MEQ and the BSI depression scale (rho = .14, p = .07). The MEQ provides useful information on drug use variables that contribute to paranoia commonly associated with MA use. Leamon MH, Flower K, Salo RE, Nordahl TE, Kranzier HR, Galloway GP. Methamphetamine and paranoia: the methamphetamine experience questionnaire. Am J Addict. 2010 Mar 1; 19(2): 155-168.

Human Sex Differences in d-Amphetamine Self-administration

Women and men may respond differently to the effects of stimulants such as amphetamine and cocaine. In order to assess potential sex differences in the reinforcing effects of d-amphetamine, a retrospective-analysis was conducted on data collected from three studies that employed similar d-amphetamine self-administration procedures and used identical subject-rated drug-effect measures. Data from 10 women and 15 men were included in the analysis. In all studies, participants sampled placebo, low (8-10 mg) or high (16-20 mg) dose oral d-amphetamine. Following sampling sessions, participants worked for capsules containing one eighth of the previously sampled dose on a modified progressive-ratio schedule of reinforcement. The authors hypothesized that women and men would be differentially sensitive to the reinforcing effects of d-amphetamine. A two-way mixed-model analysis of variance (sex and dose) and planned comparisons were used in the statistical analyses. The low dose of d-amphetamine functioned as a reinforcer in women, but not men, whereas the high dose of d-amphetamine functioned as a reinforcer in men, but not women. Men self-administered significantly more capsules under the high dose condition than women. The results of this study suggest that men are more sensitive to the reinforcing effects of a high dose of d-amphetamine than women. Future research is needed that determines prospectively the reinforcing effects of weight-adjusted doses of d-amphetamine in women and men while controlling for menstrual cycle phase. Vansickel AR, Stoops WW, Rush CR. Addiction. 2010 Feb 9. [Epub ahead of print].

Working Memory fMRI Activation in Cocaine-dependent Subjects: Association with Treatment Response

Functional magnetic resonance imaging (fMRI) studies of early abstinence cocaine users offer information about the state of the brain when most cocaine users seek treatment. This study examined the relationship between pretreatment brain function and subsequent treatment response in 19 treatment-seeking early abstinence cocaine-dependent (CD) subjects. These subjects and 14 non-drug-using control subjects underwent fMRI while performing a working memory task with three levels of difficulty. CD subjects were then randomized to treatment studies. Results showed CD subjects had significantly lower (random effects, corrected for multiple comparisons) brain activation in caudate, putamen, cingulate gyrus, middle and superior frontal gyri, inferior frontal gyrus pars triangularis and pars opercularis, precentral gyrus, and thalamus compared with non-drug-using controls. Within CD subjects, thalamic activation significantly correlated with treatment response. This study shows CD subjects in early abstinence have alterations of brain function in frontal, striatal, and thalamic brain regions known to be part of a circuit associated with motor control, reward, and cognition. Subjects with pretreatment thalamic deactivation showed the poorest treatment response, possibly related to thalamic involvement in mesocortical and mesolimbic dopamine projections. Moeller FG, Steinberg JL, Schmitz JM, Ma L, Liu S, Kjome KL, Rathnayaka N, Kramer LA, Narayana PA. Psychiatry Res. 2010 Mar 30; 181(3):174-182.

Randomized Trial of Continuing Care Enhancements for Cocaine-dependent Patients Following Initial Engagement

The effects of cognitive-behavioral relapse prevention (RP), contingency management (CM), and their combination (CM + RP) were evaluated in a randomized trial with 100 cocaine-dependent patients (58% female, 89% African American) who were engaged in treatment for at least 2 weeks and had an average of 44 days of abstinence at baseline. The participants were from intensive outpatient programs, which provide 10 hr per week of group counseling. The CM protocol provided gift certificates (maximum value $1,150; mean received = $740) for cocaine-free urines over 12 weeks on an escalating reinforcement schedule, and weekly individual RP sessions were offered for up to 20 weeks. Average number of RP sessions attended was 3 in RP and 13 in CM + RP. Generalizing estimation equation analyses over 18 months postrandomization showed significant effects for CM (but not RP) on urine toxicology and self-reported cocaine use ($p = .05$), with no significant CM x RP interactions. Secondary analyses indicated CM + RP produced better cocaine urine toxicology outcomes at 6 months than treatment as usual, odds ratio [OR] = 3.96 (1.33, 11.80), $p < .01$, and RP, OR = 4.89 (1.51, 15.86), $p < .01$, and produced better cocaine urine toxicology outcomes at 9 months than treatment as usual, OR = 4.21 (1.37, 12.88), $p < .01$, and RP, OR = 4.24 (1.32, 13.65), $p < .01$. Trends also favored CM + RP over CM at 6 months, OR = 2.93 (0.94, 9.07), $p = .06$, and 9 months, OR = 2.93 (0.94, 9.10), $p = .06$. Differences between the conditions were not significant after 9 months. These results suggest CM can improve outcomes in cocaine-dependent patients in intensive outpatient programs who have achieved initial engagement, particularly when it is combined with RP. McKay JR, Lynch KG, Coviello D, Morrison R, Cary MS, Skalina L, Plebani J. J Randomized Trial of Continuing Care Enhancements for Cocaine-dependent Patients Following Initial Engagement. Consult Clin Psychol. 2010 Feb; 78(1): 111-120.

Lower Levels of Endogenous Dopamine in Patients with Cocaine Dependence: Findings from PET Imaging of D2/D3 Receptors Following Acute Dopamine Depletion

Previous PET imaging studies have demonstrated that cocaine dependence is associated with a decrease in dopamine type 2 and 3 receptor binding in cocaine individuals relative to healthy comparison subjects. Given the nature of PET imaging, it is possible that the measured decrease in radiotracer binding results from an increase in baseline dopamine levels. The purpose of this study was to measure D2/D3 receptors following acute dopamine depletion in cocaine-dependent volunteers relative to healthy comparison subjects. Fifteen cocaine-dependent volunteers and 15 healthy matched comparison subjects were scanned using PET, with the dopamine receptor radiotracer [11C]raclopride, at baseline and again following acute depletion of endogenous dopamine via α-methyl-para-tyrosine (AMPT) administration. Changes in radiotracer binding were measured in the subdivisions of the striatum (caudate, putamen, and ventral striatum) in addition to the striatum as a whole. Findings revealed that cocaine dependent volunteers exhibited lower levels of endogenous dopamine relative to comparison subjects, which was measured as an increase in [11C]raclopride[11C]raclopride binding following AMPT administration. The increase in [11C]raclopride binding in the striatum was 11.1% (SD=4.4%) in healthy comparison subjects and 5.7% (SD=5.9%) in cocaine-dependent volunteers. Similar differences were seen in the subdivisions of the striatum. The results of the study indicate that cocaine dependence is associated with a decrease in the levels of striatal dopamine, and support a series of findings from previous studies that cocaine dependence is associated with a decrease in dopamine transmission in the striatum. This imaging study shows that cocaine dependence is associated with a reduction in endogenous dopamine. Martinez D, Greene K, Broft A, Kumar D, Liu F,

Narendran R, Slifstein M, Van Heertum R, Kleber, HD. Lower levels of endogenous dopamine in patients with cocaine dependence: findings from PET imaging of D2/D3 receptors following acute dopamine depletion. Am J Psychiatry. 2009; 166: 1170-1177.

Monetary Alternative Reinforcers More Effectively Decrease Intranasal Cocaine Choice than Food Alternative Reinforcers

Cocaine dependence continues to be a significant public health concern. Contingency management, wherein alternative reinforcers are made available upon cocaine abstinence, has shown promise for decreasing cocaine use. Other research has modeled this effect and demonstrated that alternative reinforcers also reduce cocaine self-administration in the laboratory. Results from both clinical and laboratory studies suggest that the type and value of alternative reinforcers influences their ability to decrease drug choice. The purpose of the present experiment was to determine the effect of money or food alternative reinforcers, valued at $0.01, 0.25, 0.50 and 1.00, on intranasal cocaine (4 [placebo] and 30 mg) choice. Cocaine was chosen to a greater extent than placebo across alternative reinforcer types and values, but the monetary alternative reinforcer suppressed drug choice to a greater degree than the food reinforcer. These results are concordant with previous findings and suggest that money may be a more effective alternative reinforcer for decreasing cocaine use. Future research should determine the sensitivity of this model to specific behavioral aspects of contingency management and whether food could compete with drugs as reinforcers in humans under laboratory conditions. Stoops WW, Lile JA, Rush CR. Monetary Alternative Reinforcers More Effectively Decrease Intranasal Cocaine Choice than Food Alternative Reinforcers. Pharmacol Biochem Behav. 2010 Apr; 95(2): 187-191.

Reactivity to Laboratory Stress Provocation Predicts Relapse to Cocaine

Cocaine dependence is a chronic relapsing disorder characterized by periods of abstinence and high rates of return to drug using behavior. Elevated levels of stress have been associated with relapse to cocaine; however, the nature of this association is not well understood. The relationship between reactivity to three human laboratory provocations and relapse to cocaine was investigated. Participants were 53 cocaine-dependent individuals who were admitted for a 2-day inpatient stay during which a psychosocial provocation (i.e., the Trier Social Stress Task), a pharmacological provocation (i.e., administration of 1 microg/kg corticotrophin releasing hormone; CRH), and a drug cue exposure paradigm were completed. Adrenocorticotrophic hormone (ACTH), cortisol, heart rate, and subjective cocaine craving and stress were assessed at baseline and at multiple time points post-task. Participants' cocaine use was monitored for approximately 1 month following testing. The majority (72.3%) of participants relapsed to cocaine during the follow-up period. In response to the CRH and drug cue exposure, elevated subjective craving and stress were significant predictors of cocaine use during follow-up. In response to the Trier, attenuated neuroendocrine responses were significant predictors of cocaine use. The findings provide further evidence of the ability of laboratory paradigms to predict relapse. The observed associations between stress reactivity and subsequent cocaine use highlight the clinical importance of the findings. Predictors of relapse may vary based on the type of provocation utilized. Interventions aimed at normalizing stress response, as measured using laboratory paradigms, may prove useful in relapse prevention. Back SE, Hartwell K, DeSantis SM, Saladin M, McRae-Clark AL, Price KL, Moran-Santa Maria MM, Baker NL, Spratt E, Kreek MJ, Brady KT. Reactivity to Laboratory Stress Provocation Predicts Relapse to Cocaine. Drug Alcohol Depend. 2010 Jan 1; 106(1): 21-27.

Cognitive Enhancement as a Pharmacotherapy Target for Stimulant Addiction

No medications have been proven to be effective for cocaine and methamphetamine addiction. Attenuation of drug reward has been the main strategy for medications development, but this approach has not led to effective treatments. Thus, there is a need to identify novel treatment targets in addition to the brain reward system. To propose a novel treatment strategy for stimulant addiction that will focus on medications enhancing cognitive function and attenuating drug reward. Pre-clinical and clinical literature on potential use of cognitive enhancers for stimulant addiction pharmacotherapy was reviewed. Cocaine and methamphetamine users show significant cognitive impairments, especially in attention, working memory and response inhibition functions. The cognitive impairments seem to be predictive of poor treatment retention and outcome. Medications targeting acetylcholine and norepinephrine are particularly well suited for enhancing cognitive function in stimulant users. Many cholinergic and noradrenergic medications are on the market and have a good safety profile and low abuse potential. These include galantamine, donepezil and rivastigmine (cholinesterase inhibitors), varenicline (partial nicotine agonist), guanfacine (alpha(2)-adrenergic agonist) and atomoxetine (norepinephrine transporter inhibitor). Future clinical studies designed optimally to measure cognitive function as well as drug use behavior would be needed to test the efficacy of these cognitive enhancers for stimulant addiction. Sofuoglu M. Cognitive enhancement as a pharmacotherapy target for stimulant addiction. Addiction. 2010 Jan; 105(1): 38-48.

Cocaine Abuse Versus Cocaine Dependence: Cocaine Self-administration and Pharmacodynamic Response in the Human Laboratory

Cocaine has high abuse liability but only a subset of individuals who experiment with it develop dependence. The DSM-IV (APA. Diagnostic and Statistical Manual of Mental Disorders DSM-IV-R. American Psychiatric Association, Washington, DC, 2000) provides criteria for diagnosing cocaine abuse and cocaine dependence as distinct disorders- the latter characterized by additional symptoms related to loss of control over drug use. In this study, two groups of cocaine users (n=8/group), matched on demographic factors and length of cocaine use history and meeting criteria for either cocaine abuse (CocAb) or cocaine dependence (CocDep), were compared on (1) measures related to impulsivity and sensation seeking, (2) response to experimenter-administered cocaine (0, 12.5, 25 and 50mg/70 kg, i.v.), and (3) cocaine self-administration using a Relapse Choice and a Progressive Ratio Procedure (0, 12.5 and 25mg/70 kg, i.v.). Groups did not differ on impulsivity or sensation seeking scores. After experimenter-administered cocaine, the CocAb group reported feeling more suspicious and observers rated them significantly higher on unpleasant effects (e.g., irritability, difficulty concentrating). In contrast, the CocDep group reported significantly greater desire for cocaine, which was sustained over the course of the study, and gave higher street value estimates for cocaine ($p<0.05$). While cocaine self-administration was dose-related and generally comparable across the two procedures, the CocDep users chose to take significantly more cocaine than the CocAb users. These data suggest that, while regular long-term users of cocaine with cocaine abuse or dependence diagnoses cannot be distinguished by trait measures related to impulsivity, they do exhibit significant differences with regard to cocaine-directed behavior and response to cocaine administration. Walsh SL, Donny EC, Nuzzo PA, Umbricht A, Bigelow GE. Cocaine Abuse Versus Cocaine Dependence: Cocaine self-administration and pharmacodynamic response in the human laboratory. Drug Alcohol Depend. 2010 Jan 1; 106(1): 28-37.

Delta9-tetrahydrocannabivarin Testing May Not Have the Sensitivity to Detect Marijuana use Among Individuals Ingesting Dronabinol

The purpose of this study was to determine whether Delta(9)-tetrahydrocannabivarin (THCV), a plant cannabinoid, is a sensitive measure to detect recent marijuana use in cannabis dependent patients. It has been purported that smoking an illicit plant cannabis product will result in a positive THCV urinalysis, whereas the oral ingestion of therapeutic THC such as dronabinol will result in a negative THCV urinalysis, allowing for discrimination between pharmaceutical THC products and illicit marijuana products. In a double-blind placebo-controlled trial to determine the efficacy of dronabinol in cannabis dependence, all 117 patients produced a positive urine for the marijuana metabolite 11-nor-Delta(9)-THC-9-carboxylic acid; THC-COOH, but 50% had an undetectable (<1 ng/ml) THCV-COOH test. This suggests that THCV may not be a sensitive enough measure to detect recent marijuana use in all heavy marijuana users or that its absence may not discriminate between illicit marijuana use and oral ingestion of THC products such as dronabinol. The investigators propose that the lack of THCV detection may be due to the variability of available cannabis strains smoked by marijuana users in community settings. Levin FR, Mariani JJ, Brooks DJ, Xie S, Murray KA. Delta9-tetrahydrocannabivarin testing may not have the sensitivity to detect marijuana use among individuals ingesting dronabinol. Drug Alcohol Depend. 2010 Jan 1; 106(1): 65-68.

A Double-blind, Placebo-controlled, Randomized Clinical Trial of Oral Selegiline Hydrochloride for Smoking Cessation in Nicotine-dependent Cigarette Smokers

The primary aim of this study was to determine the safety and efficacy of the monoamine oxidase-B (MAO-B) inhibitor selegiline hydrochloride (SEL, l-Deprenyl; Eldepryl) as an aid for smoking cessation in cigarette smokers. One hundred and one nicotine-dependent adult cigarette smokers without current psychiatric or substance use disorders participated in this 8-week randomized, double-blind, placebo-controlled trial. Participants received either SEL (5mg bid, n=51) or placebo (PLO, n=50), in combination with brief (<10 min) manualized smoking cessation counseling. The main smoking outcome measures were 7-day point prevalence abstinence at end of trial (EOT), 4-week continuous smoking abstinence at end of trial (CA), and 7-day point prevalence abstinence at 6-month follow-up (6MFU). Abstinence was determined by an absence of self-reported cigarette smoking and biochemically verified by expired breath carbon monoxide and plasma cotinine levels. Rates of smoking abstinence did not differ by medication group (EOT: SEL=16%, PLO=20%, p=0.57; CA: SEL=14%, PLO=18%, p=0.56; 6MFU: SEL=12%, PLO=16%, p=0.54). Adverse events were modest and comparable between medication groups. Participants receiving SEL were more likely than those receiving PLO to report dry mouth (25.5% versus 8.2%, p<0.05). Results suggest that SEL was safe and well-tolerated by adult cigarette smokers, but did not improve smoking abstinence rates compared to PLO. Weinberger AH, Reutenauer EL, Jatlow PI, O'Malley SS, Potenza MN, George TP. A double-blind, placebo-controlled, randomized clinical trial of oral selegiline hydrochloride for smoking cessation in nicotine-dependent cigarette smokers. Drug Alcohol Depend. 2010 Mar 1; 107(2-3): 188-195.

Smoking in Pregnant Women Screened for an Opioid Agonist Medication Study Compared to Related Pregnant and Non-pregnant Patient Samples

Little is known about the prevalence and severity of smoking in pregnant opioid

dependent patients. To first characterize the prevalence and severity of smoking in pregnant patients screened for a randomized controlled trial, Maternal Opioid Treatment: Human Experimental Research (MOTHER), comparing two agonist medications; and second, to compare the MOTHER screening sample to published samples of other pregnant and/or patients with substances use disorders. Pregnant women (N = 108) screened for entry into an agonist medication comparison study were retrospectively compared on smoking variables to samples of pregnant methadone-maintained patients (N = 50), pregnant opioid or cocaine dependent patients (N = 240), non-pregnant methadone-maintained women (N = 75), and pregnant non-drug-addicted patients (N = 1,516). Of screened patients, 88% (n = 95) smoked for a mean of 140 months (SD = 79.0) starting at a mean age of 14 (SD = 3.5). This rate was similar to substance use disordered patients and significantly higher compared to general pregnant patients (88% vs. 22%, $p < .001$). Aggressive efforts are needed to reduce/eliminate smoking in substance-abusing pregnant women. Jones HE, Heil SH, O'Grady KE, Martin PR, Kaltenbach K, Coyle MG, Stine SM, Selby P, Arria AM, Fischer G. Smoking in pregnant women screened for an opioid agonist medication study compared to related pregnant and non-pregnant patient samples. Am J Drug Alcohol Abuse. 2009; 35(5): 375-380.

Provision of Ancillary Medications During Buprenorphine Detoxification Does Not Improve Treatment Outcomes

For individuals dependent on opioids, recovery efforts begin with a period of withdrawal that typically includes discomfort from symptoms, possibly precipitating a return to drug use. This study investigated potential associations between provision of ancillary medications for opioid withdrawal symptoms and treatment outcomes in 139 participants receiving buprenorphine in a 13-day detoxification trial. Outcome measures include the number of opioid-free urine samples collected and retention in treatment. Ancillary medications were provided to 70% of participants: 59% received medication for insomnia, 45% for anxiety, 40% for bone pain, 35% for nausea, and 28% for diarrhea. Findings indicate no difference in the number of opioid-free urine samples between the group receiving ancillary medication and the group who did not. Tests of specific ancillary medications indicate that those who received diarrhea medication had fewer opioid-free urines than those who did not ($P = .004$). Results also indicate that participants attended fewer days of treatment if they received anxiety, nausea, or diarrhea medication compared to no medication (all P values $<.05$). Hillhouse M, Domier CP, Chim D, Ling W. J Addict Dis. 2010 Feb: 29(1): 23-29.

A Method to Diagnose Opioid Dependence Resulting from Heroin versus Prescription Opioids using the Composite International Diagnostic Interview

Treatment research with opioid-dependent populations has not traditionally distinguished between those dependent on prescription opioids versus dependent upon heroin. Evidence suggests there is a substantial subpopulation of individuals with opioid dependence resulting largely or exclusively from prescription opioid use. Because this subpopulation may respond to treatment differently from heroin users, a method for discriminating DSM-IV opioid dependence due to prescription opioid use would provide more precision when examining this population. This paper describes an innovative method using a currently available diagnostic instrument, to diagnose DSM-IV opioid dependence and distinguish between dependence resulting from prescription opioids versus dependence upon heroin. This method employs the CIDI in an enhanced format to differentiate these populations. This format includes expanded listing of drugs for reference, a change in the interview to differentiate the type of opioid and special training for staff. Eight hundred CIDI administrations have been accomplished; staff reports that the enhanced CIDI

is practicable and that participants are able to make a distinction between their heroin use and other opioid use. Potter JS, Prather K, Kropp F, Byrne M, Sullivan CR, Mohamedi N, Copersino ML, Weiss RD. Contemp Clin Trials. 2010 Mar; 31(2):185-188. Epub 2010 Jan 14.

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

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

No Excess Risk of Follicular Lymphoma in Kidney Transplant and HIV-Related Immune Deficiency

Subtype-specific incidence patterns in populations at high-risk of lymphoma offer insight into lymphomagenesis. The incidence profiles for the two most common non-Hodgkin lymphoma subtypes were compared for two immune-deficient populations, adults receiving a kidney transplant 1982-2003 (n=7,730) or diagnosed with HIV infection 1982-2004 (n=17,175). National population-based registries were linked and standardized incidence ratios (SIRs) were computed for each cohort and lymphoma subtype. Risk of diffuse large B-cell lymphoma was significantly increased after transplantation (SIR 17.83, 95%CI 13.61-22.95) and after HIV infection (SIR 58.81, 95%CI 52.59-65.56). Rates of follicular lymphoma were neither significantly increased nor decreased in transplant recipients (SIR 0.82, 95%CI 0.10-2.96) and in people with HIV (SIR 1.25, 95%CI 0.41-2.91). The findings argue against an infectious or other immune-deficiency- related aetiology for follicular lymphoma, and clearly differentiate it from diffuse large B-cell lymphoma. Vajdic CM, van Leeuwen MT, Turner JJ, McDonald AM, Webster AC, McDonald SP, Chapman JR, Kaldor JM, Grulich AE. Int J Cancer. No excess risk of follicular lymphoma in kidney transplant and HIV-related immune deficiency. Int J Cancer. 2010 Feb 22. [Epub ahead of print].

Effect of Reduced Immunosuppression After Kidney Transplant Failure on Risk of Cancer: Population Based Retrospective Cohort Study

The objective of this study was to compare cancer incidence in kidney transplant recipients during periods of transplant function (and immuno-suppression) and after transplant failure (when immunosuppression is ceased or reduced). This study used a population based retrospective cohort of 8173 Australian kidney transplant recipients registered on the Australia and New Zealand Dialysis and Transplant Registry who first received a transplant during 1982-2003. Incident cancers were ascertained using linkage with national cancer registry records. The main outcome measures were cancer-specific standardized incidence ratios for periods of transplant function and for dialysis after transplant failure. Incidence was compared between periods using multivariate incidence rate ratios adjusted for current age, sex, and duration of transplantation. All cases of Kaposi's sarcoma occurred during transplant function. Standardized incidence ratios were significantly elevated during transplant function, but not during dialysis after transplant failure, for non-Hodgkin's lymphoma, lip cancer, and melanoma. For each of these cancers, incidence was significantly lower during dialysis after transplant failure in

multivariate analysis (incidence rate ratios 0.20 (95% CI 0.06 to 0.65) for non-Hodgkin's Lymphoma, 0.04 (0.01 to 0.31) for lip cancer, and 0.16 (0.04 to 0.64) for melanoma). In contrast, standardized incidence ratios during dialysis after transplant failure remained significantly elevated for leukaemia and lung cancer, and cancers related to end stage kidney disease (kidney, urinary tract, and thyroid cancers), with thyroid cancer incidence significantly higher during dialysis after transplant failure (incidence rate ratio 6.77 (2.64 to 17.39)). There was no significant difference in incidence by transplant function for other cancers. The effect of immunosuppression on cancer risk is rapidly reversible for some, but not all, cancer types. Risk reversal was mainly observed for cancers with a confirmed infectious cause. Risk of other cancers, especially those related to end stage kidney disease, remained significantly increased after reduction of immunosuppression. van Leeuwen MT, Webster AC, McCredie MR, Stewart JH, McDonald SP, Amin J, Kaldor JM, Chapman JR, Vajdic CM, Grulich AE. Effect of reduced immunosuppression after kidney transplant failure on risk of cancer: population based retrospective cohort study. BMJ. 2010 Feb 11; 340: c570.

Per-Contact Probability of HIV Transmission in Homosexual Men in Sydney in the Era of HAART

The objective of this study is to estimate per-contact probability of HIV transmission in homosexual men due to unprotected anal intercourse (UAI) in the era of HAART. Data were collected from a longitudinal cohort study of community-based HIV-negative homosexual men in Sydney, Australia. A total of 1427 participants were recruited from June 2001 to December 2004. They were followed up with 6-monthly detailed behavioral interviews and annual testing for HIV till June 2007. Data were used in a bootstrapping method, coupled with a statistical analysis that optimized a likelihood function for estimating the per-exposure risks of HIV transmission due to various forms of UAI. During the study, 53 HIV seroconversion cases were identified. The estimated per-contact probability of HIV transmission for receptive UAI was 1.43% [95% confidence interval (CI) 0.48-2.85] if ejaculation occurred inside the rectum, and it was 0.65% (95% CI 0.15-1.53) if withdrawal prior to ejaculation was involved. The estimated transmission rate for insertive UAI in participants who were circumcised was 0.11% (95% CI 0.02-0.24), and it was 0.62% (95% CI 0.07-1.68) in uncircumcised men. Thus, receptive UAI with ejaculation was found to be approximately twice as risky as receptive UAI with withdrawal or insertive UAI for uncircumcised men and over 10 times as risky as insertive UAI for circumcised men. Despite the fact that a high proportion of HIV-infected men are on antiretroviral treatment and have undetectable viral load, the per-contact probability of HIV transmission due to UAI is similar to estimates reported from developed country settings in the pre-HAART era. Jin F, Jansson J, Law M, Prestage GP, Zablotska I, Imrie JC, Kippax SC, Kaldor JM, Grulich AE, Wilson DP. Per-contact probability of HIV transmission in homosexual men in Sydney in the era of HAART. AIDS. 2010 Mar 27; 24(6): 907-913.

Protease Polymorphisms in HIV-1 Subtype CRF01_AE Represent Selection by Antiretroviral Therapy and Host Immune Pressure

Most of our knowledge about how antiretrovirals and host immune responses influence the HIV-1 protease gene is derived from studies of subtype B virus. The effect of protease resistance-associated mutations (PRAMs) and population-based HLA haplotype frequencies on polymorphisms found in CRF01_AE pro was investigated. CRF01_AE protease sequences retrieved from the LANL database were used and regional HLA frequencies from the dbMHC database were obtained. Polymorphisms and major PRAMs in the sequences were identified using the Stanford Resistance Database, and phylogenetic and selection analyses was performed using HyPhy. HLA binding affinities were

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estimated using the Immune Epitope Database and Analysis. Overall, 99% of CRF01_AE sequences had at least 1 polymorphism and 10% had at least 1 major PRAM. Three polymorphisms (L10 V, K20RMI and I62 V) were associated with the presence of a major PRAM (P < 0.05). Compared to the subtype B consensus, six additional polymorphisms (I13 V, E35D, M36I, R41K, H69K, L89M) were identified in the CRF01_AE consensus; all but L89M were located within epitopes recognized by HLA class I alleles. Of the predominant HLA haplotypes in the Asian regions of CRF01_AE origin, 80% were positively associated with the observed polymorphisms, and estimated HLA binding affinity was estimated to decrease 19-40 fold with the observed polymorphisms at positions 35, 36 and 41. Polymorphisms in CRF01_AE protease gene were common, and polymorphisms at residues 10, 20 and 62 most likely represent selection by use of protease inhibitors, whereas R41K and H69K were more likely attributable to recognition of epitopes by the HLA haplotypes of the host population. Manosuthi W, Butler DM, PŽrez-Santiago J, Poon AF, Pillai SK, Mehta SR, Pacold ME, Richman DD, Pond SK, Smith DM. Protease polymorphisms in HIV-1 subtype CRF01_AE represent selection by antiretroviral therapy and host immune pressure. AIDS. 2010 Jan 28; 24(3): 411-416.

Large-Scale Candidate Gene Analysis of Spontaneous Clearance of Hepatitis C Virus

Human genetic variation is a determinant of recovery from acute hepatitis C virus (HCV) infection; however, to date, single-nucleotide polymorphisms (SNPs) in only a limited number of genes have been studied with respect to HCV clearance. The authors determined whether SNPs in 112 selected immune response genes are important for HCV clearance, by genotyping 1536 SNPs in a cohort of 343 persons with natural HCV clearance and 547 persons with HCV persistence. PLINK (version 1.05) and Haploview (version 4.1) software packages were used to perform association, permutation, and haplotype analyses stratified by African American and European American race. Of the 1536 SNPs tested, 1426 (92.8%) were successfully genotyped. In African Americans, 18 SNPs located in 11 gene regions associated with HCV infection outcome (empirical P value, < .01) were identified. In European Americans, there were 20 SNPs located in 8 gene regions associated with HCV infection outcome. Four of the gene regions studied (TNFSF18, TANK, HAVCR1, and IL18BP) contained SNPs for which the empirical P value was <.01 in both of the race groups. In this large-scale analysis of 1426 genotyped SNPs in 112 candidate genes, the investigators identified 4 gene regions that are likely candidates for a role in HCV clearance or persistence in both African Americans and European Americans. Mosbruger TL, Duggal P, Goedert JJ, Kirk GD, Hoots WK, Tobler LH, Busch M, Peters MG, Rosen HR, Thomas DL, Thio CL. Large-Scale Candidate Gene Analysis of Spontaneous Clearance of Hepatitis C Virus. J Infect Dis. 2010 Mar 5. [Epub ahead of print].

Hepatic Steatosis Associated with Increased Central Body Fat By Dual-Energy X-Ray Absorptiometry and Uncontrolled HIV In HIV/Hepatitis C Co-Infected Persons

The objective was to evaluate the relationship between regional body composition and liver disease (fibrosis or steatosis) in HIV/HCV co-infected individuals. Whole body dual-energy X-ray absorptiometry (DXA) was performed in 173 HIV/HCV co-infected persons within 12 months of a liver biopsy. Significant fibrosis was defined as a METAVIR stage greater than 1. Steatosis was graded as: 0, none; 1, steatosis involving less than 5% of hepatocytes; 2, 5-29%; 3, 30-60%; 4 greater than 60%, and was defined as more than 0. Poisson regression with robust variance was used to estimate prevalence ratios of the outcome measures. The population was 62% male and 84% black with a median body mass index of 25.2 kg/m (interquartile range

22.5, 29.3 kg/m). No differences in regional body fat or fat distribution were observed in 42 patients with significant fibrosis compared to others with less fibrosis. However, the 77 individuals (45%) with steatosis had greater central fat than those without steatosis [prevalence ratio 1.04 per kg trunk fat; 95% confidence interval (CI) 1.04, 1.11], after adjusting for hepatic fibrosis (prevalence ratio 1.77; 95% CI 1.29, 2.42), uncontrolled HIV replication (viral load >400 copies/ml) (prevalence ratio 1.57; 95% CI 1.12, 2.22), age, sex, race and diabetes mellitus. In HIV/HCV co-infected individuals, measures of regional body fat or fat distribution were not associated with hepatic fibrosis. In contrast, increased central adiposity by DXA, as well as concomitant fibrosis and uncontrolled HIV, were associated with hepatic steatosis. The extent to which weight loss and effective antiretroviral therapy can reduce the risk of steatosis deserves further investigation. Brown TT, Mehta SH, Sutcliffe C, Higgins Y, Torbenson MS, Moore RD, Thomas DL, Sulkowski MS. Hepatic steatosis associated with increased central body fat by dual-energy X-ray absorptiometry and uncontrolled HIV in HIV/hepatitis C co-infected persons. AIDS. 2010 Mar 27; 24(6): 811-817.

Lack of Clinically Significant Drug Interactions Between Nevirapine and Buprenorphine

This study was conducted to determine whether drug interactions of clinical importance occur between buprenorphine, an opioid partial agonist medication used in treatment of opioid dependence, and the nonnucleoside reverse transcriptase inhibitor (NNRTI) nevirapine. Opioid-dependent, buprenorphine/naloxone-maintained, HIV-negative volunteers (n = 7) participated in 24-hour sessions to determine the pharmacokinetics of buprenorphine alone and of buprenorphine and nevirapine following administration of 200 mg nevirapine daily for 15 days. Opiate withdrawal symptoms, cognitive effects, and adverse events were determined prior to and following nevirapine administration. Modest decreases were observed for AUC for buprenorphine and its metabolites. There was a trend for more rapid clearance of both buprenorphine (p = .08) and buprenorphine-3-glucuronide (p = .08). While no single effect reached statistical significance, the joint probability that the consistent declines in all measures of exposure were due to chance was extremely low, indicating that nevirapine significantly reduces overall exposure to buprenorphine and buprenorphine metabolites. Clinically significant consequences of the interaction were not observed. Buprenorphine did not alter nevirapine pharmacokinetics. Dose adjustments of either buprenorphine or nevirapine are not likely to be necessary when these drugs are coadministered for the treatment of opiate dependence and HIV disease. McCance-Katz EF, Moody DE, Morse GD, Ma Q, Rainey PM. Lack of Clinically Significant Drug Interactions between Nevirapine and Buprenorphine. Am J Addict. 2010 Jan 1; 19(1): 30-37.

Interactions between Buprenorphine and Antiretrovirals: Nucleos(t)ide Reverse Transcriptase Inhibitors (NRTI) Didanosine, Lamivudine, and Tenofovir

To improve outcomes among injection drug users with HIV and/or chronic hepatitis B, it is important to identify drug interactions between antiretroviral and opiate therapies. The investigators report the results of a study designed to examine the interaction between buprenorphine and the nucleos(t)ide reverse transcriptase inhibitors (NRTI) didanosine (ddI), lamivudine (3TC), and tenofovir (TDF). Opioid-dependent, buprenorphine/naloxone-maintained, HIV-negative volunteers (n = 27) participated in two 24-hour sessions to determine (1) pharmacokinetics of buprenorphine alone and (2) pharmacokinetics of both buprenorphine and either ddI, 3TC, or TDF. Among buprenorphine/ naloxone-maintained study participants, no significant changes in buprenorphine pharmacokinetics were observed following ddI, 3TC, or TDF administration.

Buprenorphine had no significant effect on NRTI concentrations. Concomitant use of buprenorphine with ddI, 3TC, or TDF results in neither a significant pharmacokinetic nor pharmacodynamic interaction. Baker J, Rainey PM, Moody DE, Morse GD, Ma Q, McCance-Katz EF. Interactions between Buprenorphine and Antiretrovirals: Nucleos(t)ide Reverse Transcriptase Inhibitors (NRTI) Didanosine, Lamivudine, and Tenofovir. Am J Addict. 2010 Jan 1; 19(1): 17-29.

Pharmacokinetic Interactions Between Buprenorphine/Naloxone and Tipranavir/Ritonavir in HIV-Negative Subjects Chronically Receiving Buprenorphine/Naloxone

HIV-infected patients with opioid dependence often require opioid replacement therapy. Pharmacokinetic interactions between HIV therapy and opioid dependence treatment medications can occur. HIV-seronegative subjects stabilized on at least 3 weeks of buprenorphine/naloxone (BUP/NLX) therapy sequentially underwent baseline and steady-state pharmacokinetic evaluation of open-label, twice daily tipranavir 500 mg co-administered with ritonavir 200 mg (TPV/r). Twelve subjects were enrolled and 10 completed the study. Prior to starting TPV/r, the geometric mean BUP AUC(0-24h) and C(max) were 43.9 ng h/mL and 5.61 ng/mL, respectively. After achieving steady-state with TPV/r (> or = 7 days), these values were similar at 43.7 ng h/mL and 4.84 ng/mL, respectively. Similar analyses for norBUP, the primary metabolite of BUP, demonstrated a reduction in geometric mean for AUC(0-24h) [68.7-14.7 ng h/mL; ratio=0.21 (90% CI 0.19-0.25)] and C(max) [4.75-0.94 ng/mL; ratio=0.20 (90% CI 0.17-0.23)]. The last measurable NLX concentration (C(last)) in the concentration-time profile, never measured in previous BUP/NLX interaction studies with antiretroviral medications, was decreased by 20%. Despite these pharmacokinetic effects on BUP metabolites and NLX, no clinical opioid withdrawal symptoms were noted. TPV steady-state AUC(0-12h) and C(max) decreased 19% and 25%, respectively, and C(min) was relatively unchanged when compared to historical control subjects receiving TPV/r alone. No dosage modification of BUP/NLX is required when co-administered with TPV/r. Though mechanistically unclear, it is likely that decreased plasma RTV levels while on BUP/NLX contributed substantially to the decrease in TPV levels. BUP/NLX and TPV/r should therefore be used cautiously to avoid decreased efficacy of TPV in patients taking these agents concomitantly. Bruce RD, Altice FL, Moody DE, Lin SN, Fang WB, Sabo JP, Wruck JM, Piliero PJ, Conner C, Andrews L, Friedland GH. Drug Alcohol Depend. 2009 Dec 1; 105(3): 234-239.

Methadone Maintenance Patients' Knowledge, Attitudes, Beliefs, and Experiences Concerning Treatment For Hepatitis C Virus Infection

Hepatitis C virus (HCV) knowledge, attitudes, beliefs, and experiences (KABE) of 64 HCV antibody positive methadone maintenance treatment (MMT) patients were assessed in conjunction with acceptability of an on-site semi-structured HCV education session, HCV RNA diagnostic testing, HCV treatment motivational assessment, and initiation of HCV treatment. The KABE interviews were conducted in 2006 and 2007 in an urban New York State MMT clinic in affiliation with a NIDA-funded HCV research project. The majority had basic knowledge of HCV disease, but poor understanding of HCV testing and treatment. While the majority of participants expressed fear of HCV treatment side effects, 88% accepted HCV RNA testing and 78% expressed willingness to start HCV treatment with the majority of chronically infected choosing to start HCV treatment medications. Study limitations and implications are discussed. Canfield KM, Smyth E, Batki SL. Methadone maintenance patients' knowledge, attitudes, beliefs, and experiences concerning treatment for hepatitis C virus infection. Subst Use Misuse. 2010 Mar; 45(4): 496-451.

Acceleration of HCV Envelope Evolution in Humans is Consistent with Progressive Humoral Immune Selection During the Transition from Acute to Chronic Infection

During the transition from acute to chronic infection in HCV persistently infected individuals, cellular responses initiate within the first 6 months of primary infection and collapse thereafter whereas humoral responses activate later during the chronic phase. Whether and how this deviation of immune responses specifically influences HCV evolution is unknown. To determine the pattern of HCV evolution during this critical period, the authors conducted extensive sequence analysis on annual clonal hemigenomic sequences up to three years in six well-characterized subjects, using statistical methods that accounted for repeated measures. Significantly different evolutionary rates were observed in envelope versus non-envelope genes, with increasing rate of non-synonymous change (dN) in envelope and stable dN in non-envelope genes ($p=0.006$). The ratio of envelope to non-envelope non-synonymous rate increased from 2 in year 1 to 5 in years 2 and 3. Centripetal changes (reversions toward matching of worldwide subtype 1a consensus sequence) were frequently observed during the three year transition from acute infection to chronicity, even in the presence of nAb pressure. Remarkably, HVR1 sequences remained stable for up to 21 months in the absence of nAb pressure in one subject, followed by rapid changes that were temporally associated with the detection of nAb responses, strongly suggesting that HVR1 evolution is shaped by nAb pressure. These data provide the first systematic estimates of HCV evolutionary rates in multiple genes during early infection in vivo, and provide additional evidence for deterministic, rather than random, evolution of HCV. Liu L, Fisher BE, Dowd KA, Astemborski J, Cox AL, Ray SC. Acceleration of HCV envelope evolution in humans is consistent with progressive humoral immune selection during the transition from acute to chronic infection. J Virol. 2010 Mar 3. [Epub ahead of print].

Risk Behaviors after Hepatitis C Virus Seroconversion in Young Injection Drug Users In San Francisco

The rationale for screening populations at risk for hepatitis C virus infection (HCV) includes the possibility of altering risk behaviors that impact disease progression and transmission. This study prospectively examined young injection drug users (IDU) to determine if behaviors changed after they were made aware of HCV seroconversion. The authors estimated the effects of HCV seroconversion coupled with post-test counseling on risk behaviors (alcohol use, non-injection and injection drug use, lending and sharing injecting equipment, and having sex without a condom) and depression symptoms using conditional logistic regression, fitting odds-ratios for immediately after disclosure and 6 and 12 months later, and adjusting for secular effects. 112 participants met inclusion criteria, i.e. they were documented HCV seronegative at study onset and subsequently seroconverted during the follow-up period, with infection confirmed by HCV RNA testing. HCV seroconversion was independently associated with a decreased likelihood of consuming alcohol (OR=0.52; 95% CI: 0.27-1.00, $p=0.05$) and using non-injection drugs (OR=0.40; 95% CI: 0.20-0.81, $p=0.01$) immediately after disclosure, however, results were not sustained over time. There were significant ($p<0.05$) declines in the use of alcohol, injection and non-injection drugs, and sharing equipment associated with time that were independent from the effect of seroconversion. Making young IDU aware of their HCV seroconversion may have a modest effect on alcohol and non-injection drug use that is not sustained over time. Tsui JI, Vittinghoff E, Hahn JA, Evans JL, Davidson PJ, Page K. Risk behaviors after hepatitis C virus seroconversion in young injection drug users in San Francisco. Drug Alcohol Depend. 2009 Nov 1; 105(1-2): 160-163.

Methadone and Buprenorphine Toxicity in Children

Recent years have seen very large increases in the prescribing of methadone and buprenorphine formulations for treatment of opioid addiction as well as the increasing utilization of methadone for the treatment of chronic pain. Coincident with the rise in the prescribing of these drugs has been a substantial increase in pediatric opioid toxicities and adverse events. This review will address the current state of methadone- and buprenorphine-related adverse events in children in the United States. The authors also discuss treatment of opioid toxicity in pediatric populations and make recommendations aimed at reducing these occurrences. Boyer EW, McCance-Katz EF, Marcus S. Methadone and buprenorphine toxicity in children. Am J Addict. 2010 Jan 1; 19(1): 89-95.

Indicators of Buprenorphine and Methadone Use and Abuse: What Do We Know?

Abuse of prescription opioids is a growing problem. The number of methadone pain pills distributed now exceeds liquid methadone used in opioid treatment, and the increases in buprenorphine indicators provide evidence of the need to monitor and intervene to decrease the abuse of this drug. The need for additional and improved data to track trends is discussed, along with findings as to the characteristics of the users and combinations of drugs. Data on toxicities related to methadone or buprenorphine, particularly in combination with other prescribed drugs, are presented and clinical implications and considerations are offered. These findings underscore the need for physicians to be aware of potential toxicities and to educate their patients regarding these issues. Maxwell JC, McCance-Katz EF. Indicators of buprenorphine and methadone use and abuse: what do we know? Am J Addict. 2010 Jan 1; 19(1): 73-88.

Effect of Cocaine Use on Methadone Pharmacokinetics in Humans

Chronic cocaine use has been shown to significantly decrease buprenorphine concentrations in the blood with potential for adverse events and poor treatment response. In this study, the authors investigated whether a similar drug interaction occurred between cocaine and methadone. In a retrospective analysis, methadone pharmacokinetics were compared for those who were either regular cocaine users (N = 16) or with intermittent or no cocaine use (N = 23). Participants who used cocaine regularly showed a significant decrease in C(min) ($p = .04$) and a trend for decreased AUC ($p = .09$) and more rapid methadone clearance ($p = .08$). Regular cocaine use may adversely impact treatment outcomes for opioid dependence in those receiving methadone maintenance by decreasing methadone exposure. McCance-Katz EF, Jatlow P, Rainey PM. Effect of cocaine use on methadone pharmacokinetics in humans. Am J Addict. 2010 Jan 1; 19(1): 47-52.

Effect of Cocaine Use on Buprenorphine Pharmacokinetics in Humans

The effect of chronic cocaine use on buprenorphine pharmacokinetics was investigated to identify drug interactions and potential toxicities. In a retrospective analysis, pharmacokinetics were compared for 16 studies completed on subjects who were regular cocaine users and 74 studies on subjects who used cocaine only occasionally or not at all. All participants were stably maintained on buprenorphine/naloxone 16/4 mg daily. Participants who used cocaine regularly had lower buprenorphine exposure (AUC 34% lower; C(max) 27% lower and C(24) 37% lower; $p <= .001$ for all comparisons. Regular cocaine users were younger ($p = .0007$), and used more heroin ($p = .004$) and cocaine ($p < .0001$). Regular cocaine use may result in lower

buprenorphine plasma concentrations with potential for adverse clinical outcomes. McCance-Katz EF, Rainey PM, Moody DE. Effect of cocaine use on buprenorphine pharmacokinetics in humans. Am J Addict. 2010 Jan 1; 19: 38-46.

Methamphetamine Use is Associated with Increased Dental Disease

Methamphetamine (MA) use has been anecdotally linked to rampant dental disease. UCLA based researchers sought to determine the relative prevalence of dental comorbidities in MA users, verify whether MA users have quantifiably more dental disease and report more dental problems than non-users, and establish the influence of mode of MA administration on oral health outcomes. MA-dependent adults (N = 301) underwent comprehensive medical and oral assessments by participating physicians. Patient self-reports on oral health and substance use behaviors were collected. Propensity score matching from the National Health and Nutrition Examination Survey (NHANES) showed Dental/oral disease was one of the most prevalent medical comorbidities in MA users (41.3%) although they were generally healthy. On average, MA users had significantly more missing teeth than matched NHANES controls (4.58 vs. 1.96, $p < .001$) and were more likely to report poor oral health ($p < .001$). Significant subsets of subjects expressed concerns with their dental appearance (28.6%), problems with broken/loose teeth (23.3%) and tooth grinding/erosion (22.3%). The intravenous (IV) use of MA was more likely to be associated with missing teeth than smoking MA (OR=2.47., 95% C.I., 1.3 - 4.8). The investigators conclude that overt dental disease is a key distinguishing comorbidity in MA use. Contrary to common perception, MA users who inject have higher rates of disease than those who smoke or inhale. The investigators conclude that dental disease may provide a temporally stable MA-specific medical marker with discriminant utility in many ways for identifying MA users. Concerns about "dental self-image" could be used as a trigger for targeted behavioral interventions in dental office or for referral to substance use treatment programs. Given the relative prominence of dental comorbidities, dentists can play a crucial role in the early detection of MA use and participate as integral members of a collaborative care team tending to the MA user. Shetty V, Mooney LJ, Zigler CM, Belin TR, Murphy D, Rawson R. The relationship between methamphetamine use and increased dental disease. J Am Dent Assoc. 2010 Mar; 141(3): 307-318.

Effects of Buprenorphine and Hepatitis C on Liver Enzymes in Adolescents and Young Adults

This study explored changes in transaminase values associated with buprenorphine treatment and hepatitis C status among opioid-dependent subjects aged 15 to 21 years. One hundred fifty-two subjects were randomized to 2-week detoxification with buprenorphine/naloxone (DETOX) or 12 weeks with buprenorphine/naloxone (BUP). Liver chemistries were obtained at baseline and at 4, 8, and 12 weeks. One hundred eleven patients had at least one set of transaminases during treatment and were included in analyses of treatment effects. Overall, 8 of the 60 BUP participants versus 12 of the 51 DETOX participants had ³ one elevated alanine aminotransferase value during follow-up ([chi]2 = ns). Five of the 60 BUP participants versus 11 of the 51 DETOX participants had ³ one elevated aspartate aminotransferase value (P = 0.048). Twenty eight of the 152 participants were hepatitis C (HCV) positive at baseline and 4 seroconverted within 12 weeks, 2 in each group. HCV status was significantly associated with transaminase abnormalities (P = 0.009 and 0.006 for alanine aminotransferase and aspartate aminotransferase, respectively). HCV status had a strong effect on transaminase abnormalities among participants assigned to DETOX, but not among those assigned to BUP. No evidence was found for hepatotoxicity of buprenorphine in this exploratory

analysis. HCV was present in a significant minority of participants and was a significant predictor of transaminase elevation. Results suggest that stabilization on buprenorphine may be associated with a decrease in the frequency of transaminase abnormalities associated with HCV in opioid-dependent young people. The high rate of seroconversion underscores the importance of effective treatment and prevention. Bogenschutz MP, Abbott PJ, Kushner R, Tonigan JS, Woody GE. J Addict Med. Published Ahead of Print January 22, 2010.

Sex Under the Influence of Drugs or Alcohol: Common for Men in Substance Abuse Treatment and Associated with High-risk Sexual Behavior

Sex under the influence of drugs or alcohol is associated with high-risk sexual behavior. Heterosexual men (n = 505) in substance abuse treatment completed a computer-administered interview assessing sexual risk behaviors. Most men (73.3%) endorsed sex under the influence in the prior 90 days, and 39.1% endorsed sex under the influence during their most recent sexual event. Sex under the influence at the most recent event was more likely to involve anal intercourse, sex with a casual partner, and less condom use. Patients might benefit from interventions targeting sexual behavior and substance use as mutual triggers. Calsyn DA, Cousins SJ, Hatch-Maillette MA, Forcehimes A, Mandler R, Doyle SR, Woody G. Am J Addict. 2010 Mar 1; 19(2): 119-127.

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Research Findings - Services Research

Comparative Effectiveness Trial of 5 Smoking Cessation Pharmacotherapies in Primary Care Clinics

Randomized efficacy clinical trials conducted in research settings may not accurately reflect the benefits of tobacco dependence treatments when used in real-world clinical settings. Effectiveness trials (e.g., in primary care settings) are needed to estimate the benefits of cessation treatments in real-world use. To perform this comparative effectiveness trial a total of 1346 adult primary care patients attending routine appointments were recruited by medical assistants in 12 primary care clinics in the mid-west United States. Patients were randomly assigned to 5 active pharmacotherapies: 3 monotherapies (nicotine patch, nicotine lozenge, and bupropion hydrochloride sustained release [SR]) and 2 combination therapies (patch + lozenge and bupropion SR + lozenge). Patients were referred to a telephone quit line for cessation counseling. Primary outcomes included 7-day point prevalence abstinence at 1 week, 8 weeks, and 6 months after quitting and number of days to relapse. The researchers found that among 7128 eligible smokers (> or =10 cigarettes per day) attending routine primary care appointments, 1346 (18.9%) were enrolled in the study. Six-month abstinence rates for the 5 active pharmacotherapies were the following: bupropion SR, 16.8%; lozenge, 19.9%; patch, 17.7%; patch + lozenge, 26.9%; and bupropion SR + lozenge, 29.9%. Bupropion SR + lozenge was superior to all of the monotherapies (odds ratio, 0.46-0.56); patch + lozenge was superior to patch and bupropion monotherapies (odds ratio, 0.56 and 0.54, respectively). This study showed that one in 5 smokers attending a routine primary care appointment was willing to make a serious quit attempt that included evidence-based counseling and medication. In this comparative effectiveness study of 5 tobacco dependence treatments, combination pharmacotherapy significantly increased abstinence compared with monotherapies. Provision of free cessation medications plus quit line counseling arranged in the primary care setting holds promise for assisting large numbers of smokers to quit. Smith S, McCarthy D, Japuntich S, Christiansen B, Piper M, Jorenby D, Fraser D, Fiore M, Baker T, Jackson T. Comparative effectiveness of 5 smoking cessation pharmacotherapies in primary care clinics. Arch Intern Med. 2009; 169(22): 2148-2155.

Opioid Prescriptions for Chronic Pain and Association to Overdose: A Cohort Study

Long-term opioid therapy for chronic non-cancer pain is becoming increasingly common in community practice. Concomitant with this change in practice, rates of fatal opioid overdose have increased. The extent to which overdose risks are elevated among patients receiving medically prescribed long-term opioid

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therapy is unknown. The objective of this study is to estimate rates of opioid overdose and their association with an average prescribed daily opioid dose among patients receiving medically prescribed, long-term opioid therapy. Data from 9940 persons enrolled in a large HMO in the Pacific north-west who received 3 or more opioid prescriptions within 90 days for chronic non-cancer pain between 1997 and 2005 were included in the study. Cox proportional hazards models were used to estimate overdose risk as a function of average daily opioid dose (morphine equivalents) received at the time of overdose. Average daily opioid dose over the previous 90 days was obtained from automated pharmacy data. Primary outcomes were: nonfatal and fatal overdoses--were identified through diagnostic codes from inpatient and outpatient care and death certificates and were confirmed by medical record review. The authors found 51 opioid-related overdoses, including 6 deaths. Compared with patients receiving 1 to 20 mg/d of opioids (0.2% annual overdose rate), patients receiving 50 to 99 mg/d had a 3.7-fold increase in overdose risk (95% CI, 1.5 to 9.5) and a 0.7% annual overdose rate. Patients receiving 100 mg/d or more had an 8.9-fold increase in overdose risk (CI, 4.0 to 19.7) and a 1.8% annual overdose rate. Limitations in this study are: that increased overdose risk among patients receiving higher dose regimens may be due to confounding by patient differences and by use of opioids in ways not intended by prescribing physicians. The small number of overdoses in the study cohort is also a limitation. In this study patients receiving higher doses of prescribed opioids are at increased risk for overdose, which underscores the need for close supervision of these patients. Dunn K, Saunders K, Rutter C, Banta-Green C, Merrill J, Sullivan M, Weisner C, Silverberg M, Campbell C, Psaty B, Von Korff M. Opioid prescriptions for chronic pain and association to overdose: a cohort study. Ann Intern Med. 2010; 152(2): 85-92.

Interim Methadone Reduced Heroin Use in Six New Clinics

Evidence in the US and Canada is mounting that interim methadone, providing the drug without psychosocial services for up to 120 days, reduces opiate use and increases enrollment in full treatment. Previous research at a single Baltimore clinic found interim methadone patients were more likely to enroll in treatment than those on waitlists without interim maintenance. This study evaluated expansion of interim maintenance to six new Baltimore area clinics. These results expand evidence of effectiveness. Of the 1000 patients enrolled in interim maintenance, 76% enrolled in full methadone treatment at 120 days. The sample was 56% male with an average age of 41. Seventy-one percent were African American, 29% were Caucasian. The average educational level was 11th grade, and the average days of heroin use at admission was 25. At the time of entering full treatment, positive tests for the presence of opiate metabolite dropped from 90% to 38%. The study also divided the sample into two groups; one charged a $10 weekly fee, and one charged nothing. Comparative results indicated the fee had no significant impact on enrollment rates or heroin use. Results show that expansion of interim maintenance is possible. In fact, four of the six clinics continued interim maintenance at their own expense after study support ended. One factor should be noted, implementation was delayed over six months due to the requirement to obtain special permission from local (1), state (2), and federal (1) agencies, which could be a disincentive for future expansion. Schwartz RP, Jaffe JH, O'Grady KE, Das B, Highfield DA, Wilson ME. Scaling-up interim methadone maintenance: treatment for 1,000 heroin-addicted individuals. J Subst Abuse Treat. 2009; 37: 362-367.

Methadone Patients Drop Out of Treatment Mainly Because of Program-Related Inflexibility and Incarceration

Methadone treatment was designed and implemented to be an extended program of opiate agonist maintenance. Methadone, though addicting, restores

patient cognitive-emotional functioning, and abates craving and withdrawal symptoms so patients may hold steady employment, establish a fixed residence, and begin to rebuild their lives. Unfortunately, dropout rates within the first year of treatment exceed 50%. This study interviewed 42 methadone treatment dropouts in the Baltimore Maryland area to learn why they left. The average age of the sample was 40, and average time in treatment was 138 days. Sixty-four percent were African American and 60% were males. Individual interviews were conducted using a flexibly-structured interview. Four primary factors were identified through analysis of patient remarks: Program-Related factors (40%), methadone-related concerns (12%), life events/logistics (10%), and incarceration (38%). Program factors focused on program inability to adapt to the evolving needs of patients struggling to restore their lives, usually exhibited as rule inflexibility or unwillingness to help patients transition to a different program or counselor. Methadone-related issues emphasized concerns about methadone withdrawal issues, and concern that methadone left patients still opiate-addicted. Life-event issues included relocation of partner, and getting a job too far from the clinic. Incarceration topics emphasized problems with patients not being detoxified by jailers, putting some through agonizing withdrawal episodes. Results suggest that methadone service reengineering is warranted, especially with respect to interface with the criminal justice system. Schacht Reiseinger H, Schwartz RP, Schwartz RPS, Peterson JA, Kelly SM, O'Grady KE, Marrari EA, Brown BS, Agard MH. Premature discharge from methadone treatment: patient perspectives. J Psychoactive Drugs. 2009; 41(3): 285-296.

Program-related Factors Associated with Methadone Treatment Drop-out

Longer retention in drug abuse treatment is associated with better patient outcomes, and research indicates the first 12 months of methadone treatment are critical to patient success. Nevertheless, large-scale multisite longitudinal studies over the past three decades indicate that the majority of patients drop out during the first year of methadone treatment. Through an examination of 42 qualitative interviews with patients prematurely discharged from six methadone treatment programs in Baltimore, this study highlights factors patients describe as contributing to their reasons for being discharged within the first 12 months of the treatment. The mean age of patients was 40.4 years, 25 (59.5%) were men, 31 (73.8%) reported injecting heroin, and the sample had a mean of 2.8 lifetime drug abuse treatment episodes. The length of treatment prior to discharge of the total sample ranged from two days to 363 days, with an average treatment length of 138 days. Of the interviewed participants, 27 (64.3%) were African American and 15 (35.7%) were Caucasian. The two most consistent themes on reasons for discharge were program-related factors and incarceration. Program-related reasons for discharge included a disagreement over program rules, conflict with counselor, and schedule conflicts. The factors are richly described through patients' words and underscore the ways in which patients' perceptions of control exerted by the program and by the medication and misunderstandings of program structure can lead to premature discharge. Patients' reasons for discharge were compared to counselors' reasons as indicated in discharge summary forms. An analysis of the patterns of agreement and disagreement are presented. Possible approaches to deal with program-related reasons for discharge include having rules clearly communicated to the patients at admission and throughout treatment, having a clearly described and fairly implemented system of appeal, which includes a patient advocate and appeal to an outside authority (such as the funder), and the ability to switch counselors when conflicts are insurmountable. It might also be useful to consider separating the counseling function from the rule enforcement function to try to improve rapport with counselors and improve patient satisfaction. Another alternative would be to have a discharge team of clinical experts to review each case prior to discharge

and to make alternative treatment recommendations or transfer to another program when discharge is determined to be the best course. Additional patient-centered program and policy implications are discussed. Reisinger H, Schwartz R, Mitchell S, Peterson J, Kelly S, O 'Grady K, Marrari E, Brown B, Agar M. Premature discharge from methadone treatment: patient perspectives. J Psychoactive Drugs. 2009; 41(3): 285-296.

Diverted Methadone and Buprenorphine Among Opiate-addicted Individuals

This study examined the uses of diverted methadone and buprenorphine among opiate-addicted individuals recruited from new admissions to methadone programs and from out-of-treatment individuals recruited from the streets. Self-report data regarding diversion were obtained from surveys and semi-structured qualitative interviews. Approximately 16% (n = 84) of the total sample (N = 515) reported using diverted (street) methadone two-three times per week for six months or more, and for an average of 7.8 days (SD = 10.3) within the past month. The group reporting lifetime use of diverted methadone as compared to the group that did not report such use was less likely to use heroin and cocaine in the 30 days prior to admission (ps <.01) and had lower ASI Drug Composite scores (p <.05). Participants in the qualitative sub-sample (n = 22) indicated that street methadone was more widely used than street buprenorphine and that both drugs were largely used as self-medication for detoxification and withdrawal symptoms. Participants reported using low dosages and no injection of either medication was reported. Gwin Mitchell S, Kelly S, Brown B, Schacht Reisinger H, Peterson J, Ruhf A, Agar M, O 'Grady K, Schwartz R. Uses of diverted methadone and buprenorphine by opioid-addicted individuals in Baltimore, Maryland. Am J Addict. 2009; 18(5): 346-355.

Ethnographic Investigation of Opioid Withdrawal Experiences During Incarceration

Both heroin-addicted individuals and methadone maintenance patients are likely to face untreated opioid withdrawal while incarcerated. Limited research exists concerning the withdrawal experiences of addicted inmates and their impact on individuals' attitudes and plans concerning drug abuse treatment. In the present study, 53 opioid dependent adults (32 in methadone treatment and 21 out of treatment) were interviewed in an ethnographic investigation of withdrawal experiences during incarceration. The 53 participants who discussed incarceration had a mean age of 41 years; 70% were male, 70% were African American, 62% were either divorced or had never been married, and most had completed less than 12 years of formal education. When treatment for opioid withdrawal was unavailable, detoxification experiences were usually described as negative and were often associated with a variety of unhealthy behaviors designed to relieve withdrawal symptoms. Negative methadone withdrawal experiences also negatively influenced participants' receptivity to seeking methadone treatment upon release. A minority of participants took a positive view of their withdrawal experience and saw it as an opportunity to detox from heroin or discontinue methadone. Findings support the importance of providing appropriate opioid detoxification and/or maintenance therapy to opioid-dependent inmates. Correctional institutions present a useful venue for providing, encouraging and facilitating access to substance abuse treatment. Mitchell S, Kelly S, Brown B, Reisinger H, Peterson J, Ruhf A, Agar M, Schwartz R. Incarceration and opioid withdrawal: the experiences of methadone patients and out-of-treatment heroin users. J Psychoactive Drugs. 2009; 41(2): 145-152.

Integrating Employee Assistance Programs and Managed

Behavioral Health Care Plans May Increase Access to Addiction Treatment

Claims data on 286,750 enrollees in Managed Health Network (MHN), a large national managed behavioral health care organization (MBHO) were used to explore whether or not participation in a plan that integrated the employee assistance program (EAP) benefits and MBHO benefits resulted in increased access to addiction services compared with participation in a plan where EAP and MBHO benefits and services were not integrated. The integrated plans analyzed here provided a single toll-free number for employees to access care for either EAP or managed behavioral healthcare services, allowed employees to use the EAP portion of the benefit first, if appropriate, and allowed them to remain with the same network provider once EAP benefits had been exhausted. Most, but not all, of those in the non-integrated plans had separate EAP benefits. Weighted logistic regression using exact matching (on gender, age group, census region, and spouse/dependent status) was used to estimate the relationship. The analysis revealed that participation in an integrated plan was associated with higher odds of accessing addiction services (OR = 1.23, CI 1.04-1.46, P <0.01). These results suggest that the way benefits are organized may have significant implications for the appropriate use of services although further research focused on those with addiction (as opposed to general population analyses) and using designs that can account for patient diagnoses and support causal inferences are needed to bolster that conclusion. Levy Merrick E, Hodgkin D, Horgan C, Hiatt D, McCann B, Azzone V, Zolotusky G, Ritter G, Reif S, McGuire T. Integrated employee assistance program/managed behavioral health care benefits: relationship with access and client characteristics. Adm Policy Ment Health. 2009; 36(6): 416-423.

New Process-Oriented Measure of Addiction Counselor Performance

Until now, the job of addiction counselor has not been mapped and modeled in any way that permits quantitative research. This study applied the Critical Incident Technique (CIT) commonly used in performance research by industrial/organizational (I/O) psychologists to a) develop descriptions of what counselors do, b) develop conceptual domains for building a generic performance model, and then c) build a questionnaire to validate the model. CIT sessions (14) were held at various times over an 8-month period involving 116 staff. Incidents (998) addressed those between clients and counselors and counselors and their peers, managers, and funding agencies. Respondents were 47% white, 28% African American, and 25% Hispanic, and evenly split on gender. Incidents were q-sorted by three groups of one clinical and two I/O psychologists into macro-domains (providing clinical services, actions that facilitate clinical performance (e.g. scheduling appointments), managerial behaviors, and employee citizenship behaviors. Redundant CIs were eliminating and then sorted into one of 15 quality of care-related dimensions. CIs were converted into brief descriptive item stems for rating on a five-point Likert-type scale addressing frequency of engaging in the behavior. The resulting items were administered in mailed questionnaires to 997 counselors in 51 agencies in California (39) and Maryland (12) with a 62% response rate (n=618). Respondents were 66% female; 53% were white, 31% African American, and 21% were Hispanic or Asian; and 94% had at least a GED/HS diploma with the remainder having at least some college education. Scales were validated against job satisfaction, turnover intent, and relative agency performance levels. Using classic test theory, 32 items were eliminated to yield a final instrument of 68 items with alpha reliabilities of .80 or higher. The 68-item, 15 scale version was found to have the best fit in confirmatory factor analysis with a CFI of .90, RMSEA of .05, and a significant Chi-square of 5,241.76 (p<.01, df=2,105). Interclass correlations for within-agency agreement were all significant at the p<.05 level; and validities between the 15

scales and the three outcome measures were all significant at the p<.01 level. Managerial scale scores had the strongest relationship to outcome measures with most exceeding r=.40. Results suggest that this new counselor performance measure is suitable for future health services delivery research into quality of care. Mael FA, O'Shea PG, Smith MA, Burling AS, Carman KL, Haas A, Rogers KS. Development of a model and measure of process-oriented quality of care for substance abuse treatment. J Behav Health Serv Res. 2010; 37(1): 4-24.

Clinic Directors Experiencing Burn Out and Intention to Quit Position

A national sample of 410 addiction treatment clinic directors were surveyed (66% response rate) to determine their experienced levels of emotional exhaustion and intent to quit their jobs. The sample was evenly split for gender, with 67% holding masters degrees, and average levels of tenure in their position of 9.6 years. Using structural equation modeling, the degree of emotional exhaustion reported by respondents on the Maslach burnout inventory was found to be positively and directly related to turnover intention. Those in organizations emphasizing centralized (as opposed to more participative) decision-making reported higher intention to quit, but it did not affect burnout levels. Respondents who engaged in more long-range planning were less likely to report emotional exhaustion, as well as turnover intent, thereby demonstrating that planning had a moderating effect on turnover intention. Likewise, those with less autonomy and freedom for innovative decision-making were more likely to want to quit. All correlations between these variables were significant (p<.01). Knudsen HK, Ducharme LJ, Roman PM. Adapting the Job Demands-Resources Model to leaders of addiction treatment organizations. J Occupational Health Psy. 2009; 14(1): 84-95.

Organizational Adaptations May Undermine Essential Elements of Therapeutic Communities

Traditional therapeutic communities (TCs) are characterized by confrontational group therapy, treatment phases, a tenure-based resident hierarchy, and long-term residential care. In recent years, many TCs have modified the structure and intensity of the traditional model, tailored services for specific patient populations, and hired more professionally trained staff. Using data obtained from interviews with directors of a nationally representative sample of 380 TCs, this study examined the extent to which these recent modifications affect the underlying core technology of the TC modality. Results from a structural equation model indicate that TCs offering services for specific populations and professionalization of staff has had limited impact on six core TC elements as defined by the TC Survey of Essential Elements Questionnaire (SEEQ). Modifications to structure and intensity of TC programming evidenced the strongest effect. Outpatient-only TCs showed significantly lower adherence to five of the six elements. Short-term residential programs showed a similar negative trend. These findings are important because organizations implement changes in response to consumer demand and resource constraints (i.e., shortened intensity and duration of treatment); such changes have the potential to alter the core technology of treatment modalities. Research is needed to determine whether these adaptations have deleterious effects on patient outcomes. Dye MH, Ducharme LJ, Johnson JA, Knudsen HK, Roman PM. Modified Therapeutic Communities and adherence to traditional elements. J Psychoactive Drugs. 2009; 41(3): 275-283.

Therapist Behavior in Multi-systemic Therapy as a Predictor of Black and White Caregiver Responsiveness

The present study addressed two gaps in the emerging literature on the mechanisms of evidence-based family therapies. The first pertains to the need to examine what the multi-systemic therapy (MST) therapist does in therapy sessions to propel change, and how caregivers respond to those therapist behaviors. Consistent with family systems theory, the MST model of change emphasizes the role of family transactions in maintaining adolescent problem behavior. Therefore, as in many family treatments, therapeutic interventions typically attempt to change family patterns of interaction. The second gap in the literature pertains to the lack of therapy process research focusing specifically on minority populations. Although evidence-based family therapies have been used successfully with minority samples, little research has examined whether different therapist skills are required to engage caregivers from different racial backgrounds in treatment. This study examined the relationship between observed therapist behaviors and positive in-session caregiver responses and engagement using audiotapes from a randomized clinical trial of the effectiveness of integrating MST into juvenile drug court. In that study families in two MST conditions (drug court with MST, and drug court with MST enhanced with contingency management) showed significantly better substance use outcomes than in other conditions. Eighty-nine families who had participated in MST conditions (including some pilot families) were included in the present study. For 67% of these families, caregivers self-identified as Black and the rest as White. This study examined whether (a) therapist behaviors thought to enhance family treatment predicted caregiver in-session responses, and (b) caregiver race, racial match between caregiver and therapist, and family financial hardship moderated the relationships between therapist and caregiver behavior. Observers coded caregiver and therapist behavior during one session of MST for substance abusing adolescents. Therapist teaching, focusing on strengths, making reinforcing statements, problem solving, and dealing with practical family needs predicted caregiver engagement and/or positive response, regardless of race, racial match, or financial hardship. Caregiver race, financial hardship, and therapist-caregiver racial match occasionally moderated the relationship between other therapist and caregiver behaviors. Findings suggest both commonalities and differences in how therapist behavior may function to engage caregivers in family treatment, depending on diversity-related factors. Foster S, Cunningham P, Warner S, McCoy D, Barr T, Henggeler S. Therapist behavior as a predictor of black and white caregiver responsiveness in multisystemic therapy. J Fam Psychol. 2009; 23(5): 626-635.

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Research Findings - CTN-Related Research

Special Issue of the Journal of Substance Abuse Treatment (JSAT)

In January 2010, JSAT released the electronic pre-publication version of a special supplement focused on the CTN and its accomplishments. Developed in honor of the CTN's 10th anniversary, this special issue -- **"A Decade of Research by the National Drug Abuse Treatment Clinical Trials Network"** -- features overview articles describing the completed studies and outcomes from the past decade of CTN research. It also reviews several ancillary and secondary investigations, where data from original CTN trials is analyzed to reveal new correlations, identify subpopulation variations and propose future research directions. J Subst Abuse Treat. 2010 Jun;38 Suppl 1:S1-124.

The First Decade of the National Drug Abuse Treatment Clinical Trials Network: Bridging the Gap Between Research and Practice to Improve Drug Abuse Treatment

The network brings providers from community-based drug abuse treatment programs and scientists from university-based research centers together in an alliance that fosters bidirectional communication and collaboration. Collaboration enhanced the relevance of research to practice and facilitated the development and implementation of evidence-based treatments in community practice settings. The CTN's 20 completed trials tested pharmacological, behavioral, and integrated treatment interventions for adolescents and adults; more than 11,000 individuals participated in the trials. The article reviews the rationale for the CTN, describes the translation of its guiding principles into research endeavors, and anticipates the future evolution of clinical research within the Network. Tai B, Straus MM, Liu D, Sparenborg S, Jackson R, McCarty D. J Subst Abuse Treat. 2010 Jun;38 Suppl 1:S4-13.

Study Results from the Clinical Trials Network's First 10 Years: Where Do They Lead?

Since 2000, 24 discrete clinical trials were launched, 20 are completed, and 15 have published main outcomes papers. Of the latter, 4 tested pharmacological treatment, 8 psychosocial/behavioral treatment, 1 a combination of medication and counseling, and 2 targeted HIV/hepatitis C virus behavior. The main study findings are reviewed to identify the incremental progress toward improving drug treatment made by these trials and to propose next steps for the CTN and for the field arising from these studies. Wells EA, Saxon AJ, Calsyn DA, Jackson TR, Donovan DM. J Subst Abuse Treat. 2010 Jun;38 Suppl 1:S14-30.

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Partnerships and Pathways of Dissemination: The National Institute on Drug Abuse-Substance Abuse and Mental Health Services Administration Blending Initiative in the Clinical Trials Network

The article describes the CTN's integral role in the Blending Initiative, key partnerships and dissemination pathways through which the results of CTN trials are developed into blending products and then transferred to community treatment programs and blending initiatives involving buprenorphine, motivational incentives, and motivational incentives, and motivational interviewing. The Blending Initiative has resulted in high utilization of its products, preparation of more than 200 regional trainers, widespread training of service providers in most U.S. States, Puerto Rico, and the U.S. Virgin Islands and movement toward the development of Web-based implementation support and technical assistance. Martino S, Brigham GS, Higgins C, Gallon S, Freese TE, Albright LM, Hulsey EG, Krom L, Storti SA, Perl H, Nugent CD, Pintello D, Condon TP. J Subst Abuse Treat. 2010 Jun;38 Suppl 1:S31-43.

A Longitudinal Study of Organizational Formation, Innovation Adoption, and Dissemination Activities within the National Drug Abuse Treatment Clinical Trials Network

First, a longitudinal dataset is used to examine CTN's formation as a network of interorganizational interaction among treatment practitioners and researchers. Data indicate strong relationships of interaction and trust, but a decline in problem-centered interorganizational interaction over time. Second, adoption of buprenorphine and motivational incentives among CTN's affiliated community treatment programs is examined over three waves of data. Although adoption is found to increase with CTPs' CTN participation, there is only modest evidence of widespread penetration and implementation. Third, CTPs' pursuit of the CTN's dissemination goals are examined, indicating that such organizational outreach activities are underway and likely to increase innovation diffusion in the future. Roman PM, Abraham AJ, Rothrauff TC, Knudsen HK. J Subst Abuse Treat. 2010 Jun;38 Suppl 1:S44-52.

From Research to the Real World: Buprenorphine in the Decade of the Clinical Trials Network

Initial CTN efforts addressed the use of buprenorphine as treatment for opioid dependence. This article reviews CTN-based buprenorphine research and related efforts to overcome challenges to the implementation of buprenorphine therapy in mainstream practice. The most notable aspect of the CTN's buprenorphine research in the community setting is its demonstration that quality data can be generated without advocating any specific treatment philosophy. CTN provided valid and reliable data and gave clinicians the opportunity to incorporate the data into their own treatment philosophy. This article explores current issues and future challenges that may require additional CTN efforts. Ling W, Jacobs P, Hillhouse M, Hasson A, Thomas C, Freese T, Sparenborg S, McCarty D, Weiss R, Saxon A, Cohen A, Straus M, Brigham G, Liu D, McLaughlin P, Tai B. J Subst Abuse Treat. 2010 Jun;38 Suppl 1:S53-60.

Motivational Incentives Research in the National Drug Abuse Treatment Clinical Trials Network

The article reviews both main findings and secondary analyses from studies of abstinence incentives conducted in CTN. Previous research has supported the efficacy of tangible incentives provided contingent on evidence of recent drug abstinence. CTN conducted the first multisite effectiveness trial of this novel

intervention. Study participants were stimulant abusers (N = 803) in treatment at 14 clinical sites randomly assigned to treatment as usual with or without a prize draw incentive program. Participants could earn up to $400 over 3 months for submission of drug-free urine and breath (BAL) specimens. Three-month retention was significantly improved by incentives offered to psychosocial counseling clients (50% incentive vs. 35% control retained). Ongoing stimulant drug use was significantly reduced in methadone maintenance clients (54.4% incentive vs. 38.7% control samples testing stimulant-negative). In both settings, duration of continuous abstinence achieved was improved in the incentive condition. These studies support effectiveness of one abstinence incentive intervention and highlight the different outcomes that can be expected with application in methadone maintenance versus psychosocial counseling treatment settings. Secondary analyses have shown the importance of early treatment positive versus negative urine screens in moderating the outcome of abstinence incentives and have explored both safety and cost-effectiveness of the intervention. Stitzer ML, Petry NM, Peirce J. J Subst Abuse Treat. 2010 Jun;38 Suppl 1:S61-69.

Using a Latent Variable Approach to Inform Gender and Racial/ethnic Differences in Cocaine Dependence: A National Drug Abuse Treatment Clinical Trials Network Study

This study applies a latent variable approach to examine gender and racial/ethnic differences in cocaine dependence, to determine the presence of differential item functioning (DIF) or item-response bias to diagnostic questions of cocaine dependence, and to explore the effects of DIF on the predictor analysis of cocaine dependence. The analysis sample included 682 cocaine users enrolled in two national multisite studies of the National Drug Abuse Treatment Clinical Trials Network (CTN). There were no racial/ethnic differences in cocaine dependence; however, DIF by race/ethnicity was noted. Wu LT, Pan JJ, Blazer DG, Tai B, Stitzer ML, Woody GE. J Subst Abuse Treat. 2010 Jun;38 Suppl 1:S70-79.

Pain and Continued Opioid Use in Individuals Receiving Buprenorphine-Naloxone for Opioid Detoxification: Secondary Analyses from the Clinical Trials Network

Pain complaints are common among individuals with opioid dependence. However, few studies investigate pain during opioid detoxification or the impact this pain has on continued opioid use. This secondary analysis utilized data from two Clinical Trials Network randomized controlled trials of buprenorphine-naloxone for short-term opioid detoxification to examine the extent to which pain was associated with continued opioid use during and immediately following a 13-day detoxification protocol. At follow-up, more severe pain was associated with a greater number of self-reported days of opioid use during the prior 30 days ($p < .05$) but was not associated with urine toxicology results collected at follow-up. These results, although mixed, have potentially important clinical implications for assessing and addressing pain during opioid detoxification. Pain that is experienced during and immediately following medically monitored detoxification may be associated with continued opioid use. These findings lend further support for continued research on pain among patients with opioid dependence. Potter JS, Chakrabarti A, Domier CP, Hillhouse MP, Weiss RD, Ling W. J Subst Abuse Treat. 2010 Jun;38 Suppl 1:S80-86.

Predicting Outpatient Treatment Entry Following Detoxification for Injection Drug Use: The Impact of Patient and Program Factors

This article examines variables that predicted outpatient treatment entry within 6 months of residential detoxification. Patient data were collected from 632 injection drug users enrolled in a randomized trial conducted at eight detoxification programs within the National Drug Abuse Treatment Clinical Trials Network (CTN) with follow-up assessments conducted at 2, 8, 16, and 24 weeks. Detoxification program characteristics were collected during this study and from a survey of CTN treatment organizations. Survival analysis found that estimated proportions of reported outpatient treatment entry varied across sites from .06 to .72. A model-building approach determined variables significantly associated with outpatient treatment entry. The best predictive model contained five program-level variables: accreditation, fewer beds, longer stays, shorter distance between detoxification and outpatient unit, and larger city population. One patient-level variable trended toward being a significant predictor: criminal justice involvement. In this model, other patient-related variables did not significantly predict entry into post-detox outpatient treatment. These included stage of change, number of previous alcohol detoxifications, heroin use in the last 30 days, living arrangements, and reporting that detox staff had recommended further treatment. Results suggest the importance of detoxification program characteristics in facilitating further treatment and the need for systems modifications to improve continuity of care. Campbell BK, Tillotson CJ, Choi D, Bryant K, DiCenzo J, Provost SE, Zammarelli L, Booth RE, McCarty D. J Subst Abuse Treat. 2010 Jun;38 Suppl 1:S87-96.

Multisite Effectiveness Trials of Treatments for Substance Abuse and Co-occurring Problems: Have We Chosen the Best Designs?

As of December 2009, the primary outcome paper had been published for 16 of the multisite randomized clinical trials conducted in the CTN, testing various treatments for drug abuse, HIV risk behavior, or related problems. This paper systematically examines, for each of the completed trials, the experimental design type chosen and its original rationale, the main findings of the trial, and the strengths and weaknesses of the design in hindsight. Based on this review, recommendations are generated to inform the design of future effectiveness trials on treatments for substance abuse, HIV risk, and other behavioral health problems. Nunes EV, Ball S, Booth R, Brigham G, Calsyn DA, Carroll K, Feaster DJ, Hien D, Hubbard RL, Ling W, Petry NM, Rotrosen J, Selzer J, Stitzer M, Tross S, Wakim P, Winhusen T, Woody G. J Subst Abuse Treat. 2010 Jun;38 Suppl 1:S97-112.

Equivalence of Family Functioning and Externalizing in Adolescent Substance Users of Different Race/Ethnicity

Brief Strategic Family Therapy (BSFT) for Adolescent Drug Abuse clinical trial of 480 adolescents boys and girls age 12 to 17 and their parents was designed to maximize the chance that a sufficient number of Hispanic and Black adolescents would be included to allow valid subgroup comparisons. Examination of measurement invariance is an important step to ensure valid analysis. Two construct areas important to the analysis of trial results, adolescent problem behaviors and family functioning showed a high degree of measurement invariance, which allowed valid comparisons of mean baseline differences across groups. Results showed that Black families had significantly higher initial levels of family functioning and lower levels of adolescent externalizing than either Hispanic or White non-Hispanic families. This pattern is consistent with an increased likelihood of referral of Black adolescents with more severe problems to restricted setting rather than to outpatient drug abuse treatment. This possibility highlights the importance of considering differing baseline characteristics of subgroups prior to assessing differential treatment effectiveness to prevent confounding. Feaster DJ, Robbins MS, Henderson C, Horigian V, Puccinelli MJ, Burlew KA, Szapocznik J. J Subst Abuse

Treat. 2010 Jun;38 Suppl 1:S113-S124.

The Relationship between Depression and Smoking Cessation Outcomes in Treatment-seeking Substance Abusers

The National Drug Abuse Treatment Clinical Trials Network (CTN) recently completed a randomized, open label trial comparing treatment as usual (TAU) combined with nicotine patches plus cognitive behavioral group counseling for smoking cessation (n = 153) to TAU alone (n = 72) for patients enrolled in treatment programs for drug or alcohol dependence, who were interested in quitting smoking. Secondary analysis considered the effect of depressive symptomatology (n = 70) or history of depression (n = 110) on smoking cessation outcomes. A significant association was seen between measures of depression and difficulty quitting cigarettes. Specifically, there was a greater probability for smoking abstinence for those with lower baseline Beck Depression Inventory II (BDI-II) scores. These data suggest that evaluation and treatment of depressive symptoms may play an important role in improving smoking cessation outcomes. Sonne SC, Nunes EV, Jiang H, Tyson C, Rotrosen J, Reid MS. Am J Addict. 2010 Mar 1;19(2):111-118.

OROS-Methylphenidate or Placebo for Adult Smokers with Attention Deficit Hyperactivity Disorder: Racial/Ethnic Differences

The purpose of this study was to explore racial/ethnic differences in OROS-methylphenidate (OMPH) efficacy when added to nicotine patch and counseling for treating nicotine dependence among adult smokers with attention deficit hyperactivity disorder (ADHD). Participants (202 whites and 51 non-whites) were randomly assigned to OMPH or placebo in a multi-site, randomized controlled trial. Study outcomes were complete, prolonged, and point-prevalence abstinence at the end of treatment, and weekly ratings of ADHD symptoms, tobacco withdrawal symptoms, and desire to smoke. The rate of four-week complete abstinence was significantly higher with OMPH than placebo among non-white (OMPH=42.9%, placebo=13.3%, chi(2)(1)=5.20, p=0.02) but not white participants (OMPH=23.1%, placebo=23.5%, chi(2)(1)=0.00, p=0.95). Patterns of prolonged and point-prevalence abstinence among non-whites were similar but fell short of statistical significance. OMPH reduced ADHD symptoms in both racial/ethnic groups, and produced greater reductions in desire to smoke and withdrawal symptoms among the non-white than white participants. Change in desire to smoke, but not in withdrawal or ADHD symptoms predicted abstinence. The ability of OMPH to reduce desire to smoke among non-whites appeared to mediate the medication's positive effect on abstinence. Differential efficacy favoring non-whites of a medication for achieving smoking cessation is a potentially important finding that warrants further investigation. Covey LS, Hu MC, Winhusen T, Weissman J, Berlin I, Nunes EV. Drug Alcohol Depend. 2010 Mar 8. [Epub ahead of print].

Substance Use and High Risk Sexual Behaviors Among Women In Psychosocial Outpatient and Methadone Maintenance Treatment Programs

This study assessed the association between substance use diagnosis and sexual risk behaviors among women enrolled in both psychosocial outpatient (PS) and methadone maintenance (MM) treatment and involved in a HIV prevention intervention study within the National Institute on Drug Abuse Clinical Trials Network. Five hundred and fifteen sexually active women reported on unprotected sexual occasions (USO), anal sex, sex trading, sex with drug occasions, and multiple male sex partners at the baseline assessment. Within the PS sample, cocaine use diagnosis was associated with more than twice the risk of having multiple partners, trading sex for drugs,

having anal sex, or having sex with drugs; alcohol or opioid use diagnosis was associated with fewer risk behaviors. Within the MM sample, cocaine use, alcohol use and opiate use diagnoses were each associated with one to two risk behaviors. Associations between sexual risk and substance using days were less frequent in both samples. These findings highlight the need for integration of HIV sexual prevention interventions that address the relationship between sexual risk behavior and substance use diagnoses into substance abuse treatment programs. Tross S, Hanner J, Hu MC, Pavlicova M, Campbell A, Nunes EV. Am J Drug Alcohol Abuse. 2009; 35(5): 368-374.

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Research Findings - International Research

HHH Fellow: Stephen E. Nsimba, Tanzania, 2005-2006
Nsimba SE.
Anti-retroviral (ARV) Rationing Schemes in Developing Countries: A Review Article on Strategies and Ethical Issues Related to the Successes and failures of ARV Programmes.
East African Journal of Public Health. 2009 Aug; 6(2): 219-222.

When a patient receives a counterfeit drug, he/she becomes a victim of fraud medicine and is put at risk of developing adverse effects from unwanted medication that is not prescribed. These individuals health also becomes compromised because they are cheated of both successful treatment regimens and economically. Indeed counterfeit drugs pose many threats to society; not only to the individual in terms of the health side effects experienced, but also to the public in terms of trade relations, economic implications, and the effects on global pandemics. Apart from the pharmaceutical aspect in producing substandard drugs, there area also climatic or environmental factors as well as patients and economic factors. All these need to be addressed when considering any proper rationing strategy for antiretroviral drugs (ARVs) in sub-Saharan countries.

HHH Fellow: Chung Tai Lee, South Korea, 1994-1995
Lee SJ, Lee HK, Kweon YS, Lee CT, Lee KU.
The Impact of Executive Function on Emotion Recognition and Emotion Experience in Patients with Schizophrenia.
Psychiatry Investigation. 2009 Sep; 6(3): 156-162. Epub 2009 Jun 23.

This study investigated the impact of executive function on the performance of two different affective tasks, the Facial Affect Identification Task (FAIT) and the Iowa Gambling Task (IGT), in patients with schizophrenia. Thirty-nine patients with schizophrenia and 33 healthy controls completed the FAIT and the IGT, followed by the Wisconsin Card Sorting Test (WCST) and the intelligence quotient (IQ) test. In addition to correlation analysis, regression analysis was used to determine the extent to which the performance of the WCST, in particular, perseverative error (PE), accounted for the variation in both the FAIT and the IGT. Relative to normal controls, patients with schizophrenia showed significant impairments in the IGT, the FAIT and the WCST even after controlling for IQ. While normal controls did not show any relationships between the WCST and two affective tasks, patients with schizophrenia showed that variables in the WCST correlated not only with the FAIT total correct score ($r=-0.503$, $p=0.001$ for PE) but also with the IGT net score ($r=0.385$, $p=0.016$ for PE). The PE score was a better predictor of the performance on the FAIT ($R(2)=0.25$) than that of the performance on the IGT ($R(2)=0.15$). These findings imply that deficits in executive function in schizophrenia can affect performance on facial emotion recognition tasks more than performance on

tasks based on emotion experience, that is, the feedback from the body. Therefore, more consideration is needed of the impact of executive function when interpreting the result of "conventional" facial affect recognition tests as opposed to interpreting the IGT.

HHH Fellow: Nimesh Desai, India, 1999-2000
Pandurangi AK, Desai NG.
Report of the Indo-US Health Care Summit 2009 - Mental Health Section.
Indian Journal of Psychiatry. 2009 Oct-Dec; 51(4): 292-301.

The 2nd Indo-US Health Care Summit held in January 2009 was a forum to discuss collaboration between physicians in the US and India on medical education, health care services and research. Six specialties were represented including Mental Health (MH). Using Depression as the paradigmatic disorder, the following objectives were developed. Objective I - Leadership and Public Education: Linkage with like-minded agencies and organizations. The core message should be simple. Major Depression is a brain disorder. Depression is treatable. Timely treatment prevents disability and suicide. Objective II - Medical Education: To improve psychiatric education, it was proposed that (1) relations between US/UK and Indian mid-level institutions be established, (2) teaching methods such as tele-psychiatry and online courses be pursued, (3) use models of teaching excellence to arouse student interest, and (4) develop core curricula for other branches of medicine, and CME. Objective III - Reduce Complications of Depression (Suicide, Alcoholism): Goals include (1) decriminalizing attempted suicide, (2) improving reporting systems, and including depression, psychosis, alcoholism, and suicide in the national registry, (3) pilot studies in vulnerable groups on risk and interventions, and (4) education of colleagues on alcoholism as a link between psychiatric and medical disorders. Objective IV - Integrating MH Treatment & Primary Health Care: The focus should be on training of general practitioners in psychiatry. Available training modules including long distance learning modules to be suitably modified for India. Collaborations and specific project designs are to be developed, implemented and monitored by each specialty group and reviewed in future summits. PMID: 20048457 [PubMed - in process]

HHH Fellow: Arun Kumar Sharma, India 2004-2005
Ghosh R, Sharma AK.
Intra- and Inter-Household Differences in Antenatal Care, Delivery Practices and Postnatal Care between Last Neonatal Deaths and Last Surviving Children in a Peri-Urban Area of India.
Journal of Biosocial Science. 2010 Mar 5:1-20. [Epub ahead of print]

Nearly a quarter of the world's neonatal deaths take place in India. The state of Uttar Pradesh alone accounts for one-quarter of all neonatal deaths in the country. In this study 892 married women aged less than 50 years living in a peri-urban area of Kanpur city in Uttar Pradesh were interviewed. In all, 109 women reported neonatal deaths. Characteristics of the last neonatal deaths of these 109 women were compared with those of the last surviving children. Also, characteristics of women who had a neonatal death were compared with those of 783 women who had no neonatal death. It was found that as compared with neonatal deaths, the last surviving children of the 109 women had: (a) significantly better antenatal tests during pregnancy, intake of iron/folic acid tablets and higher percentage of tetanus toxoid immunization; (b) safer delivery practices such as a higher percentage of institutional delivery, sterilization of instruments and application of antiseptic after removal of umbilical cord; (c) postnatal care, such as application of antiseptic to the navel and postnatal checkups; and (d) higher maternal age and greater birth spacing. Likewise, better antenatal care and safer delivery practices and postnatal care were observed among the 783 women with no neonatal deaths, when compared with women who had experienced neonatal death. The

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complexities of inter- and intra-household differences in health care are discussed. The paper concludes that to improve child survival general education and awareness regarding safe delivery should be increased. Continuing cultural stigmas and misconceptions about birth practices before, during and after childbirth should be an important part of the awareness campaigns.

HHH Fellow: Rouman Sedefov, Bulgaria, 1994-1995
Hillebrand J, Olszewski D, Sedefov R.
Legal Highs on the Internet.
Substance Use & Misuse. 2010 Feb; 45(3): 330-340.

This article describes the findings of a descriptive analysis of 27 online drug retailers selling legal alternatives to illegal drugs, commonly referred to as "herbal highs" and "legal highs" in 2008 . The study attempted to quantify the online availability of drug retailers, to describe common products and characteristics in EU-based retail sales. The findings highlight the concern about the lack of objective information about products offered, including potential risks to health. Systems should be developed to assess the contents of products and the accuracy of information provided on the Internet, alongside continued monitoring of this market for "legal high" substances. PMID: 20141450 [PubMed - in process]

HHH Fellow: Alisher Latypov, Tajikistan 2002-2003
Latypov A.
Opioid Substitution Therapy in Tajikistan: Another Perpetual Pilot?
International Journal on Drug Policy. 2010 Feb 23. [Epub ahead of print]

Opioid substitution therapy (OST) continues to face strong resistance in the former Soviet Central Asian republics. OST was discontinued by the Uzbek government in 2009. In Kyrgyzstan, with about 950 people currently receiving OST, the programme was about to be suspended in 2009. In Kazakhstan, a small pilot project serves 50 clients. Turkmenistan may introduce OST in 2010, while the Tajik Ministry of Health approved the introduction of an OST pilot in summer 2009. This paper draws upon the analysis of interests of the OST-affected groups in Tajikistan as a case study to understand the roots of resistance to OST. In Tajikistan, OST may be contrary to the interests of some narcologists, law enforcement officers and drug dealers. People who use drugs do not play any role in national drug-policy making. The HIV prevention community within the Tajik executive bodies receives major financial support from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) to respond to an IDU driven epidemic, and yet it is the only group which has nothing to gain from the absence of OST. The Tajik government agreed to introduce OST in order not to jeopardize its future funding from GFATM. If the interests of the OST-affected groups are ignored, there is a high chance that OST in Tajikistan may remain a perpetual pilot project even despite all the necessary resources would come from GFATM and other donors. Putting "narcology on pilot" may prove helpful in both tackling the OST "perpetual pilots" and shifting the focus of public attention towards major inadequacies of the existing state-funded drug treatment systems in the region.

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Research Findings - Intramural Research

Chemistry and Drug Metabolism

Is There a Better Biological Matrix for Drug Monitoring in Drug Treatment, Drug Court, Workplace and Criminal Justice Drug Testing than Urine?

Oral fluid (saliva) is an important new biological matrix for drug monitoring in drug treatment, research trials, workplace, and criminal justice (drug court) programs. This technology was proposed by the Substance Abuse Mental Health Services Administration for approval for drug testing in 2004, but it was never finalized because of the possibility of false positive results from passive inhalation of cannabis smoke. IRP researchers developed and fully validated a new analytical method to monitor the inactive metabolite 11-nor-9-carboxy-Æ9-tetrahydrocannabinol (THCCOOH) in oral fluid in the pg/mL concentration range, as well as the parent THC. THCCOOH is not present in cannabis smoke, documenting that the individual actually metabolized the drug. This could pave the way for approval of this important new matrix that will be highly useful for monitoring drug relapse in treatment programs. In clinical trials of cannabis dependence and evaluation of treatment modalities, drug testing to identify drug relapse is one of the most important objective outcome measures. Unfortunately, following chronic daily cannabis, urinary excretion can be extended for more than 30 days. This makes differentiation of new cannabis use from residual drug excretion highly difficult. Oral fluid testing may be a more effective means of identifying new drug use due to its shorter detection window. Identification of THCCOOH in oral fluid provides a solution to the problem of passive exposure. The authors are now evaluating this method in clinical studies of chronic cannabis users and in controlled drug administration studies, none of which could have been possible without this new analytical method. This paper has important public health consequences. Milman G, Barnes AW, Lowe RW, Huestis MA. Simultaneous quantification of cannabinoids and metabolites in oral fluid by two-dimensional gas chromatography mass spectrometry. Journal of Chromatography A 2010 Feb 26; 1217(9): 1513-1521. Epub 2010 Jan 4.

Clinical Pharmacology and Therapeutics

Nicotine Psychopharmacology Section/Clinical Pharmacology and Therapeutics Branch

Breath Carbon Monoxide and Saliva Cotinine as Biomarkers for Smoking

As a biomarker of smoking, semiquantitative analysis of cotinine (NicAlert¨) offers several advantages over breath carbon monoxide (CO) and quantitative analysis of cotinine. Recent studies have used urine NicAlert¨ and breath CO in

combination to verify abstinence. However, no studies have evaluated the performance of saliva NicAlert¨ against or in combination with breath CO. Breath CO, saliva NicAlert¨, and smoking history were compared in an urban population of daily smokers (n = 24) and nonsmokers (n = 25). Saliva NicAlert¨ predicted self-reported smoking with 100% sensitivity and 96% specificity. At a cutoff of > 5 ppm, breath CO had 100% sensitivity and 100% specificity in predicting self-reported smoking. Breath CO was positively correlated with saliva NicAlert¨ and negatively correlated with minutes since last cigarette. Saliva NicAlert¨ had high sensitivity and specificity in identifying daily smokers. Compared to saliva NicAlert¨, breath CO level was more indicative of recent smoking. Future treatment studies should evaluate the performance of saliva NicAlert¨ as an alternative to the urine test. Marrone GF, Paulpillai M, Evans RJ, Singleton EG, Heishman SJ. Breath carbon monoxide and semiquantitative saliva cotinine as biomarkers for smoking. Hum Psychopharmacol Clin Exp. 2010; 25: 80-83.

Puffing Behavior During the Smoking of a Single Cigarette in Tobacco-dependent Adolescents

Adult and adolescent smokers regulate their nicotine and smoke intake by smoking low-yield cigarettes more intensely than high-yield cigarettes. One likely mechanism of nicotine regulation is altered puffing topography, which has been demonstrated in adult smokers. The purpose of this study was to examine the pattern of puffing behavior during the smoking of a single cigarette in adolescents. Tobacco-dependent adolescents (n = 89) were enrolled in a treatment trial testing the efficacy of nicotine replacement therapy. About 1 week before their quit date, participants smoked ad libitum one of their usual brand of cigarettes during a laboratory session. Smoking topography measures included puff volume, puff duration, puff velocity, and interpuff interval. Controlling for sex, race, and number of puffs, puff volume and puff duration decreased 12.8% and 24.5%, respectively, from the first three to the last three puffs. Puff velocity and interpuff interval increased 14.8% and 13.5%, respectively. Puff volume was positively correlated with puff duration and puff velocity, whereas puff duration and puff velocity were negatively correlated. However, none of the topography measures were correlated with smoking history variables. These results suggest that adolescent smokers, like adults, are able to regulate smoke and nicotine intake on a puff-by-puff basis, therefore indicating that this aspect of smoking control is acquired early in the tobacco-dependence process. Collins, CC, Epstein DH, Parzynski CS, Zimmerman D, Moolchan ET, Heishman SJ. Puffing behavior during the smoking of a single cigarette in tobacco-dependent adolescents. Nicotine Tob Res. 2010; 12: 164-167.

Behavioral Neuroscience Research Branch

Amphetamine Administration Into the Ventral Striatum Facilitates Behavioral Interaction With Unconditioned Visual Signals In Rats

Administration of psychomotor stimulants like amphetamine facilitates behavior in the presence of incentive distal stimuli, which have acquired the motivational properties of primary rewards through associative learning. This facilitation appears to be mediated by the mesolimbic dopamine system, which may also be involved in facilitating behavior in the presence of distal stimuli that have not been previously paired with primary rewards. However, it is unclear whether psychomotor stimulants facilitate behavioral interaction with unconditioned distal stimuli. IRP researchers found that noncontingent administration of amphetamine into subregions of the rat ventral striatum, particularly in the vicinity of the medial olfactory tubercle, facilitates lever pressing followed by visual signals that had not been paired with primary rewards. Noncontingent administration of amphetamine failed to facilitate lever pressing when it was followed by either tones or delayed presentation or absence of visual signals, suggesting that visual signals are key for enhanced behavioral interaction. Systemic administration of amphetamine markedly

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increased locomotor activity, but did not necessarily increase lever pressing rewarded by visual signals, suggesting that lever pressing is not a byproduct of heightened locomotor activity. Lever pressing facilitated by amphetamine was reduced by co-administration of the dopamine receptor antagonists SCH 23390 (D1 selective) or sulpiride (D2 selective). These results suggest that amphetamine administration into the ventral striatum, particularly in the vicinity of the medial olfactory tubercle, activates dopaminergic mechanisms that strongly enhance behavioral interaction with unconditioned visual stimuli. Shin R, Cao J, Webb SM, Ikemoto S. Amphetamine administration into the ventral striatum facilitates behavioral interaction with unconditioned visual signals in rats PLoS One, 2010 Jan 15: 5(1): e8741.

Integrative Neuroscience Section

Signal-Averaged Electrocardiogram In Physically Healthy, Recently Abstinent Chronic Cocaine Users

Cocaine use is associated with cardiac arrhythmias, but predicting who is at risk is difficult. Signal-averaged electrocardiography (SA-ECG), unlike standard ECG, can detect markers of ventricular late potentials (VLP), which may be a precursor to malignant ventricular arrhythmias. IRP scientists evaluated SA-ECG parameters in 60 medically screened, physically healthy, recently abstinent, chronic cocaine users and in 54 non-drug-using controls. SA-ECGs were done periodically for up to 12 weeks of monitored abstinence in 25 of the cocaine users. Cocaine users differed significantly from controls in only one of three SA-ECG parameters considered markers of VLPs. The proportion of subjects with abnormal SA-ECG parameters did not differ significantly between male cocaine users and male controls. There were no significant changes over time in either the mean values or proportion of subjects with abnormal values for any SA-ECG parameter. There were significant gender differences among controls, but not among cocaine users. These findings suggest that chronic cocaine use is not associated with a higher prevalence of abnormal SA-ECG parameters in physically healthy users. Kanneganti P, Copersino ML, Nelson RA, et al. Signal-averaged electrocardiogram in physically healthy, recently abstinent chronic cocaine users. Journal of Addiction Medicine. 2009;3(3):128-133.

Interest In Marijuana Treatment Programs Among Teenage Smokers and Nonsmokers

Many adolescents smoke marijuana, but little is known about adolescents' interest in marijuana treatment programs. IRP scientists evaluated this question by telephone interview in a convenience sample of 575 adolescents (13-17 years old) responding to advertisements for tobacco research studies at the NIDA IRP. 81% of respondents endorsed the need for marijuana treatment programs for adolescents. These adolescents were younger and less likely to smoke tobacco, smoke marijuana, or use alcohol than those not endorsing such a need. Among the 192 marijuana smokers, the 58.8% who endorsed the need for marijuana treatment programs took their first puff of marijuana at a younger age than those who did not endorse the need. Those who were willing to participate in a marijuana treatment program were more likely African-American and took their first marijuana puff at a younger age than those not interested in treatment. These findings suggest that a majority of adolescent marijuana smokers endorse the need for and are willing to attend marijuana treatment programs. Sheer AJ, Gorelick DA, Collins CC, et al. Interest in marijuana treatment programs among teenage smokers and nonsmokers. Journal of Substance Abuse Treatment. 2009; 37(4):421-425.

Behavioral Neuroscience Research Branch

Mu Opioid Receptors in the Ventral Tegmental Area Regulate Somatodendritic Dopamine Release By Affecting GABA and Glutamate

Transmission

The rewarding effect of opiates and other drugs of abuse has been attributed to increased dopamine transmission within the mesolimbic system which originates in the ventral tegmental area (VTA) and projects to the nucleus accumbens and prefrontal cortex. The activity of VTA dopamine neurons is controlled by their intrinsic properties, as well as inhibitory and excitatory inputs from local neurons and from other brain areas. Mu opioid receptors are enriched in the VTA and their activation increases dopamine release. Although this effect has been attributed to the activation of opioid receptors on GABA neurons and the resulting disinhibition of dopamine neurons, evidence in support of this hypothesis was obtained in anesthetized animals and slice preparations. Importantly, however, the functional connectivity of these preparations differs from that in the intact or awake animal. Furthermore, the role of mu opioid receptors in modulating glutamate input to the VTA is unclear. The use of in-vivo microdialysis has provided direct neurochemical evidence that activation of mu opioid receptors in the VTA of the freely moving animal produces a concentration-dependent decrease in local GABA levels and an augmentation of somatodendritic dopamine levels. Constitutive deletion of the mu opioid receptor led to an elevation of basal GABA overflow and a reduction in glutamate levels in the VTA. Although, gene deletion did not alter basal somatodendritic dopamine overflow, a significant correlation between basal dopamine levels and the glutamate/GABA ratio in wildtype but not knock out mice was seen. Mu opioid receptors have been implicated in modulating the rewarding effects of various drugs of abuse. Mu opioid receptor knock out mice demonstrate reduced sensitivity to the reinforcing properties of various drugs of abuse, including morphine, heroin, alcohol, δ9-tetrahydrocannabinol, nicotine, and cocaine. The present findings suggest that this reduction may result from loss of the intricate balance between glutamatergic and GABAergic neurotransmission in the VTA. This in turn leads to an increase in the frequency of spontaneous inhibitory postsynaptic currents, a decrease in the firing activity of dopaminergic neurons and inhibition of dopamine release in the nucleus accumbens. Furthermore, they provide new evidence that VTA mu opioid receptors may contribute to addiction vulnerability by modulating GABAergic and glutamatergic inputs to dopaminergic neurons. Chefer VI, Denoroy L, Zapata A, Shippenberg TS. Eur J Neurosci 2009; 30: 272-278.

Delta Opioid Receptor Antagonism Prevents Sensitization to the Conditioned Reinforcing Effects of Morphine

Functional interactions between mu and delta opioid receptors are implicated in the development of morphine tolerance and dependence. Antisense oligonucleotides to the delta opioid receptor attenuate the development of morphine dependence. Similarly, pharmacological antagonism or genetic deletion of this opioid receptor type reduces opiate dependence and analgesic tolerance. Other studies have shown that repeated mu opioid receptor agonist administration increases delta opioid receptor cell surface expression in brain and spinal cord. These data demonstrate that delta opioid receptor function is altered following chronic morphine exposure and suggest that aberrant activity of this opioid receptor system may contribute to the dysregulation of behavior that occurs following repeated administration of morphine and other mu opioid receptor agonists. The contribution of delta opioid receptors to the conditioned rewarding effects of morphine and the enhanced conditioned response that occurs after repeated morphine administration is unknown. This information, however, is important in view of the documented role of environmental stimuli previously associated with opiate administration in drug-craving and relapse to addiction. The present study addressed this issue using the conditioned place preference procedure in rats. Subjects received home cage injections of saline or morphine (5.0 mg/kg/day x 5 days) before conditioning. For sensitization studies, the delta opioid receptor antagonists (DOPr1/2: naltrindole, DOPr2: naltriben, DOPr1: 7-benzylidenenaltrexone) were administered before morphine injections. Conditioning sessions (2 morphine; 2 saline) commenced 3 days later. To assess the influence of acute delta opioid receptor blockade on

the conditioning of morphine reward in na•ve animals, 3 morphine and 3 saline conditioning sessions were employed. Antagonists were administered before morphine conditioning sessions. Morphine was ineffective as a conditioning stimulus after two conditioning sessions in na•ve rats. However, doses of 3.0 mg/kg and greater produced significant conditioned place preferences in morphine pre-exposed rats, confirming that sensitization develops to the conditioned rewarding effects of morphine. In animals that received morphine pre-exposure with naltrindole or naltriben but not 7-benzylidenenaltrexone, sensitization was prevented. No attenuation of morphine place conditioning was observed in animals that received delta opioid receptor antagonists acutely, before conditioning sessions. These data indicate a critical role of delta opioid receptor systems in mediating sensitization to the conditioned rewarding effects of morphine. The efficacy of naltrindole and naltriben in preventing the enhanced response to morphine suggest the specific involvement of the delta opioid receptor-2 subtype in the sensitization process. Shippenberg TS, Thompson A, Chefer VI. Biological Psychiatry 2009; 65(2): 169-174.

The Endogenous Cannabinoid, Anandamide, Modulates Dopamine Transporter Function and Cell Surface Expression By a Receptor-Independent Mechanism

Systemic administration of the endocannabinoid, anandamide (AEA), increases extracellular dopamine (DA) concentrations in the nucleus accumbens, a brain region implicated in mediating the abuse liability of various psychoactive drugs. Increased DA concentrations are also observed in response to synthetic cannabinoid agonists. Although these effects have been attributed to alterations in DA release, AEA and other cannabinoids inhibit dopamine uptake in native tissue and heterologous expression systems suggesting that AEA may modulate DA transmission by regulating the DA transporter. The cellular mechanisms mediating the functional interaction of AEA with the dopamine transporter are unclear. The present studies used live cell confocal microsopy and the fluorescent high affinity DA transporter substrate, ASP+ to address this issue. AEA addition to EM4 cells expressing yellow fluorescent protein-tagged human DAT (hDAT) produced a concentration-dependent inhibition of ASP+ accumulation (IC50: 3.2 ± 0.8 μM). This effect occurred within 1 min after AEA addition and persisted for 10 min thereafter. Pertussis toxin did not attenuate the effects of AEA suggesting a mechanism independent of Gi/Go coupled receptors. Amidohydrolase inhibiton failed to alter the AEA-evoked inhibition of ASP+ accumulation. Methanandamide, a metabolically stable analogue of AEA inhibited accumulation whereas arachidonic acid was without effect suggesting that the effects of AEA are not mediated by its metabolic products. The extent of AEA inhibition of ASP+ accumulation was not altered in cells pre-treated with a specific and potent fatty acid amide hydrolase inhibitor or with the cyclooxygenase inhibitor, indomethacin. Live cell imaging revealed a significant redistribution of the transporter from the membrane to the cytosol in response to AEA treatment consistent with transporter internalization. Similarly biotinylation experiments revealed that the decrease in DA transporter function was associated with a reduction in transporter cell surface expression. These results demonstrate that AEA modulates dopamine transporter function via a cannabinoid receptor-independent mechanism and suggest that AEA may produces this effect, in part, by modulating transporter trafficking. These findings add to a growing body of evidence indicating cannabinoid receptor-independent actions of AEA. Additional studies examining the role of transporter regulation to AEA-evoked alteration in of DA transmission function observed in-vivo are warranted. Oz M, Jaligam V, Galadari S, Petroianu G, Shuba YM, Shippenberg TS. J Neurochem 2010; 112: 1454 - 1464. Preclinical Pharmacology Section

Animal Models

This book chapter provides an overview of animal models used to study drug addiction, focusing on two important elements of these models: reinforcement and the effects of environmental cues. The reinforcing effects of drugs are

believed to be responsible for the development of drug abuse. Features of the environment that are associated with the drug's reinforcing effects are believed to guide and maintain the long chains of behavior required to ingest the drug, and they may also induce relapse to drug use after a period of abstinence. Drug self-administration is the gold standard among the available models. The chapter describes how the schedule of reinforcement (which stipulates the relationship between behavior, environmental cues, and drug delivery within the self-administration procedure) can be manipulated to focus on specific aspects of addiction. Other models are also described and compared, including conditioned place preference, drug discrimination, intracranial electrical self-stimulation, and locomotor sensitization. When combined with neuroscience techniques, these animal models allow researchers to study the relationships between behavior and the underlying brain mechanisms involved in all stages of addiction. Panlilio LV, Schindler CW, Goldberg SR. Animal Models. In PG Miller, J Strang, PM Miller (Eds), Addiction Research Methods, pp. 269-284. Oxford, England: Blackwell Publishing Ltd., 2010.

Dopaminergic Augmentation of Delta-9-tetrahydrocannabinol (THC) Discrimination: Possible Involvement of D(2)-induced Formation of Anandamide

Although delta-9-tetrahydrocannabinol (THC)-induced elevations in accumbal dopamine levels are believed to play an important role in the abuse-related effects of cannabis, little direct evidence has been provided that the dopaminergic system is involved in the psychotropic effects of THC. The objective of this study is to investigate whether drugs activating or blocking the dopaminergic system modulate the discriminative effects of THC. In rats that had learned to discriminate 3 mg/kg of THC from vehicle injections, the indirect dopaminergic agonists cocaine and amphetamine, the D(1)-receptor agonist SKF-38393, and the D(2)-receptor agonists quinpirole and apomorphine did not produce significant THC-like discriminative effects. However, both cocaine and amphetamine and D(2)-, but not the D(1)-, receptor agonists, augmented THC discrimination. Neither the D(1)-receptor antagonist SCH-23390 nor the D(2)-receptor antagonist raclopride reduced the discriminative effects of THC, even at doses that significantly depressed baseline operant responding. However, the D(2)-, but not the D(1)-, antagonist counteracted the augmentation of THC's discriminative effects produced by cocaine and amphetamine. The authors hypothesized that release of anandamide by activation of D(2) receptors was responsible for the observed augmentation of THC discrimination. This hypothesis was supported by two findings. First, the cannabinoid CB(1)-receptor antagonist rimonabant blocked quinpirole-induced augmentation of THC discrimination. Second, inhibition of anandamide degradation by blockade of fatty acid amide hydrolase augmented the THC-like effects of quinpirole. The authors conclude that dopamine does not play a major role in THC discrimination. However, activation of the dopaminergic system positively modulates the discriminative effects of THC, possibly through D(2)-induced elevations in brain levels of anandamide. Solinas M, Tanda G, Wertheim CE, Goldberg SR. Psychopharmacology, 2010, 209(2): 191-202.

Effects Of Cannabinoid Receptor Antagonists On Maintenance and Reinstatement Of Methamphetamine Self-Administration In Rhesus Monkeys

Cannabinoid receptor antagonists have shown some promise as treatments capable of reducing abuse and relapse to a number of abused drugs. In rodents, such effects have been observed with methamphetamine self-administration. However, the effects of cannabinoid receptor antagonists on methamphetamine self-administration and relapse have not been studied in primates. In the present study, rhesus monkeys were trained to respond on a three-component operant schedule. During the first 5-min component, fixed-ratio responses were reinforced by food, during the second 90- or 180-min component fixed-ratio responses were reinforced by i.v. methamphetamine. The third component was identical to the first. There was a 5-min timeout

between each component. The effects of the cannabinoid receptor antagonists AM 251 and rimonabant were tested at various doses against self-administration of 3microg/kg/injection methamphetamine, and 1mg/kg AM 251 and 0.3mg/kg rimonabant were tested against the methamphetamine dose-effect function. The 1mg/kg dose of AM 251 was also tested for its ability to alter reinstatement of extinguished self-administration responding. The cannabinoid receptor antagonist AM 251 was found to reduce methamphetamine self-administration at doses that did not affect food-reinforced responding. The cannabinoid receptor antagonist rimonabant had similar, but less robust effects. AM 251 also prevented reinstatement of extinguished methamphetamine seeking that was induced by re-exposure to a combination of methamphetamine and methamphetamine-associated cues. These results indicate that cannabinoid receptor antagonists might have therapeutic effects for the treatment of methamphetamine dependence. Schindler CW, Panlilio LV, Gilman JP, Justinova Z, Vemuri VK, Makriyannis A, Goldberg SR. European Journal of Pharmacology, 2010, 633: 44-49.

Methamphetamine Self-Administration Is Associated With Persistent Biochemical Alterations In Striatal and Cortical Dopaminergic Terminals In the Rat

Methamphetamine (meth) is an illicit psychostimulant that is abused throughout the world. Repeated passive injections of the drug given in a single day or over a few days cause significant and long-term depletion of dopamine and serotonin in the mammalian brain. Because meth self-administration may better mimic some aspects of human drug-taking behaviors, IRP researchers examined to what extent this pattern of drug treatment might also result in damage to monoaminergic systems in the brain. Rats were allowed to intravenously self-administer meth (yoked control rats received vehicle) 15 hours per day for 8 days before being euthanized at either 24 hours or at 7 and 14 days after cessation of drug taking. Meth self-administration by the rats was associated with a progressive escalation of daily drug intake to 14 mg/kg per day. Animals that self-administered meth exhibited dose-dependent decreases in striatal dopamine levels during the period of observation. In addition, there were significant reductions in the levels of striatal dopamine transporter and tyrosine hydroxylase proteins. There were also significant decreases in the levels of dopamine, dopamine transporter, and tyrosine hydroxylase in the cortex. In contrast, meth self-administration caused only transient decreases in norepinephrine and serotonin levels in the two brain regions, with these values returning to normal at seven days after cessation of drug taking. Importantly, meth self-administration was associated with significant dose-dependent increases in glial fibrillary acidic protein in both striatum and cortex, with these changes being of greater magnitude in the striatum. These results suggest that meth self-administration by rats is associated with long-term biochemical changes that are reminiscent of those observed in post-mortem brain tissues of chronic meth abusers. Krasnova IN, Justinova Z, Ladenheim B, Jayanthi S, McCoy MT, Barnes C, Warner JE, Goldberg SR, Cadet JL. PLoS One, 2010, 5(1): e8790.

Role of the Central Ascending Neurotransmitter Systems in the Psychostimulant Effects of Caffeine

Caffeine is the most consumed psychoactive drug in the world. It is a non-selective adenosine receptor antagonist that in the brain targets mainly adenosine A_{1} and A_{2A} receptors. The same as classical psychostimulants, caffeine produces motor-activating, reinforcing and arousing effects. This depends on the ability of caffeine to counteract multiple effects of adenosine in the central ascending neurotransmitter systems. Motor and reinforcing effects depend on the ability of caffeine to release pre- and postsynaptic brakes that adenosine imposes on the ascending dopaminergic system. By targeting A_{1}-A_{2A} receptor heteromers in striatal glutamatergic terminals and A_{1} receptors in striatal dopaminergic terminals (presynaptic brake), caffeine induces glutamate-dependent and glutamate-

independent release of dopamine. These presynaptic effects of caffeine are potentiated by the release of the postsynaptic brake imposed by antagonistic interactions in the striatal A_{2A}-D_{2} and A_{1}-D_{1} receptor heteromers. Arousing effects of caffeine depend on the blockade of multiple inhibitory mechanisms that adenosine, as an endogenous sleep-promoting substance, exerts on the multiply interconnected ascending arousal systems. Those mechanisms include a direct A_{1}-receptor mediated modulation of the corticopetal basal forebrain system and an indirect A_{2A}-receptor mediated modulation of the hypothalamic histaminergic and orexinergic systems. FerrŽ S. J Alzheimers Dis. 2010 Feb 24. [Epub ahead of print]

Oligomerization of G-protein-coupled Receptors: A Reality

G-protein-coupled receptors (GPCRs) have been classically perceived as receptors that do not Ôneed' to oligomerize to be functional, to execute their basic function of transducing a signal from ligand binding to G-protein activation. In fact, recent studies have shown that monomers of class A GPCRs (adrenergic beta2, rhodopsin, and opioid mu receptors) reconstituted in lipid vesicles couple and activate their respective G proteins upon agonist binding. Also monomeric rhodopsin in solution can activate its G-protein transducin. Nevertheless, the authors have now an important amount of experimental evidence that indicates that GPCR oligomerization, including homomerization and heteromerization, is a general phenomenon and it still needs to be determined if GPCR monomers are functionally present in the cellular plasma membrane. Ferre S, Franco R. Current Opinion in Pharmacology, 2010, 10(1): 105.

Chemical Biology Research Branch

Evidence That Intrathecal Morphine-3-Glucuronide May Cause Pain Enhancement

Via Toll-Like Receptor 4/MD-2 and Interleukin-1β Morphine-3-glucoronide (M3G) is a major morphine metabolite detected in cerebrospinal fluid of humans receiving systemic morphine. M3G has little-to-no affinity for opioid receptors and induces pain by unknown mechanisms. The pain enhancing effects of M3G have been proposed to significantly and progressively oppose morphine analgesia as metabolism ensues. IRP scientists have recently documented that morphine activates toll-like receptor 4 (TLR4), beyond its classical actions on mu-opioid receptors. This suggests that M3G may similarly activate TLR4. This activation could provide a novel mechanism for M3G-mediated pain enhancement, as (a) TLR4 is predominantly expressed by microglia in spinal cord and (b) TLR4 activation releases pain-enhancing substances, including interleukin-1 (IL-1). IRP scientists present in vitro evidence that M3G activates TLR4, an effect blocked by TLR4 inhibitors, and that M3G activates microglia to produce IL-1. In vivo, intrathecal M3G (0.75 microg) induced potent allodynia and hyperalgesia, blocked or reversed by interleukin-1 receptor antagonist, minocycline (microglial inhibitor), and (+)- and (-)-naloxone. This latter study extends the authors' prior demonstrations that TLR4 signaling is inhibited by naloxone nonstereoselectively. These results with (+)-and (-)-naloxone also demonstrate that the effects cannot be accounted for by actions at classical, stereoselective opioid receptors. Hyperalgesia (allodynia was not tested) and in vitro M3G-induced TLR4 signaling were both blocked by 17-DMAG, an inhibitor of heat shock protein 90 (HSP90) that can contribute to TLR4 signaling. Providing further evidence of proinflammatory activation, M3G upregulated TLR4 and CD11b (microglial/macrophage activation marker) mRNAs in dorsal spinal cord as well as IL-1 protein in the lumbosacral cerebrospinal fluid. Finally, in silico and in vivo data support that the glucuronic acid moiety is capable of inducing TLR4/MD-2 activation and enhanced pain. These data provide the first evidence for a TLR4 and IL-1 mediated component to M3G-induced effects, likely of at least microglial origin. Lewis SS, Hutchinson MR, Rezvani N, Zhang Y, Maier SF,

Rice KC, Watkins LR. Neuroscience. 2010 Jan 20; 165(2): 569-583.

Possible Involvement Of Toll-Like Receptor 4/Myeloid Differentiation Factor-2 Activity Of Opioid Inactive Isomers Causes Spinal Proinflammation and Related Behavioral Consequences

Opioid-induced glial activation and its proinflammatory consequences have been associated with both reduced acute opioid analgesia and the enhanced development of tolerance, hyperalgesia and allodynia following chronic opioid administration. Intriguingly, recent evidence demonstrates that these effects can result independently from the activation of classical, stereoselective opioid receptors. Here, a structurally disparate range of opioids cause activation of signaling by the innate immune receptor toll like receptor 4 (TLR4), resulting in proinflammatory glial activation. In the present series of studies, IRP investigators demonstrate that the (+)-isomers of methadone and morphine, which bind with negligible affinity to classical opioid receptors, induced upregulation of proinflammatory cytokine and chemokine production in rat isolated dorsal spinal cord. Chronic intrathecal (+)-methadone produced hyperalgesia and allodynia, which were associated with significantly increased spinal glial activation (TLR4 mRNA and protein) and the expression of multiple chemokines and cytokines. Statistical analysis suggests that a cluster of cytokines and chemokines may contribute to these nociceptive behavioral changes. Acute intrathecal (+)-methadone and (+)-morphine were also found to induce microglial, interleukin-1 and TLR4/myeloid differentiation factor-2 (MD-2) dependent enhancement of pain responsivity. In silico docking analysis demonstrated (+)-naloxone sensitive docking of (+)-methadone and (+)-morphine to human MD-2. Collectively, these data provide the first evidence of the pro-nociceptive consequences of small molecule xenobiotic activation of spinal TLR4 signaling independent of classical opioid receptor involvement. Hutchinson MR, Lewis SS, Coats BD, Rezvani N, Zhang Y, Wieseler JL, Somogyi AA, Yin H, Maier SF, Rice KC, Watkins LR. Neuroscience. 2010 Feb 21. [Epub ahead of print]

Effects Of Kappa Opioids In An Assay Of Pain-Depressed Intracranial Self-Stimulation In Rats

Selective, centrally acting kappa opioid agonists produce antinociception in a wide range of preclinical assays, but these compounds perform poorly as analgesics in humans. This discrepancy may be related to the behavioral depressant effects of kappa agonists. Kappa antagonists do not typically produce antinociception, but they produce antidepressant-like effects in some preclinical assays. The objective of this study was to test the hypothesis that the kappa agonist U69,593 and the kappa antagonist norbinaltorphimine would produce pronociceptive and antinociceptive effects, respectively, in an assay of pain-depressed behavior. Effects of U69,593 (0.056-0.56 mg/kg), norbinaltorphimine (10-32 mg/kg), and morphine (3.2 mg/kg) were evaluated on the stimulation of a stretching response and the depression of intracranial self-stimulation (ICSS) of the medial forebrain bundle produced in rats by a common noxious stimulus (intraperitoneal administration of dilute lactic acid). U69,593 produced a dose-dependent blockade of acid-stimulated stretching but only exacerbated acid-induced depression of ICSS. Thus, U69,593 produced antinociception in the assay of pain-stimulated behavior but pronociceptive effects in the assay of pain-depressed behavior. Norbinaltorphimine did not alter acid-stimulated stretching or acid-induced depression of ICSS. The mu opioid agonist morphine blocked both acid-stimulated stretching and acid-induced depression of ICSS. These results support the hypothesis that prodepressant effects of kappa agonists may limit their clinical utility as analgesics. These results do not support the use of kappa antagonists to treat depressant effects of pain. These findings illustrate the potential value of using complementary assays of pain-stimulated and pain-depressed behaviors for preclinical evaluation of candidate analgesics. Negus SS, Morrissey EM, Rosenberg M, Cheng K, Rice KC. Psychopharmacology (Berl). 2010 Jan 26. [Epub ahead of print]

Modulation Of Delta Opioid Agonist-Induced Antinociception By Repeated Morphine Pretreatment In Rhesus Monkeys

Repeated treatment with morphine increases antinociceptive effects of delta opioid agonists in rodents by a mechanism that may involve increased cell-surface expression of delta receptors. The present study evaluated effects of repeated morphine treatment on behavioral effects of the delta agonist SNC80 and the mu agonist fentanyl in rhesus monkeys. In an assay of schedule-controlled responding, three monkeys responded for food reinforcement under a fixed-ratio 30 schedule. In an assay of thermal nociception, tail-withdrawal latencies were evaluated in three monkeys using thermal stimulus intensities of 48 and 54 degrees C. In both assays, the effects of SNC80 (0.032-3.2mg/kg) and fentanyl (0.001-0.056 mg/kg) were evaluated after repeated treatment with saline or a regimen of morphine doses modeled on the regimen that enhanced delta agonist antinociception and apparent delta receptor availability in previous rodent studies. Both SNC80 and fentanyl dose-dependently decreased rates of schedule-controlled responding, and repeated morphine treatment did not significantly alter these effects. In the assay of thermal nociception, SNC80 had little effect on tail-withdrawal latencies from water heated to 48 or 54 degrees C, whereas fentanyl increased tail-withdrawal latencies at both temperatures. Repeated morphine tended to increase the antinociceptive effects of SNC80 and to decrease the antinociceptive effects of fentanyl, but these effects of repeated morphine were small and were significant only at the higher stimulus intensity (54 degrees C). These results provide limited support for the proposition that prior stimulation of mu receptors selectively increases the antinociceptive effects of delta agonists in rhesus monkeys. Negus SS, Banks ML, Folk JE, Rice KC. Life Sci. 2010 Mar 13; 86(11-12):385-392. Epub 2010 Jan 21.

Differential Effects of Serotonin 5-HT1A Receptor Agonists on the Discriminative Stimulus Effects of the 5-HT2A Receptor Agonist 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane in Rats and Rhesus Monkeys

Although many drugs act by indirectly stimulating multiple receptors (e.g., reuptake inhibitors), relatively little is known about interactions between agonism at different receptors. This study compared the effect of serotonin (5-HT)(1A) receptor agonists with the discriminative stimulus effects of the 5-HT(2A) receptor agonist 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) in rats and rhesus monkeys. Eight rats discriminated 0.56 mg/kg i.p. DOM and responded under a fixed ratio (FR) 10 schedule of food presentation, whereas three rhesus monkeys discriminated 0.32 mg/kg s.c. DOM and responded under an FR 5 schedule of stimulus shock termination. DOM and the 5-HT(2A) receptor agonists 2,5-dimethoxy-4-n-propylthiophenethylamine (2C-T-7) and dipropyltryptamine (DPT), but not the 5-HT(1A) receptor agonists 8-hydroxy-2-(di-npropylamino) tetralin hydrochloride (8-OH-DPAT) and 3-chloro-4-fluorophenyl-(4-fluoro-4-([(5-methyl-6-methylaminopyridin-2-ylmethyl) amino) methyl] piperidin-1-yl) methanone (F13714), occasioned responding on the DOM-associated lever in rats and monkeys. Both 8-OH-DPAT and F13714 attenuated the discriminative stimulus effects of DOM in monkeys but not in rats; these effects of 8-OH-DPAT and F13714 were prevented by the 5-HT(1A) receptor antagonist N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide (WAY 100635). DPT and 2C-T-7 enhanced the discriminative stimulus effects of DOM in rats and monkeys in an additive manner. Taken together, the results suggest that the DOM discriminative stimulus is pharmacologically similar and mediated by 5-HT(2A) receptors in rats and monkeys; however, the ability of 5-HT(1A) receptor agonists to modify the effects of DOM is markedly different between these species. These results indicate possible differences in the neurobiology of 5-HT systems that could be important for studying drugs that have multiple mechanisms of action (e.g., reuptake inhibitors that indirectly stimulate multiple receptors). Li JX, Koek W, Rice KC, France CP. J Pharmacol Exp Ther. 2010 Apr; 333(1): 244-

252. Epub 2010 Jan 6.

Synthesis and Preliminary Biochemical Evaluation of Novel Derivatives of PCP
(±)-Trans-Ph/Et and (±)-cis-Ph/Et 1-(2-ethyl-1-phenylcyclohexyl)piperidine were synthesized from 2-ethylcyclohexanone. In contrast to the corresponding trans-substituted 2-methyl compound which is 5x more potent than PCP, the trans-2-ethyl derivative has a 75x lower affinity for the PCP binding site. The cis-2-ethyl isomer is inactive like the cis-2-methyl derivative. (±)-1-(1-Phenylcyclohexyl)-2-methylpiperidine is almost as active as the parent PCP. Reduction of the aromatic ring or quaternization of the piperidine in PCP reduces the affinity for the PCP site. Linders JTM, Furlano DC, Mattson MV, Jacobson AE, Rice KC. Letters In Drug Design and Discovery 2010; 7: 79-87.

Cellular Neurobiology Research Branch

Development and Plasticity Section, Cellular Neurobiology Research Branch

Prenatal Exposure To Cocaine Causes Cytoarchitectural Alterations In The Developing Neocortex
Previously, IRP scientists reported that cocaine inhibits neural progenitor cell proliferation through oxidative endoplasmic reticulum stress and consequent down-regulation of cyclin A, whereas cyclin A expression was increased in astrocytes. In the present study, cell type-specific responses to cocaine were further explored. Gene expression profiles were examined in 5 types of cells obtained from the human fetal cerebral cortex at 20 weeks gestation. Cells were treated with 100 μM cocaine in vitro for 24 hours, followed by gene expression analysis using a human neural/stem cell/drug abuse-focused cDNA array, with verification by quantitative real-time reverse-transcriptase polymerase chain reaction. Cocaine influenced transcription of distinct categories of genes in a cell type-specific manner. Cocaine down-regulated cytoskeleton-related genes including ezrin, γ2 actin, α3d tubulin, and α8 tubulin in neural and/or A2B5+ progenitor cells. In contrast, cocaine modulated immune and cell death-related genes in microglia and astrocytes. In microglia, cocaine up-regulated the immunoregulatory and proapoptotic genes interleukin-1β and BCL2-associated X protein. In astrocytes, cocaine down-regulated the immune response gene glucocorticoid receptor and up-regulated the antiapoptotic genes 14-3-3 ε and HVEM. Therefore, cell types comprising the developing neocortex show differential responses to cocaine. These data suggest that cocaine causes cytoskeletal abnormalities leading to disturbances in neural differentiation and migration in progenitor cells, while altering immune and apoptotic responses in glia. Understanding the mechanisms of cocaine's effects on human central nervous system cells may help in the development of therapeutic strategies to prevent or ameliorate cocaine-induced impairments in fetal brain development. Gene expression profiling reveals distinct cocaine-responsive genes in human fetal CNS cell types. Lee CT, Lehrmann E, Hayashi T, Amable R, Tsai SY, Chen J, Sanchez J, Shen J, Becker KG, Freed WJ. J Addict Med 2010; 3(4): 218-226.

Pathobiology Research Section, Cellular Neurobiology Research Branch

Opioids Have Been Demonstrated To Play An Important Role In CNS Development By Affecting Proliferation and Differentiation In Various Types Of Neural Cells
This study examined the effect of a stable delta opioid peptide [D-Ala(2), D-Leu(5)]-enkephalin (DADLE) on proliferation and differentiation in an AF5 CNS neural progenitor cell line derived from rat mesencephalic cells. DADLE (1 pM, 0.1 nM, or 10 nM) caused a significant growth inhibition on AF5 cells. The opioid antagonist naltrexone at 0.1 nM also caused growth inhibition in the same cells. When DADLE and naltrexone were both added to the AF5 cells, the

resultant growth inhibition was apparently additive. DADLE alone or DADLE in combination with naltrexone did not cause apoptosis as evidenced by negative TUNEL staining. The cell-cycle progression analysis indicated that both DADLE (0.1 nM) and naltrexone (0.1 nM) caused an arrest of AF5 cell cycle progression at the G1 checkpoint. Neuronal marker indicated that DADLE- or naltrexone-treated AF5 cells tend to differentiate more when compared to controls. Results demonstrate the nonopioid action of both DADLE and naltrexone on cell cycle arrest and differentiation in a CNS neural progenitor cell line. Results also suggest some potential utilization of DADLE and/or naltrexone in stem cell research. Tsai SY, Lee CT, Hayashi T, Freed WJ, Su TP. Delta opioid peptide DADLE and naltrexone cause cell cycle arrest and differentiation in a CNS neural progenitor cell line. Synapse 2010; 64(4):267-273.

Cholesterol At the Endoplasmic Reticulum: Roles Of the Sigma-1 Receptor Chaperone and Implications Thereof In Human Diseases

Despite substantial data elucidating the roles of cholesterol in lipid rafts at the plasma membrane, the roles of cholesterol and related lipids in lipid raft microdomains at the level of subcellular membrane, such as the endoplasmic reticulum (ER) membrane, remain less understood. Growing evidence, however, begins to unveil the importance of cholesterol and lipids on the lipid raft at the ER membrane. A few ER proteins including the sigma-1 receptor chaperone were identified at lipid raft-like microdomains of the ER membrane. The sigma-1 receptor, which is highly expressed at a subdomain of ER membrane directly apposing mitochondria and known as the mitochondria-associated ER membrane or MAM, has been shown to associate with steroids as well as cholesterol. The sigma-1 receptor has been implicated in ER lipid metabolisms/transports, lipid raft reconstitution at the plasma membrane, trophic factor signalling, cellular differentiation, and cellular protection against beta-amyloid-induced neurotoxicity. Recent studies on sigma-1 receptor chaperones and other ER proteins clearly suggest that cholesterol, in concert with those ER proteins, may regulate several important functions of the ER including folding, degradation, compartmentalization, and segregation of ER proteins, and the biosynthesis of sphingolipids. Hayashi T, Su TP. Cholesterol at the endoplasmic reticulum: Roles of the sigma-1 receptor chaperone and implications thereof in human diseases. Subcell Biochem. 2010; 51: 381-398.

Sigma-1 Receptors Regulate Hippocampal Dendritic Spine Formation Via A Free Radical-Sensitive Mechanism Involving Rac1xGTP Pathway

Sigma-1 receptors (Sig-1Rs) are endoplasmic reticulum (ER)-resident proteins known to be involved in learning and memory. Dendritic spines in hippocampal neurons play important roles in neuroplasticity and learning and memory. This study tested the hypothesis that Sig-1Rs might regulate denritic spine formation in hippocampal neurons and examined potential mechanisms therein. In rat hippocampal primary neurons, the knockdown of Sig-1Rs by siRNAs causes a deficit in the formation of dendritic spines that is unrelated to ER Ca(2+) signaling or apoptosis, but correlates with the mitochondrial permeability transition and cytochrome c release, followed by caspase-3 activation, Tiam1 cleavage, and a reduction in Rac1. GTP. Sig-1R-knockdown neurons contain higher levels of free radicals when compared to control neurons. The activation of superoxide dismutase or the application of the hydroxyl-free radical scavenger N-acetyl cysteine (NAC) to the Sig-1R-knockdown neurons rescues dendritic spines and mitochondria from the deficits caused by Sig-1R siRNA. Further, the caspase-3-resistant TIAM1 construct C1199DN, a stable guanine exchange factor able to constitutively activate Rac1 in the form of Rac1.GTP, also reverses the siRNA-induced dendritic spine deficits. In addition, constitutively active Rac1.GTP reverses this deficit. These results implicate Sig-1Rs as endogenous regulators of hippopcampal dendritic spine formation and suggest a free radical-sensitive ER-mitochondrion-Rac1.GTP pathway in the regulation of dendritic spine formation in the hippocampus. Tsai SY, Hayashi T, Harvey BK, Wang Y, Wu WW, Shen RF,

Zhang Y, Becker KG, Hoffer BJ, Su TP. Sigma-1 receptors regulate hippocampal dendritic spine formation via a free radical-sensitive mechanism involving Rac1xGTP pathway. Proc Natl Acad Sci USA. 2009; 106(52): 22468-22473.

Proteomics Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Localization and Imaging of Sialylated Glycosphingolipids in Brain Tissue Sections by MALDI Mass Spectrometry

In this study, IRP researchers describe a simple and efficient method for mapping the distribution and localization of all sialylated sphingoglycolipids present in coronal mouse brain sections using a conventional axial MALDI-TOF. A single scan of a histological tissue section gives a complete profile of ganglioside species, without derivatization or labeling. IRP researchers have developed and tested a new matrix preparation (2,6-dihydroxyacetophenone (DHA)/ammonium sulfate/ heptafluorobutyric acid (HFBA)) to maximize the detection of all ganglioside species, the ammonium sulfate limits the formation of salt adducts while the addition of HFBA increases the stability of DHA in vacuum thus facilitating imaging applications. These results, in both extracted samples and whole tissue sections using negative ion reflectron and linear mode, show differences in localization in several brain regions depending on the sialic acids and the ceramide associated core gangliosides. Colsch B, Woods AS. Localization and imaging of sialylated glycosphingolipids in brain tissue sections by MALDI Mass Spectrometry. Glycobiology. 2010 Feb 28. [Epub ahead of print]

Simultaneous Imaging Of Small Metabolites and Lipids In Rat Brain Tissues At Atmospheric Pressure By Laser Ablation Electrospray Ionization Mass Spectrometry

Atmospheric pressure imaging mass spectrometry is a rapidly expanding field that offers advantages in the ability to study biological systems in their native condition, simplified sample preparation, and high-throughput experiments. In laser ablation electrospray ionization (LAESI), the native water molecules in biological tissues facilitate sampling by a focused mid-infrared laser beam. The ionization of the ablated material is accomplished by electrospray postionization. In this work, IRP scientists demonstrate that the imaging variant of LAESI simultaneously provides lateral distributions for small metabolites and lipids directly in rat brain sections. To cope with the fragile nature and potential dehydration of the brain tissue due to drying in the ambient environment as well as to minimize analyte redistribution, a Peltier cooling stage is integrated into the LAESI imaging system. The authors demonstrate the utility of high-resolution (m/Deltam > 6000) time-of-flight mass spectrometry with LAESI to deconvolute spatial distributions of different chemical species with identical nominal mass. To help with the evaluation of the massive data sets, Pearson colocalization maps are calculated for selected small metabolites and lipids. The authors show that this approach reveals biologically meaningful correlations between these two classes of biomolecules. Nemes P, Woods AS, Vertes A. Simultaneous imaging of small metabolites and lipids in rat brain tissues at atmospheric pressure by laser ablation electrospray ionization mass spectrometry. Anal Chem. 2010; 82(3): 982-988.

Molecular Neurobiology Research Branch

Editor, Addiction Reviews 2 Annals of the New York Academy of Sciences, v 1187, 2010 appeared online February, 2010

This volume provides 19 state of the art reviews relevant to addictions from US, EU and Asian authors in this series, for which Dr Uhl is the founding editor. It initiates a new section "places in the addictions" for which the inagural article describes the Office of National Drug Control Policy.

David SP, Mezuk B, Zandi PP, Strong D, Anthony JC, Niaura R, Uhl GR, Eaton

WW. Sex differences in TTC12/ANKK1 haplotype associations with daily tobacco smoking in Black and White Americans. Nicotine Tob Res. 2010 Mar;12(3):251-62. Epub 2010 Feb 4.

This paper describes gender differences in effects of DRD2 locus haplotypes on smoking in ECA study participants from Baltimore.

Drgon T, Zhang PW, Johnson C, Walther D, Hess J, Nino M, Uhl GR. Genome wide association for addiction: replicated results and comparisons of two analytic approaches. PLoS One. 2010 Jan 21;5(1):e8832.

This paper describes 1M SNP genome wide association studies in MNB subjects who were dependent on at least one illegal substance vs controls, as well as the convergence of these results using two distinct analytic approaches to this "nontemplate" genome wide association method. This extensive work provides the first report of genome wide association results with this density of SNPs, validates the pooling method as used herein, and confirms many other modest sized effects on individual differences in vulnerability to developing dependence on an addictive substance. While there is no large effect at any specific locus, this work provides the most up to date and densest information on molecular genetics of illicit substance dependence.

Jones JD, Hall FS, Uhl GR, Riley AL. Dopamine, norepinephrine and serotonin transporter gene deletions differentially alter cocaine-induced taste aversion. Pharmacol Biochem Behav. 2010 Feb;94(4):580-587. Epub 2009 Dec 4. Stimulants produce aversive effects, which can be identified in conditioned taste aversion assays, as well as rewarding effects. This paper describes, for the first time, differences in the aversive effects of stimulants when NET, DAT or SERT are deleted.

Li B, Arime Y, Hall FS, Uhl GR, Sora I. Impaired spatial working memory and decreased frontal cortex BDNF protein level in dopamine transporter knockout mice. Eur J Pharmacol. 2010 Feb 25;628(1-3):104-107. Epub 2009 Nov 22. Neurotrophins including BDNF are associated with altered mnemonic processes. This work with Japanese collaborators studies a possible contribution of BDNF to the altered mnemonic processes that we and others have identified in DAT KO mice.

Drgonova J, Zimonjic DB, Hall FS, Uhl GR. Effect of KEPI (Ppp1r14c) deletion on morphine analgesia and tolerance in mice of different genetic backgrounds: when a knockout is near a relevant quantitative trait locus. Neuroscience. 2010 Feb 3;165(3):882-895. Epub 2009 Oct 9.

This paper describes contributions of deletion of a morphine-regulated protein phosphatase 1 inhibitor (KEPI) that was discovered in MNB to behavioral adaptations to morphine, as well as other behaviors. In addition, it identifies and provides a novel method for eliminating the effects of nearby genetic background (since the KEPI gene is close to that for the mu opiate receptor whose variants do provide a major quantitative trait locus for morphine effects in mice strains).

Psychobiology Section, Medications Discovery Research Branch

Reinforcing Effects of σ-receptor Agonists in Rats Trained to Self-administer Cocaine

Sigma receptor (σR) antagonists have been reported to block certain effects of psychostimulant drugs. IRP investigators found that these same σR antagonists did not affect cocaine self-administration. Interestingly, these drugs block conditioned place preference induced by cocaine indicating that the two procedures used to assess abuse liability of drugs tap different aspects of the activity of drugs of abuse. In contrast to the inactivity of σR antagonists against cocaine self administration, σR agonists were effective reinforcers in

subjects trained to self administer cocaine. In addition, σR agonists, like dopamine uptake inhibitors, potentiated the reinforcing effects of cocaine in the self-administration procedure. The σR antagonists antagonized the self administration of σR agonists, despite their inactivity against cocaine. Response rates maintained by maximally effective doses of σR agonists were selectively decreased by σR antagonists (effective doses did not alter response rates maintained by food reinforcement). Although σR antagonists block some cocaine-induced effects, the lack of effect on cocaine self-administration suggests that the primary reinforcing effects of cocaine do not involve direct effects at σRs. However, the self-administration of σR agonists in cocaine-trained subjects, potentiation of cocaine self-administration by σR-agonists suggest enhanced abuse-related effects resulting from concomitant dopaminergically-mediated actions and σR-mediated actions of the drugs.Hiranita T, Soto PL, Tanda G, Katz JL. Reinforcing effects of σ-receptor agonists in rats trained to self-administer cocaine. Journal of Pharmacology and Experimental Therapeutics 2010; 332: 515-524.

Cognitive Safety of a Benztropine Analog with Preclinical Efficacy for ADHD

The evidence for efficacy of atypical dopamine transport inhibitors was reviewed along with techniques for examining cognitive effects of drugs in a symposium entitled "Cognitive safety - a new framework for the safety of drugs" at the 83rd Annual Meeting of the Japanese Pharmacological Society. March 16-18, 2010, Osaka, Japan. Katz JL, Soto PL, Koffarnus M. Cognitive safety of a benztropine analog with preclinical efficacy for ADHD. Journal of Pharmacological Sciences 2010; 112, Suppl. 1, 17P.

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Program Activities

New NIDA PAs and RFAs

On January 26, 2010, NIDA issued a Program Announcement (PA) entitled **Pre-Application for the 2010 NIDA Translational Avant-Garde Award for Medication Development for Diseases of Addiction (X02) (PAR-10-095).** 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, the National Institute on Drug Abuse (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. This announcement will utilize the X02 mechanism for submission and consideration of pre-applications. The X02 pre-application is a first step in applying for a Translational Avant-Garde Award. Application Due Date(s): March 22, 2010.

On January 27, 2010, NIDA issued a PA entitled **Technology-Based Adherence Interventions for Substance Abusing Populations with HIV (R01) (PAS-10-097).** Through this FOA, NIDA seeks to stimulate and support research on the determination of efficacy and potency of interventions that utilize technological tools (e.g., mobile enabling technologies, Ecological Momentary Assessment (EMA), enhanced Medication Event Monitoring System, computer software, portable digital devices, cell phone and/or Digital Assistant Device among others) to foster adherence to Human Immunodeficiency Virus (HIV) treatment regimens among substance abusing populations in naturally occurring timeframes and contexts. Multidisciplinary collaboration between social scientists, medical (physician/nurse) researchers and technology experts to develop and refine mobile technological instrumentation, e-health technology and software as interventions (or as part of interventions) that foster adherence to HIV treatment regimens and access to care in "real time" is encouraged. This FOA will utilize the R01 grant mechanism and runs in parallel with FOA of identical scientific scope, PAS-10-098 that encourages applications under the R34 mechanism.

On January 27, 2010, NIDA issued a PA entitled **Technology-Based Adherence Interventions for Substance Abusing Populations with HIV (R34) (PAS-10-098).** Through this FOA, the National Institute on Drug Abuse (NIDA) seeks to stimulate and support research on the development, determination of feasibility, and pilot testing of interventions that utilize technological tools (e.g., mobile enabling technologies, Ecological Momentary Assessment (EMA), enhanced Medication Event Monitoring System, computer software, portable digital devices, cell phone and/or Digital Assistant Device among others) to foster adherence to Human Immunodeficiency Virus (HIV) treatment regimens among substance abusing populations in naturally occurring timeframes and contexts. Multidisciplinary collaboration between social scientists, medical (physician/nurse) researchers and technology experts to develop and refine mobile technological instrumentation, e-health technology and software as interventions (or as part of interventions) that foster adherence to HIV treatment regimens and access to care in "real time" is encouraged. This FOA will utilize the R34 grant mechanism and runs in parallel with FOA of identical scientific scope, PAS-10-097 that encourages applications under the R01 mechanism.

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On March 11, 2010, NIDA issued a PA entitled **Drug Abuse Aspects of HIV/AIDS (R01) (PA-10-129).** This FOA encourages Research Project Grant (R01) applications to examine the drug abuse aspects of HIV/AIDS, including research on drug-related risk behaviors, addiction and HIV disease, and drug use/HIV-related comorbidities and consequences. Proposals are needed to identify and predict changes in the epidemiology of HIV/AIDS among injection and non-injection drug users and among their sexual partners, to develop and test primary and secondary drug abuse and HIV prevention and treatment interventions, to improve HIV testing, counseling, and treatment services for those living with HIV/AIDS, and to address basic mechanisms involved in HIV infection and AIDS pathogenesis in the context of drug abuse and addiction. This FOA will utilize the R01 grant mechanism, and runs in parallel with a FOA of identical scientific scope, PA-10-130, that encourages applications under the R21 and PA-10-131 that encourages applications under the R03 mechanism.

On March 11, 2010, NIDA issued a PA entitled **Drug Abuse Aspects of HIV/AIDS (R21) (PA-10-130).** This FOA encourages Exploratory Developmental Research Grant (R21) applications for early and conceptual stages of research on drug abuse aspects of HIV/AIDS, including research on drug-related risk behaviors, addiction and HIV disease, and drug use/HIV-related comorbidities and consequences. Proposals are needed to identify and predict changes in the epidemiology of HIV/AIDS among injection and non-injection drug users and among their sexual partners, to develop and test primary and secondary drug abuse and HIV prevention and treatment interventions, to improve HIV testing, counseling, and treatment services for those living with HIV/AIDS, and to address basic mechanisms involved in HIV infection and AIDS pathogenesis in the context of drug abuse and addiction. This FOA will use the NIH Exploratory/ Developmental (R21) award mechanism and runs in parallel with a FOA of identical scientific scope, PA-10-129 that encourages applications under the R01 and PA-10-131 that encourages applications under the R03 mechanism.

On March 11, 2010, NIDA issued a PA entitled **Drug Abuse Aspects of HIV/AIDS (R03) (PA-10-131).** This FOA encourages Small Grant (R03) applications for pilot or feasibility studies, secondary data analysis, and small, self-contained research projects on drug abuse aspects of HIV/AIDS, including research on drug-related risk behaviors, addiction and HIV disease, and drug use/HIV-related comorbidities and consequences. Proposals are needed to identify and predict changes in the epidemiology of HIV/AIDS among injection and non-injection drug users and among their sexual partners, to develop and test primary and secondary drug abuse and HIV prevention and treatment interventions, to improve HIV testing, counseling, and treatment services for those living with HIV/AIDS, and to address basic mechanisms involved in HIV infection and AIDS pathogenesis in the context of drug abuse and addiction. This FOA will utilize the NIH Small Research Grant (R03) award mechanism and runs in parallel with an FOA of identical scientific scope, PA-10-129 that encourages applications under the R01 and PA-10-130 that encourages applications under the R21 mechanism.

On March 8, 2010, NIDA issued a PA entitled **Collaborative Clinical Trials in Drug Abuse (Collaborative R01) (PAR-10-099).** This FOA seeks to support collaborative clinical trials in drug abuse (CCTDA) through the funding of "linked" Research Project Grant (R01) applications across different study sites (e.g., different institutions, organizations, and/or multiple campuses within a single institution or university system). Each research group must submit a separate R01 application, but should conduct clinical trials utilizing one common research plan. A lead group should be designated as the coordinating site. Although a foreign institution may be included as a participating site, the coordinating site must be a domestic institution/organization. Through this FOA, NIDA seeks to increase the clinical collaboration of investigators between multiple clinical research groups, while simultaneously facilitating the study of outcome measures and/or patient populations that require larger numbers of subjects than any single site can reasonable enroll. This FOA will utilize the NIH Research Project Grant (R01) award mechanism.

On April 20, 2010, NIDA issued a PA entitled **NIDA Research Education Program for Clinical Researchers and Clinicians (R25) (PAR-10-173).** The NIDA Research Education Program will support research education and training for those in clinically focused careers. Participants (those receiving the research education and training) should be training for careers as clinical researchers, clinicians/service providers, or optimally, a combination of the two. This mechanism may not be used for support of non-research related clinical training. In addition, applicant organizations may only propose research education experiences at the following levels of professional career development: medical/graduate student, postdoctoral fellow, medical resident, and/or independent scientist. Research education and training

activities may be in any topic area related to substance use/abuse/addiction; however, the following are examples of particular relevance to this FOA: etiology; clinical assessment and diagnostics; treatment; prevention; health services; clinical neuroscience; medical consequences of drug abuse; and pre-clinical research as it pertains to translational research. Interdisciplinary research education is encouraged and may include co-morbid conditions and consequences of drug use such as HIV/AIDS. Education partnerships and collaborations are also encouraged. This FOA will use the NIH Research Education (R25) grant mechanism. Research education programs may not be transferred from one institution to another, unless strongly justified (see Section VI.2). Letters of Intent Receipt Date(s): 30 days prior to the application submission date; Application Submission/Receipt Date(s): May 25, 2010, May 25, 2011, and May 25, 2012.

On January 22, 2010, NIDA issued an RFA entitled **Systems Biology, HIV/AIDS, and Substance Abuse (R01) (RFA-DA-10-014).** The purpose of this FOA is to solicit applications utilizing systems biology approaches to interrogate and integrate multiple complex databases in order to discover new paradigms that may lead to unanticipated avenues of research at the interface of HIV/AIDS and substance use and abuse. This FOA will utilize the R01 award mechanism. Letters of Intent Receipt Date(s): March 29, 2010; Application Due Date(s): April 29, 2010.

On January 26, 2010, NIDA issued an RFA entitled **2010 NIDA Translational Avant-Garde Award for Medication Development for Diseases of Addiction (DP1) (RFA-DA-10-013).** 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, the National Institute on Drug Abuse (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 pharmacotherapy 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 2010 Translational Avant-Garde Award competition will proceed in two phases. The first phase is a pre-application phase in response to PAR-10-095. Pre-applications will be evaluated by a group of external reviewers. Those investigators whose submissions are judged to be the most outstanding will be notified of the opportunity to submit full applications under this FOA (DP1). The 2010 Avant-Garde awardees will be selected from this group of applicants. This FOA will utilize the DP1 grant mechanism. Pre-applications for 2010 Translational Avant-Garde Awards were encouraged under PAR-10-095. Application Due Date(s): July 2, 2010.

On January 26, 2010, NIDA issued an RFA entitled **Medications Development for Substance Related Disorders (R01) (RFA-DA-10-018).** Through this FOA, NIDA is soliciting grant (R01) applications to support a diverse array of preclinical and/or clinical research projects that accelerate the translational discovery/ development of safe and effective medications for the treatment of substance-related disorders (SRDs), with the ultimate goal of moving closer to, or gaining FDA approval of medications for the treatment of these disorders. This FOA will utilize the R01 award mechanism. Letters of Intent Receipt Date(s): March 29, 2010; Application Due Date(s): April 29, 2010.

On January 26, 2010, NIDA issued an RFA entitled **Deep Sequencing and Analysis of Pharmacogenomic Regions: Discovery and Analysis of Genetic Variants Contributing to Drug Abuse and Addiction (R01) (RFA-DA-10-019).** Genome-wide association studies (GWAS) have been critical for identifying genomic regions associated with addiction phenotypes, and have highlighted several areas that require further refinement using deep sequencing approaches. The goal of this FOA is to support studies proposing to use next-generation sequencing technologies to identify the structural variants and SNP variants with rare to moderate frequencies that affect addiction risk in well-characterized samples with drug abuse phenotypes. Applications may propose strategies for deep sequencing based on family based designs; deep sequencing of regions identified by GWAS to be associated with addiction risk; sequencing candidate genes in individuals with extreme phenotypes; or other analytic approaches that capitalize on the genetic architecture. Applicants must use existing

DNA samples with appropriately obtained consents for broad data sharing. This FOA will utilize the R01 award mechanism. Letters of Intent Receipt Date(s): March 29, 2010; Application Due Date(s): April 29, 2010.

PAs/RFAs Issued with Other NIH Components/Agencies

On February 3, 2010, NIDA and several other NIDA components jointly issued a PA entitled **Scientific Meetings for Creating Interdisciplinary Research Teams (R13) (PA-10-106).** This FOA encourages Research Conference Grant (R13) applications from institutions and organizations that propose to develop interdisciplinary research teams. Teams must include investigators from the social and/or behavioral sciences, and may include the life and/or physical sciences. The goal is to broaden the scope of investigation into scientific problems, yield fresh and possibly unexpected insights, and increase the sophistication of theoretical, methodological, and analytical approaches by integrating the analytical strengths of two or more disparate scientific disciplines while addressing gaps in terminology, approach, and methodology. This program will allow investigators from multiple disciplines to hold meetings in order to provide the foundation for developing interdisciplinary research projects. This FOA will utilize the R13 grant mechanism.

On February 16, NIDA and 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-10-107).** 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. This FOA will utilize the NIH Ruth L. Kirschstein National Research Service Award (NRSA) award mechanism for Individual Predoctoral MD/PhD and other dual-degree Fellows (F30).

On February 16, 2010, NIDA and numerous other NIH components jointly issued a PA entitled **Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellows (Parent F31) (PA-10-108)**. 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. This FOA will utilize the NIH Ruth L. Kirschstein Individual Predoctoral National Research Service Award (NRSA) award mechanism (F31).

On February 16, 2010, NIDA and numerous other NIH components jointly 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-10-109).** 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. This FOA will utilize the NIH Ruth L. Kirschstein Individual Predoctoral National Research Service Award (NRSA) award mechanism (F31).

On February 16, 2010, NIDA and numerous other NIH components issued a PA entitled **Ruth L. Kirschstein National Research Service Awards (NRSA) for Individual Senior Fellows (Parent F33) (PA-10-111)**. The National Institutes of Health (NIH) awards individual senior level research training fellowships to experienced scientists who wish to make major changes in the direction of their research careers or who wish to broaden their scientific background by acquiring new research capabilities as independent investigators in research fields relevant to the missions of participating NIH Institutes and Centers. This FOA will utilize the Ruth L. Kirschstein Individual Postdoctoral National Research Service Award (NRSA) award mechanism (F33).

On March 5, 2010, NIDA participated in the issuance of the NIH-wide announcement entitled **Recovery Act Limited Competition: The NIH Director's ARRA Funded**

Pathfinder Award to Promote Diversity in the Scientific Workforce (DP4) (RFA-OD-10-013). This NIH Funding Opportunity Announcement (FOA), supported by funds provided to the NIH under the American Recovery & Reinvestment Act of 2009 ("Recovery Act" or "ARRA"), Public Law 111-5, invites applications for the NIH Director's ARRA Pathfinder Award to Promote Diversity in the Scientific Workforce. The NIH recognizes a unique and compelling need to promote diversity in the biomedical, behavioral, clinical and social sciences research workforce. The NIH expects all of its efforts to diversify the workforce to lead to the recruitment of the most talented researchers from all groups; to improve the quality of the educational and training environment; to balance and broaden the perspective in setting research priorities; to improve the ability to recruit subjects from diverse backgrounds into clinical research protocols; and to improve the Nation's capacity to address and eliminate health disparities. This new FOA introduces a new research grant program to encourage exceptionally creative individual scientists to develop highly innovative and possibly transforming approaches for promoting diversity within the biomedical research workforce. To be considered highly innovative, the proposed research must reflect ideas substantially different from those already being pursued or it must apply existing research designs in new and innovative ways to unambiguously identify factors that will improve the retention of students, postdocs and faculty from diverse backgrounds. Awardees must commit a major portion (generally 30% or more) of their research effort to activities supported by the Director's Pathfinder Award and the proposed research must be endorsed by the highest levels of institutional management. This FOA will utilize the DP4 grant mechanism. Letters of Intent Receipt Date(s): April 5, 2010; Application Due Date(s): May 4, 2010.

On March 5, 2010, NIDA participated in the issuance of a PA entitled **SHIFT Award: Small Businesses Helping Investigators to Fuel the Translation of Scientific Discoveries [SBIR: R43/R44] (PA-10-122)**. The primary objectives of the SHIFT SBIR initiative are: (1) to foster research that is translational in nature and (2) to transform academic scientific discoveries into commercial products and services. Academic researchers can be a driving force for new products and services in a small business concern (SBC). A major feature of the SHIFT program includes the requirement for an investigator who is primarily employed by a United States research institution at the time of application to transition to a small business concern (SBC) and be primarily employed (more than 50% time) by the SBC by or at the time of award. A SHIFT SBIR grant enables an SBC to increase both its scientific research staff and its core competencies. The Project Director/Principal Investigator (PD/PI) may also facilitate SBC licensing of intellectual property (IP) from the PD/PI's prior academic institutions, promote collaboration opportunities with academic investigators, and enable better access to academic resources. This FOA will utilize the SBIR (R43/R44) grant mechanisms for Phase I, Phase II, and Fast-Track applications.

On March 2, 2010, NIDA, in collaboration with numerous other NIH components issued a PA entitled **Jointly Sponsored Ruth L. Kirschstein National Research Service Award Institutional Predoctoral Training Program in the Neurosciences (T32) (PAR-10-116)**. The Jointly Sponsored NIH Predoctoral Training Program in the Neurosciences supports broad and fundamental, early-stage graduate research training in the neurosciences via institutional NRSA research training grants (T32) at domestic institutions of higher education. Trainees are supported during years 1 and 2 of their graduate research training when they are typically not committed to a dissertation laboratory. The primary objective is to prepare qualified individuals for careers in neuroscience that have a significant impact on the health-related research needs of the Nation. This Funding Opportunity Announcement (FOA) will utilize the Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grants (T32) award mechanism. Letters of Intent Submission Date(s): April 25, 2010; Application Submission Date(s): May 25, 2010.

On March 15, 2010, NIDA participated in the issuance of a FOA with other HHS and NIH components entitled **The Medical Education Partnership Initiative (MEPI) (R24)**. This NIH Funding Opportunity Announcement (FOA), supported by funds provided to the NIH and HRSA under the "Tom Lantos and Henry Hyde United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Reauthorization Act of 2008," Public Law 110-293 (more commonly known as the U.S. President's Emergency Plan for AIDS Relief [PEPFAR]), invites proposals from foreign Institutions in Sub-Saharan African countries which receive PEPFAR support (http://www.pepfar.gov/countries/index.htm) and their partners to develop or expand and enhance models of medical education in Sub-Saharan Africa. These models are intended to support PEPFAR's goal of increasing the number of new health care

workers by 140,000, strengthen medical education systems in the countries in which they exist, and build clinical and research capacity in Africa as part of a retention strategy for faculty of medical schools and clinical professors. The strategy of this initiative is to build human capacity for health in Africa by strengthening the medical education system in an environment that values and nurtures research and which will contribute to the sustainability and quality of the overall effort. These models will also contribute to the sustainability of the PEPFAR investments through the provision of excellence in clinical training and the capacity of medical students and faculty to participate in and carry out multidisciplinary locally driven research (e.g. implementation science and/or clinical, health services, and operations research) that responds to the health needs of their communities and country and improves health outcomes for men, women, and children. In addition to PEPFAR support for strengthening medical education in African institutions, funds are also being provided from the Office of AIDS Research (OAR), located within the NIH Office of the Director, in support of the research capacity building component of this initiative and building on OAR's long-term support for NIH efforts to build sustainable research and training partnerships between U.S. and African educational and research institutions. Linked awards that focus on diseases and priority health areas related to and/or beyond HIV/AIDS will also be available through the NIH Common Fund initiative (http://commonfund.nih.gov/), managed by the Office of Strategic Coordination (OSC), located within the NIH Office of the Director. These awards are part of the NIH Director's decision to make global health one of the NIH's highest priorities. This FOA will utilize the NIH Resource-Related Research Project (R24) grant award mechanism for all applications submitted. Letters of Intent Receipt Date: April 12, 2010; Application Due Date: May 12, 2010.

On March 18, 2010, NIDA and numerous other NIH components jointly issued a PA entitled **Behavioral and Social Science Research on Understanding and Reducing Health Disparities (R01) (PAR-10-136)**. The purpose of this FOA is to encourage behavioral and social science research on the causes and solutions to health and disabilities disparities in the U. S. population. Health disparities between, on the one hand, racial/ethnic populations, lower socioeconomic classes, and rural residents and, on the other hand, the overall U.S. population are major public health concerns. Emphasis is placed on research in and among three broad areas of action: 1) public policy, 2) health care, and 3) disease/disability prevention. Particular attention is given to reducing "health gaps" among groups. Proposals that utilize an interdisciplinary approach, investigate multiple levels of analysis, incorporate a life-course perspective, and/or employ innovative methods such as system science or community-based participatory research are particularly encouraged. This FOA will utilize the NIH Research Project Grant (R01) award mechanism and runs in parallel with an FOA of identical scientific scope, PAR-10-137, that encourages applications under the R21. Letters of Intent Receipt Date(s): August 14, 2010, December 11, 2010, April 11, 2011, August 14, 2011, December 11, 2011, April 11, 2012, August 14, 2012, December 14, 2012, April 11, 2013. Application Due Date(s): September 14, 2010, January 11, 2011, May 11, 2011, September 14, 2011, January 11, 2012, May 11, 2012, September 14, 2012, January 14, 2013, May 11, 2013.

On March 18, 2010, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Behavioral and Social Science Research on Understanding and Reducing Health Disparities (R21) (PAR-10-137)**. The purpose of this FOA is to encourage behavioral and social science research on the causes and solutions to health and disabilities disparities in the U. S. population. Health disparities between, on the one hand, racial/ethnic populations, lower socioeconomic classes, and rural residents and, on the other hand, the overall U.S. population are major public health concerns. Emphasis is placed on research in and among three broad areas of action: 1) Public policy, 2) health care, and 3) disease/disability prevention. Particular attention is given to reducing "health gaps" among groups. Proposals that utilize an interdisciplinary approach, investigate multiple levels of analysis, incorporate a life-course perspective, and/or employ innovative methods such as system science or community-based participatory research are particularly encouraged. This FOA will use the NIH Exploratory/ Developmental (R21) grant mechanism and runs in parallel with a FOA of identical scientific scope, PAR-10-136, that encourages applications under the R01. Letters of Intent Receipt Date(s): August 14, 2010, December 11, 2010, April 11, 2011, August 14, 2011, December 11, 2011, April 11, 2012, August 14, 2012, December 14, 2012 April 11, 2013. Application Due Date(s): September 14, 2010, January 11, 2011, May 11, 2011, September 14, 2011, January 11, 2012, May 11, 2012, September 14, 2012, January 14, 2013, May 11, 2013.

On March 19, 2010, NIDA participated in the issuance of a PA entitled **Social Network Analysis and Health (R01)**. This FOA encourages research that aims to

accomplish one or more specific goals: (1) generate new theories that would enhance the capabilities and value of Social Network Analysis (SNA); (2) address fundamental questions about social interactions and processes in social networks; (3) address fundamental questions about social networks in relation to health and health-related behaviors; (4) develop innovative methodologies and technologies to facilitate, improve, and expand the capabilities of SNA. This FOA will utilize the R01 grant mechanism and runs in parallel with a FOA of identical scientific scope, PAR-10-146, that encourages applications under the R21 grant mechanism. Letters of Intent Receipt Date(s): May 3, 2010; April 11, 2011; April 11, 2012. Application Due Date(s): June 3, 2010; May 11, 2011; May 11, 2012.

On March 19, 2010, NIDA participated in the issuance of a PA entitled **Social Network Analysis and Health (R21) (PAR-10-146)**. This FOA encourages basic research that will: generate new theories that can further social network analysis; address fundamental questions about the relationship between social networks and health; and develop methodological and technological innovations to facilitate and extend social network analyses. This FOA will use the NIH Exploratory/Developmental (R21) award mechanism and runs in parallel with a FOA of identical scientific scope, PAR-10-145, that encourages applications under the R01 grant mechanism. Letters of Intent Receipt Date(s): May 3, 2010; April 11, 2011; April 11, 2012; Application Due Date(s): June 3, 2010; May 11, 2011; May 11, 2012.

On March 25, 2010, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Innovative Neuroscience K-12 Education (SBIR [R43/R44]) (PAR-10-154)**. 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 (for further information, see http://neuroscienceblueprint.nih.gov/). This Funding Opportunity Announcement (FOA) is released in affiliation with the Neuroscience Blueprint, with Institutes and Centers participating independently. This Funding Opportunity Announcement (FOA) encourages Small Business Innovation Research (SBIR) grant applications from small business concerns (SBCs) that propose to develop innovative neuroscience educational tools to be used by or benefit children in kindergarten through 12th grade (K-12). Educational tools can be designed using any media (e.g., paper, electronic, etc.) or format (e.g., simulations, games, videos, notebooks, etc.) for use in or out of school settings, targeting children in groups or alone, with or without adult or teacher participation. Innovative neuroscience educational tools should promote neuroscience knowledge acquisition and application of that knowledge to one's own life, promote an interest in neuroscience learning and careers, and present a positive and realistic representation of the diversity of people who engage in neuroscience-related research and occupations. Educational tools targeted to increase the diversity of students (i.e., Native American, Black, Hispanic, female, disabled, or otherwise underrepresented) pursuing neuroscience learning are especially encouraged. This FOA will utilize the SBIR (R43/R44) grant mechanisms for Phase I, Phase II, and Fast-Track applications. Letters of Intent Receipt Date(s): May 1, 2010; Application Due Date(s): June 1, 2010, April 4, 2011, April 4, 2012.

On April 6, 2010, NIDA in collaboration with numerous other NIH components, issued a PA entitled **Bioengineering Nanotechnology Initiative (STTR [R41/R42])(PA-10-149)**. Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modeling, and manipulating matter at this length scale. The purpose of this trans-NIH Funding Opportunity Announcement (FOA) is to stimulate Small Business Technology Transfer (STTR) grant applications that employ nanotechnology to enable the development of diagnostics and interventions for treating diseases. This FOA will utilize the STTR (R41/R42) grant mechanisms for Phase I, Phase II, and Fast-Track applications and runs in parallel with a FOA of identical scientific scope, PA-10-150, that encourages applications under the Small Business Innovation Research (SBIR) (R43/R44) grant mechanisms.

On April 6, 2010, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Bioengineering Nanotechnology Initiative (STTR [R43/R44])(PA-10-150)**. Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modeling, and manipulating matter at this length scale. The purpose of this trans-NIH Funding Opportunity Announcement (FOA) is to stimulate Small Business Innovation Research (SBIR) grant applications that employ nanotechnology to enable the development of diagnostics and

interventions for treating diseases. This FOA will utilize the SBIR (R43/R44) grant mechanisms for Phase I, Phase II, and Fast-Track applications and runs in parallel with a FOA of identical scientific scope, PA-10-149, which encourages applications under the Small Business Technology Transfer (STTR) (R41/R42) grant mechanisms.

On April 13, 2010, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **International Neuroscience Fellowship (F05) (PAR-10-167)**. 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 (U.S.). 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. This Funding Opportunity Announcement (FOA) will utilize the international research fellowship (F05) grant mechanism. Letters of Intent Receipt Date(s): July 16, 2010, 2011, 2012; Application Due Date(s): August 16, 2010, 2011, 2012.

On January 28, 2010, NIDA and several other NIH components jointly issued an RFA entitled **Recovery Act Limited Competition: Program to Enhance NIH-supported Global Health Research Involving Human Subjects (S07) (RFA-OD-10-006)**. This NIH Funding Opportunity Announcement (FOA), supported by funds provided to the NIH under the American Recovery & Reinvestment Act of 2009 ("Recovery Act" or "ARRA"), Public Law 111-5, invites applications from U.S. institutions for one year of support for resources and activities that will strengthen oversight of NIH supported human subjects research conducted collaboratively with institutions in low- to middle-income countries (LMIC). This FOA will utilize the NIH Biomedical Research Support Grants (S07) mechanism. Letters of Intent Receipt Date: February 22, 2010; Application Due Date: March 22, 2010.

On January 26, NIDA and several other NIH components issued an RFA entitled **Recovery Act Limited Competition: Framework Programs for Global Health Signature Innovations Initiative (R24) (RFA-OD-10-007)**. This NIH Funding Opportunity Announcement (FOA), supported by funds provided to the NIH under the American Recovery & Reinvestment Act of 2009 ("Recovery Act" or "ARRA"), Public Law 111-5, invites applications from U.S. institutions and their partners to enhance the infrastructure and opportunities at the participating institutions for training postdoctoral investigators to carry out innovative, multidisciplinary research in Global Health. The initiative emphasizes hands on, problem solving, and collaborative approaches and may require the development of new training models and new partnerships within and beyond the university community. This FOA will utilize the NIH Resource-Related Research Project (R24) award mechanism. Letters of Intent Receipt Date: February 22, 2010; Application Due Date: March 22, 2010.

Other Program Activities

Clinical Trials Network (CTN) Update

Protocols: A total of 43 protocols have been initiated since 2001, including multi-site clinical trials (29), multi-site surveys (3), studies in special populations (5), and secondary analyses of data across various trials (6). In addition, 19 ancillary studies have been supported by CTN and non-CTN funds. There are about 11,500 participants 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

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 0010**, Buprenorphine/Naloxone-Facilitated Rehabilitation for Heroin Addicted Adolescents/Young Adults
- **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 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.

In addition, the following protocols have submitted primary paper:

- **Protocol CTN 0017**, HIV and HCV Intervention in Drug Treatment Settings
- **Protocol CTN 0030A2**, Effects of Chronic Opioids in Subjects with a History of Opioid Use

The following protocols have locked data:

- **Protocol CTN 0014**, Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT)
- **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) is a randomized 2-phase, open-label, multi-center study in outpatient treatment settings. Pre-screening began in May 2006. The study, carried out in 9 sites, has randomized 653 participants into phase 1 and 360 participants into phase 2 and is currently in the close-out phase.
- **Protocol CTN 0030A1**, Collection of Economic Data for the Prescription Opioid Addiction Treatment Study. This ancillary study was conducted in collaboration with NIDA DESPR and it is in the data analysis phase.
- **Protocol CTN 0032**, HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the U.S. **This study randomized 1281 participants to evaluate the most effective strategy to ensure that persons in drug treatment programs are tested for HIV and receive their HIV test results. The protocol has completed enrollment and is currently in the data analysis phase.**

The following protocols has ended new enrollment, and are in the follow-up

or data-lock phase:

- **Protocol CTN 0027**, Starting Treatment with Agonist Replacement Therapies (START) is a randomized, open-label, multi-center study that was developed in collaboration with the Division of Pharmacotherapies & Medical Consequences of Drug Abuse (DPMCDA). 1,269 participants were randomized. Data collection is expected to end in June, 2010.
- **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 expected to end in June, 2010.
- **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 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.
- **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 who completed the data collection and blood draw procedures.
- **Protocol CTN 0031A2**, The Role of Alcohol Consumption in Classifications of Alcohol Use Disorders: A Clinical Study. In collaboration with DESPR. The baseline data obtained in this research formed the foundation for an R01 grant awarded to Joseph Guydish, PhD, at the University of California, San Francisco.
- **Protocol CTN 0031A3**, Organizational and Practitioner Influences on Implementation of STAGE-12. The study assesses the influence of counselor and organizational variables on fidelity of the STAGE-12 intervention during the clinical trial, tests the impact of fidelity on clinical trial participant outcomes, and explores the influence of counselor and organizational variables on sustainability of the STAGE-12 intervention following completion of the clinical trial. Study staff has already collected the organizational and counselor level data from all ten STAGE-12 sites. The baseline data obtained in this research formed the foundation for an R01 grant awarded by DESPR to Joseph Guydish, PhD, at the University of California, San Francisco.
- **Protocol CTN 0032A1**, Economic Analysis of HIV Rapid Testing in Drug Abuse Treatment Programs. This ancillary study is an assessment of the cost-effectiveness of on-site HIV testing in drug abuse treatment settings vs. referral for off-site testing. The PI is Dr. Bruce Schackman. The project is conducted in collaboration with NIDA's DESPR.
- **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 will be conducted in the Pacific Northwest Node.
- **Protocol CTN 0035-Ot**, Access to HIV and Hepatitis Screening and Care among Ethnic Minority Drug Users In and Out of Drug Treatment. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and is being conducted in the California/Arizona Node.
- **Protocol CTN 0036-Ot**, Epidemiology and Ethnographic Survey of "Cheese" Heroin Use among Hispanics in Dallas County. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and is being conducted in the Texas Node.

The following protocols are currently enrolling:

- **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 is in the development phase.
- **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 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.

The following protocols are in the development phase:

- **Protocol CTN 0037**, Exercise as a Treatment for Substance Use Disorders. This clinical trial will test the effectiveness of the addition of exercise in improving drug abuse treatment outcomes.
- **Protocol CTN-0038-Ot**, Barriers to Substance Abuse Treatment among Asian Americans and Pacific Islanders. The objective of this study is to gain a better understanding of the factors that may influence the under-utilization of substance abuse treatment services by Asian Americans and Pacific Islanders (AAPIs) and the readiness of substance abuse treatment programs serving AAPIs to participate in clinical trials and adopt evidence based practices. This study is a collaboration with NIH NCMHD.
- **Protocol CTN 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.
- **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-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.
- **Protocol CTN-0048**, Screening, Motivational Assessment, Referral and Treatment in Dental Clinics. This concept is currently being developed into a protocol, in collaboration with the NIDCR and their clinical networks.
- **Protocols CTN-0037-A1, CTN-0044-A1 and CTN0046-A1**, Organizational and Practitioner Influences on Patient Outcomes. This series of ancillary studies will assess associations between site organizational and practitioner variables and site differences in clinical trial outcomes.

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);
2. Pattern of alcohol use and alcohol-related diagnoses among drug abusing/dependent participants, PIs: Dennis Donovan and Bryan Hartzler (Pacific Northwest Node);
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);
4. The Efficacy of Motivational Enhancement Therapy for African Americans, PI: Kathleen Burlew (Ohio Valley Node);
5. Substance Abuse Treatment Outcomes in Racial/Ethnic Minority Populations, PI: Carmen Masson (California-Arizona Node).

There are also about 44 funded studies supported by independent grants that use CTN studies as a platform.

NIDA's New and Competing Continuation Grants Awarded Since February 2010

Abood, Mary E. -- Temple University
Pamoic Acid Analogues as Potent GPR35 Agonists Inducing Antinociception

Akbarian, Schahram -- University of Massachusetts Medical School, Worcester
Transgenic Mice to Label Cell-Specific Nuclei in Brain

Akins, Chana K. -- University of Kentucky
Enhancement of Sexual Motivation

Al-Harthi, Lena -- Rush University Medical Center
Protective Pathways Against Methamphetamines Abuse and HIV Neuropathogenesis

Benamar, Khalid -- Temple University
Gp120 in the Brain and Opioid Medications: Functional Interactions

Biernacka, Joanna M. -- Mayo Clinic College of Medicine, Rochester
Methods for Detecting Interacting Risk Factors for Addictions

Blitzer, Robert D. -- Mount Sinai School of Medicine of NYU
Reversing Cocaine-Induced Plasticity with GSK3 Inhibitors

Bogen, Debra L. -- University of Pittsburgh at Pittsburgh
Randomized Clinical Trial of High vs. Standard-Calorie Formula for Methadone-Expo

Boger, Dale L. -- Scripps Research Institute
Inhibitors of Fatty Acid Amide Hydrolase (FAAH)

Bolanos, Carlos A. -- Florida State University
Ontogeny of Drug Exposure and Mood Dysregulation

Booth, Robert E. -- University of Colorado, Denver
Peer Leaders as HIV Risk Reduction Change Agents Among IDUs in Ukraine

Bourgois, Philippe -- University of Pennsylvania
The Logics for HIV Risk Among Street-Based Heroin Injectors

Bowman, Anna Louise -- Northeastern University
Virtual Screening to Identify Novel, Selective Monoacylglycerol Lipase Inhibitors

Brown, Louis Davis -- Pennsylvania State University-University Park
Using Coalitions to Support Evidence-Based Programs and Prevent Drug Abuse

Chandra, Siddharth -- Michigan State University
Drug Consumption and Disease Mortality: Population-Level Analyses

Chou, Chih-Ping -- University of Southern California
Effects of Developmental Stage and Transitions on Drug Use Trajectories

Ciccarone, Daniel H -- University of California, San Francisco
Heroin Price, Purity and Outcomes Study

Civelli, Olivier -- University of California, Irvine
A Novel Neuropeptide System Involved in Drug Abuse

Coors, Marilyn E -- University of Colorado, Denver
Ethical Issues in Broad Data Sharing for Addiction Research: Best Research Practice

Czoty, Paul W. -- Wake Forest University Health Sciences
Brain Imaging and Cognitive Effects of Cocaine Self-Administration in Monkeys

Daughters, Stacey B -- University of Maryland College, Park Campus
Depression Treatment for Urban Low Income Minority Substance Users

Dunlap, Eloise Emma -- National Development and Research Institutes
Stages of Drug Market Disruption and Reformulation in Disaster Cities

Edlin, Brian R. -- Suny Downstate Medical Center
Integrated vs. Separate Care for Hepatitis C, Substance Abuse, and HIV Prevention

Feldstein Ewing, Sarah W. -- The Mind Research Network
Adolescent Response to Psychotherapy: The Role of Neuronal Networks

Fishbein, Diana H. -- Research Triangle Institute
Transdisciplinary Approach to Understand Variability in Preventive Intervention

France, Charles P. -- University of Texas Health Science Center, San Antonio
Discriminative Stimulus Effects of Opioid Withdrawal

Freeman, Willard M. -- Pennsylvania State University, Hershey Medical Center
Gene Promoter DNA Methylation with Cocaine Self-Administration and Abstinence

Fuchs Lokensgard, Rita A. -- University of North Carolina, Chapel Hill
Drug Context-Induced Instrumental Cocaine Seeking: Influence of Memory Reconsolidation

Galizio, Joseph Mark -- University of North Carolina, Wilmington
Drugs of Abuse and Memory Span

Glasner-Edwards, Suzette V. -- University of California, Los Angeles
Mindfulness Based Relapse Prevention for Stimulant Users

Golder, Seana -- University of Louisville
Victimization and Women in the Criminal Justice System

Grafsky, Erika L. -- Ohio State University
Formative Research on Substance Use and Disclosure for GLB Youth and Their Families

Grandy, David Kilgore -- Oregon Health and Science University
Role of TAAR1 in Methamphetamine Self-Administration

Gruol, Donna L. -- Scripps Research Institute
An Integrative Structure/Functional Analysis of Mu-Opioid Receptor Variants

Hackenberg, Timothy D. -- Reed College
Behavioral Economics in a Laboratory-Based Token Economy

Haggerty, Kevin P. -- University of Washington
Exploring Implementation of Drug Abuse Prevention in Treatment Settings

Hahn, Britta -- University of Maryland, Baltimore
Nicotinic Modulation of the Default Network of Resting Brain Function

Hayashida, Kenichiro -- Wake Forest University Health Sciences
Mechanisms and Consequences of Locus Coeruleus Activation

He, Johnny J. -- Indiana University-Purdue University at Indianapolis
HIV Interaction with Drugs of Abuse and Adult Neurogenesis

Henderson, Craig E. -- Sam Houston State University
Integrative Data Analysis of Gender and Ethnic Differences in MDFT RCTs

Hennrikus, Deborah J. -- University of Minnesota, Twin Cities
An Integrated Work Safety - Smoking Cessation Program for Small Worksites

Hillard, Cecilia J. -- Medical College of Wisconsin
Cannabinoid Regulation of Glycogen Synthase Kinase-3

Ho, Wenzhe -- Temple University
Opioids, LPS and HIV

Horgan, Constance M. -- Brandeis University
Provision of Drug Abuse Treatment Services Under Parity

Hough, Lindsay -- Albany Medical College
P450 Epoxygenase Mechanisms of Opioid Analgesia

Howell, Leonard L. -- Emory University
Cocaine Use and Monoamine Function

Hurd, Yasmin L. -- Mount Sinai School of Medicine of NYU
Cannabidiol as Treatment Intervention for Opiate Relapse

Itzhak, Yossef -- University of Miami School of Medicine
A Novel Paradigm for Context and Cue Conditioning: Relevance for Drug Addiction

Izenwasser, Sari -- University of Miami School of Medicine
Social and Environmental Factors in Adolescent Stimulant Abuse

Jacobson, Jeffrey M. -- Drexel University
Long-Acting HIV Therapy for Injection Drug Users

Jacobson, Mark W. -- University of California, San Diego
Impact of White Matter Integrity on Functional MRI in HIV and Methamphetamine

Kalivas, Peter W. -- Medical University of South Carolina
Glutamate and Craving for Cocaine

Kaul, Marcus -- Burnham Institute for Medical Research
Combined Effect of Methamphetamine, HIV and HAART on Neurons and Macrophages

Kellar, Kenneth J. -- Georgetown University
Novel Ligands That Selectively Desensitize Alpha4beta nACHRs for Smoking Cessation

Khoshbouei, Habibeh -- Meharry Medical College
Methamphetamine and Amphetamine Differentially Affect Dopamine Transporter Activity

Kidorf, Michael S. -- Johns Hopkins University
Community-Based Intervention at Needle Exchange Sites

King, Jean A. -- University of Massachusetts Medical School, Worcester
Possible Significance of Cholinergic Influence in ADHD

Kippin, Tod E. -- University of California, Santa Barbara
Chromatin Remodeling in the Prefrontal Cortex in Cocaine Addiction

Kippin, Tod E. -- University of California, Santa Barbara
Interactions Between Prenatal Stress and Genetics in Cocaine Responsiveness

Kish, Stephen John -- Centre for Addiction and Mental Health
Pet Imaging Study of Brain VMAT2 in Human Methamphetamine Users

Lai, Shenghan -- Johns Hopkins University
Subclinical Atherosclerosis in HIV Plus Black Cocaine Users

Larimer, Mary E. -- University of Washington
RCT of WEB vs. In-Person SUDCSnd Cormorbity Treatment

Ledoux, Joseph E. -- New York University
Brain Mechanisms of Avoidance: Implications for Addiction

Lee, Daeyeol -- Yale University
Decision Making and Orbitofrontal Cortex

Lindberg, Iris -- University of Maryland, Baltimore
Opioid Peptide Synthesizing Enzymes

Loffredo, Christopher A. -- Georgetown University
Prevalence and Correlates of Youth Drug Abuse in Egypt

Lucas, Gregory M. -- Johns Hopkins University
Early-Stage Chronic Kidney Disease in HIV-Infected Individuals

Mackie, Kenneth P. -- Indiana University, Bloomington
Do Organophosphates Impair Neurodevelopment through Inhibition of Endocannabinoid

Maes, Hermine H. -- Virginia Commonwealth University
Developmental Genetic Epidemiology of Smoking

Mantsch, John R. -- Marquette University
GCF, CRF and Stressor-Induced Relapse

Marriott, Karla-Sue Camille -- Savannah State University
Synthesis of Novel Agents for Use in Addiction Treatment

Marshal, Michael P. -- University of Pittsburgh at Pittsburgh
HIV Risk Behavior and Drug Use Over Time: Syndemic Production in High Risk Youth

Mello, Nancy K. -- McLean Hospital (Belmont, MA)
Sex/Gender and Nicotine Addiction: Hormones, Behavior and Neuroimaging

Merchant, Roland C. -- Rhode Island Hospital
Increasing Viral Testing in the Emergency Department

Montaner, Luis J. -- Wistar Institute
NK Cell Activation and Function in HIV-1 Exposed Uninfected IV Drug Users

Morgan, Peter T. -- Yale University
Modafinil, Sleep Architecture, and Cocaine Relapse

Muilenburg, Jessica L. -- University of Georgia (UGA)
Smoking Cessation Interventions and Program Availability for Drug and Alcohol ADD

Nunes, Edward V. -- New York State Psychiatric Institute
Training Motivational Interviewing Using Live Supervision

Ozechowski, Timothy J. -- Oregon Research Institute
Therapist-Family Interactions in Functional Family Therapy for Drug Abusing Youth

Pan, Ying-Xian -- Sloan-Kettering Institute for Cancer Research
Exploring Functions of Mu Opioid Receptor Carboxyl Termini by Gene Targeting

Pasternak, Gavril W. -- Sloan-Kettering Institute for Cancer Research
Pharmacology of Opioid Receptor Subtype

Patterson, Thomas L. -- University of California, San Diego
Safer Sex Intervention for Male Clients of Female Sex Workers in Tijuana, Mexico

Petrache, Irina -- Indiana University-Purdue University at Indianapolis
Molecular Mechanism of Alveolar Injury Caused by Cigarette Smoke

Polcin, Douglas L. -- Public Health Institute
Community Impact on Adoption of Sober Living Houses

Prisinzano, Thomas Edward -- University of Kansas, Lawrence
Investigation of Neoclerodanes as Novel Opioid Ligands

Raines, Douglas E. -- Massachusetts General Hospital
Preclinical Studies of Carbo-Etomidate: An Etomidate Analogue for Use in Sepsis

Rauh, Virginia A. -- Columbia University Health Sciences
Assess the Effects of ETs on Neurodevelopment

Reed, Brian -- Rockefeller University
18F-Beta-Endorphin Imaging: Translational Study of an Opioid Peptide Radiotracer

Reynolds, Brady A. -- Research Institute Nationwide Children's Hospital
Web-Based Contingency Management for Smoking Abstinence with Adolescents

Roitman, Jamie D. -- University of Illinois at Chicago
Cortico-Striatal Signaling in Risk Preference

Rosen, Marc I. -- Yale University
Improving Clinician Ratings of Money Mismanagement: Addiction's Impact

Roth, Bryan L. -- University of North Carolina, Chapel Hill
Diterpines as Selective Kappa Opioid Receptor Agonists

Rudnick, Gary W. -- Yale University
Neurotransmitter Transport

Santisteban, Daniel A. -- University of Miami, Coral Gables
Culturally Informed Family Based Treatment of Adolescents: A Randomized Trial

Sazonov, Edward S. -- Clarkson University
The Development of a Noninvasive Monitoring System for Cigarette Smoking

Schiffer, Wynne K. -- Feinstein Institute for Medical Research
Imaging the Causes and Consequences of Adolescent Inhalant Abuse

Schnoll, Robert A. -- University of Pennsylvania
Efficacy of Varenicline for Smokeless Tobacco Use in India

Schwendt, Marek -- Medical University of South Carolina
Striatal RGS4 Interacts with mGLuR5 Signaling in Relapse to Cocaine-Seeking

Self, David W. -- University of Texas SW Medical Center, Dallas
Role of Endogenous Opiate Systems in Cocaine Relapse After Long-Term Abstinence

Shetty, Vivek -- University of California, Los Angeles
The Oral and Dental Consequences of Methamphetamine Use

Simone, Donald A. -- University of Minnesota, Twin Cities
Cannabinoid Modulation of Hyperalgesia

Stanger, Catherine -- University of Arkansas Medical Sciences, Little Rock
The Neuroeconomics of Behavioral Therapies for Adolescent Substance Abuse

Sternberg, Paul Warren -- California Institute of Technology
Machine Vision Analysis of C. Elegans Phenotypic Patterns

Stout, Robert L. -- Pacific Institute for Research and Evaluation
Longitudinal Study of Mechanisms of Drug Abuse Recovery-Pilot

Strathearn, Lane -- Baylor College of Medicine
Maternal Brain and Behavioral Responses to Infant Cues in Cocaine Exposed Mothers

Stuber, Garret D. -- Ernest Gallo Clinic and Research Center
Optogenetic Control of Excitatory Synapses in the Accumbens During Behavior

Subramanian, Kumara Vadivel -- Northeastern University
Synthesis of Novel 2-Arachidonoylglycerol Analogs

Sumikawa, Katumi -- University of California, Irvine
Mechanisms of Nicotine-Induced Neuroplasticity

Sundquist, Jan O. -- Lund University
Genetics, Family Environment, and Neighborhood: Impact on Mental Disorders

Taylor, Jane R. -- Yale University
Cognitive Dysfunction After Chronic Cocaine

Teplin, Linda A. -- Northwestern University
Drug Abuse, Incarceration and Health Disparities in HIV/AIDS: A Longitudinal Study

Terry, Alvin V. -- Medical College of Georgia (MCG)
Drug Discovery for Cognitive Impairment Associated with Drugs of Abuse

Thornberry, Terence P. -- University of Maryland, College Park Campus
Intergenerational Transmission of Risk for Drug Use

Tiburu, Elvis K. -- Northeastern University
Ligand-Assisted Structural Studies of the Human Cannabinoid Receptor 2, Using NMR

Todorovic, Slobodan M. -- University of Virginia, Charlottesville
Validation of Voltage-Dependent T-Channel Blockers in Treatment of Neuropathic Pain

Unger, Jennifer Beth -- Claremont Graduate University

Drug Use Among Hispanic Emerging Adults

Varga, Eva V. -- University of Arizona
A Novel Pharmacological Target to Prevent Sustained-Morphine-Mediated Pain Sensitivity

Walker, Denise D. -- University of Washington
Reaching and Motivating Change in Teen Marijuana Smokers

Wallis, Jonathan D. -- University of California, Berkeley
Neural Representation of Reward in Frontal Cortex

Weinberger, Andrea Hope -- Yale University
Gender Differences in the Association of Depression to Transitions in Smoking

Weller, Joshua -- Decision Research
Risky Decision Making in Girls with Foster Care Involvement: Prevention Implications

Wickman, Kevin D. -- University of Minnesota, Twin Cities
Trek Channels and Opioid Signaling in the Ventral Tegmental Area

Wilbrecht, Linda E. -- Ernest Gallo Clinic and Research Center
Effects of Adolescent Cocaine on Frontal Spine Turnover, Synapses, and Behavior

Williams, John T. -- Oregon Health and Science University
Cocaine Effects on Neurons

Wiltgen, Brian J. -- University of Virginia, Charlottesville
Motivational Control of Goal-Directed Actions and Habits

Winder, Danny G. -- Vanderbilt University
Noradrenergic Regulation in the BNST

Wood, Evan -- University of British Columbia
Initiation of Injection Drug Use and HIV Risks Among Street-Involved Youth

Xie, Xiang-Qun -- University of Pittsburgh at Pittsburgh
Structure/Function of the CB2 Receptor Binding and G-Protein Recognition Pockets

Yaksh, Tony L. -- University of California, San Diego
The Pharmacology of Spinal Analgesics

Yi, Richard -- University of Arkansas Medical Sciences, Little Rock
Soft Commitment as a Mechanism to Prevent Preference Reversals in Smokers

Young, Michael E. -- Southern Illinois University, Carbondale
Waiting for a Better Future: Deciding When to "Cash in" When Outcomes Are Continuing

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1485 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 1053 applications.

OEA arranged and managed 18 grant review meetings in which 321 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 review meetings.

NIDA has one standing chartered committee, NIDA-K (Training Committee). Applications formerly assigned to NIDA E (Treatment Review Committee), NIDA-F (Health Services Review Committee), and NIDA-L (Medications Development Committee) are now reviewed in CSR.

OEA staff managed 17 Special Emphasis Panels to review grant applications for a variety of reasons:

- Conflicts with the chartered committee
- Center Grant Applications
- Program Project Grant Applications (P01)
- Behavioral Science Track Award for Rapid Transition (B/START)
- Imaging Science Track Award for Research Transition (I/START)
- Conference Grants (R13)
- Cutting-Edge Basic Research Awards (CEBRA)
- Diversity-promoting Institutions Drug Abuse Research Program (DIDARP-R24)
- Loan Repayment Applications
- Requests for Applications (RFAs)

OEA managed the following RFA reviews:

- DA10-001/002 - Substance Use and Abuse among U.S. Military Personnel, Veterans and their Families (R01 & R21)
- DA10-005 - Targeted Library Synthesis and Screening at Novel Targets for Potential Drug Addiction Treatments and Research Tools (R21/R33)
- DA10-008 - International Research Collaborations on HIV/AIDS and Drug Use (R01)
- DA10-009 - The National Drug Abuse Treatment Clinical Trials Network

(U10)

- DA10-010/011 - Exploring Epigenomic Processes and Non-Coding RNAs in HIV/AIDS (R01 & R21)

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

R&D and non-R&D Contract Reviews

- NO1DA-10-2221 - Clinical Coordinating Support for NIDA Center for Clinical Trials Network (CCTN)

Phase II SBIR Contract Reviews

- N44DA-10-5556 - Rapid Assessment for Drug Abuse and Risky Sex
- N44DA-10- 5555 - Rapid Assessment Tools of Sexual and Drug Use Risk Behaviors
- N44DA-10- 4411 - Web-Enabled Cognitive/Neuropsychological Evaluation System
- N44DA-10-1138 - Development of Science Education Materials or Programs
- N44DA-10-5544 - Virtual Reality Simulations to Train Caregivers/Providers
- N44DA-10-5541 - Instrument Development

Certificates of Confidentiality

Between January 5, 2010 and April 2, 2010, OEA processed 75 Certificate of Confidentiality applications, including 12 amendments for either extension of expiration date or protocol change.

CTN-Related Review Activities

The CTN Protocol Review Board met on January 26, 2010 to review the study proposal CTN 0047, Screening, Motivational Assessment, Referral and Treatment in Emergency Departments (SMART-ED).

The Protocol Review Board met on January 29, 2010 to review the study proposal CTN 0048, Cocaine Use Reduction with Buprenorphine (CURB).

The Data and Safety Monitoring Board met March 22, 2010 to discuss the final study report for CTN 0030, Prescription Opioid Addiction Treatment Study (POATS).

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: Enhancing Peer Review: New Application Forms and Instructions; Demonstration of Secondary PO and Conflict Of Interest functionality in NEPS, by James Wilson (IRMB) and Meena Hiremath (OEA); and a presentation on the Freedom of Information Act, by Susan Cornell, NIH FOIA Officer.

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Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Congressional Affairs (Prepared April 21, 2010)

Appropriations

The President's Fiscal Year 2011 budget request includes $32.1 billion for NIH, a $1 billion (3.2%) increase over FY 2010. For NIDA, the request includes $1.094 billion, $34.6 million (3.3%) over the FY 2010 level.

Legislation of Particular Interest

Health Reform - On March 22, the President signed H.R. 3590, the Patient Protection and Affordable Care Act, becoming P.L. 111-148. Summaries of the new law are widely available. Summaries of provisions of particular interest to NIH should be publically available soon. Of particular interest to the substance abuse and addiction field, go to http://lac.org/index.php/lac/383 for information from the Legal Action Center.

SBIR/STTR - H.R. 2965, the Enhancing Small Business Research and Innovation Act of 2009, as passed by the House, would loosen the requirements for venture capital-backed small businesses to receive funding from the SBIR and STTR programs without set-aside increases, as does the Senate reauthorization bill, S. 1233.

H.R. 2965 would also: provide special consideration for small business projects that include energy-related research, rare disease-related research, transportation and infrastructure research and research related to nanotechnology; reauthorize the SBIR/STTR programs only through fiscal 2011; and increase small business award levels (raise to $250,000 from $100,000 for participation in the Phase I level; and raise to $2 million from $750,000 for participation in Phase II)

S. 1233 also includes some change in the venture capital provisions. It would also increase the SBIR set-aside from 2.5 percent to 3.5 percent over the period of FY 2011-2020, and double the STTR from 0.3 percent to 0.6 percent from FY 2011 to FY 2015. Award levels would also rise, from $100,000 to $150,000 for Phase I awards and $750,000 to $1 million for Phase II awards - and the language also would limit awards from exceeding 50 percent above the recommended award levels.

The current, short-term extension of the program's authorization is scheduled to expire on April 30, 2010. We continue to await Congressional action to extend the date further, and to pass a longer term reauthorization bill.

Bills of Interest

[For the full text and additional information about any bill, go to the Library of

Congress website at http://thomas.loc.gov].

H.R. 18 - On January 6, Representative Roscoe Bartlett (R-MD) introduced the "Powder-Crack Cocaine Penalty Equalization Act of 2009," to amend the Controlled Substances Act and the Controlled Substances Import and Export Act with respect to penalties for powder cocaine and crack cocaine offenses. The bill was referred to the Judiciary and Energy and Commerce Committees.

H.R. 179 - On January 6, Representative Jose Serrano (D-NY) introduced the Community AIDS and Hepatitis Prevention Act, to permit the use of federal funds for syringe exchange programs for purposes of reducing the transmission of bloodborne pathogens, including HIV and viral hepatitis. The bill was referred to the House Committee on Energy and Commerce.

H.R. 265 - On January 7, Representative Sheila Jackson-Lee (D-TX) introduced the Drug Sentencing Reform and Cocaine Kingpin Trafficking Act of 2009, to target cocaine kingpins and address sentencing disparity between crack and powder cocaine. The bill was referred to the Judiciary and Energy and Commerce Committees. See S.1789.

H.R. 439 - On January 9, Representative Dennis Rehberg (R-MT) introduced the Family-Based Meth Treatment Access Act of 2009, to amend the Public Health Service Act regarding residential treatment programs for pregnant and parenting women, a program to reduce substance abuse among nonviolent offenders, and for other services. The bill was referred to the Committee on Energy and Commerce.

H.R. 554 - On February 11, the House passed the National Nanotechnology Initiative Amendments (NNI) of 2009. The measure was introduced by Representative Bart Gordon (D-TN) on January 15. In general, H.R. 554 would require all agencies participating in the NNI to support the setting of standards for nanotechnology. The bill was sent to the Senate where it is pending before the Committee on Commerce, Science, and Transportation.

H.R. 756 - On March 30, the House passed the National Pain Care Policy Act. Relevant to NIH, the bill would (1) encourage the NIH Director, through the NIH Pain Consortium, to continue and expand an aggressive pain research program, (2) require the NIH Pain Consortium to submit annual recommendations on pain research initiatives that could be paid for by the Common Fund, and (3) require the HHS Secretary to establish an Interagency Pain Research Coordinating Committee, which would include NIH membership. The bill is pending in the Senate as S. 660. (Note: many aspects of this bill were included in the new health reform law.)

H.R. 758 - On January 28, Representative Diana DeGette (D-CO) introduced the Pediatric Research Consortia Establishment Act to amend Title IV of the PHS Act to provide for the establishment of pediatric research consortia. The bill was referred to the House Committee on Energy and Commerce. See S.353

H.R. 836 - On February 3, Representative Earl Pomeroy (D-ND) introduced the Brewers Excise and Economic Relief (BEER) Act, which if enacted would effectively return the federal beer excise tax to its pre-1991 levels. In the House the bill has 242 cosponsors. The bill was referred to the Committee on Ways and Means. See S. 1058

H.R. 872 - On February 4, Representative Diana DeGette (D-CO) introduced the Stem Cell Research Improvement Act of 2009. The bill would require the Secretary to conduct and support research that uses human embryonic stem cells, regardless of the date on which such cells were derived. The bill outlines certain ethical criteria, and would require that the Secretary, in consultation with the Director of NIH, issue guidelines to carry out the provisions of the legislation within 90 days of enactment. H.R. 872 also provides that the Secretary may issue guidelines on research involving other human stem cells,

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as determined to be scientifically warranted by the Director of NIH. The bill was referred to the House Committee on Energy and Commerce.

H.R. 873 - On February 4, Representative Diana DeGette (D-CO) introduced H.R. 873, the Stem Cell Research Enhancement Act of 2009. Like H.R. 872, the bill would require the Secretary to conduct and support research that uses human embryonic stem cells. The bill sets out certain ethical criteria, and would require that the Secretary, in consultation with the Director of NIH, issue final guidelines to carry out the provisions of the legislation within 60 days of enactment. H.R. 873 was referred to the House Committee on Energy and Commerce. See S. 487

H.R. 877 - On February 4, Representative Randy Forbes (R-VA) introduced H.R. 877, the Patients First Act of 2009. The bill would require the Secretary of HHS to conduct and support research using stem cells, including pluripotent stem cells that "have the flexibility of embryonic stem cells (whether or not such pluripotent stem cells have an embryonic source)." The Secretary, after consultation with Director of NIH, would be required to issue guidelines within 90 days that would prioritize research that has the "potential for near term clinical benefit in human patients." The bill also would add "stem cells" to the list of issues for which a summary of research activities is required as part of the NIH biennial report. H.R. 877 was referred to the House Committee on Energy and Commerce.

H.R. 1011 - February 12, Representative Gene Green (D-TX) introduced the Community Mental Health Services Improvement Act, to amend the Public Health Service Act with respect to mental health services. The bill was referred to the Energy and Commerce Committee. See S. 1188

H.R. 1028 - On February 12, Representative Lucille Roybal-Allard (D-CA) introduced the Support 21 Act of 2009, to provide additional support for the efforts of community coalitions, health care providers, parents and others to prevent and reduce underage drinking, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

H.R. 1429 - On March 17, the House passed the Stop AIDS in Prison Act of 2009, to provide for an effective HIV/AIDS program in Federal prisons. The bill was transmitted to the Senate, where it is pending in the Committee on the Judiciary.

H.R. 1459 - On March 12, Representative Bobby Scott (D-VA) introduced the Fairness in Cocaine Sentencing Act of 2009, to amend the Controlled Substance Act and the Controlled Substances Import and Export Act regarding penalties for cocaine offenses. The bill was reported from the Judiciary Committee and is pending in the Energy and Commerce Committee. See H.R. 3245

H.R. 1483 - On March 12, Representative Patrick Kennedy (D-RI) introduced the National Neurotechnology Initiative Act, to direct the Secretary of HHS to implement a National Neurotechnology Initiative, and for other purposes. The bill was referred to the Committee on Energy and Commerce. See S. 586

H.R. 1715 - On March 25, Representative Diana DeGette (D-CO) introduced H.R. 1715, the Protection for Participants in Research Act of 2009. The bill includes several modifications to the current system for protections of human research participants. H.R. 1715 was referred to the House Committee on Energy and Commerce.

H.R. 2134 - On April 28, Representative Eliot Engel (D-NY) introduced the Western Hemisphere Drug Policy Commission Act of 2009, to establish the Western Hemisphere Drug Policy Commission. The bill was passed on December 8, and is currently pending in the Senate. It has been referred to the Senate Committee on Foreign Relations.

H.R. 2138 - On April 28, Representative Patrick Kennedy (D-RI) introduced the Services, Education and Rehabilitation for Veterans (SERV) Act, to provide grants to establish veterans treatment courts. The bill was referred to the Committee on the Judiciary. See S. 902

H.R. 2354 - On May 12, Representative Janice Schakowsky (D-IL) introduced the Health Promotion Funding Integrated Research, Synthesis, and Training Act or the Health Promotion FIRST Act. Provisions relevant to NIH would require the Director of NIH, acting through OBSSR, to develop a plan on how best to develop the science of health promotion at the agency. The plan must provide for the allocation of resources for the research. The bill would also require the Director of NIH, acting through OBSSR, to conduct or support early research programs and research training regarding health promotion. The bill was referred to the House Committee on Energy and Commerce. See S. 1001

H.R. 2369 - On May 12, Representative Patrick Kennedy (D-RI) introduced the Improving the Quality of Mental and Substance Use Health Care Act of 2009, to improve mental and substance use health care. The bill was referred to the Energy and Commerce Committee.

H.R. 2502 - On May 19, Representative Kurt Schrader (D-OR) introduced the Comparative Effectiveness Research (CER) Act of 2009. The bill would establish a nonprofit corporation called the Health Care Comparative Effectiveness Research Institute to contract with appropriate Federal agencies or the private sector to conduct comparative effectiveness research. The Institute would be responsible for (1) establishing and carrying out a research project agenda [in carrying out a research agenda, Institute is authorized to enter into contracts with Federal government agencies with experience in conducting CER], (2) establishing a methodology committee to develop scientifically-based methodological standards for comparative clinical effectiveness research [would be required to consult or contract with IOM, AHRQ, NIH (can contract with one or more) in developing and updating standards], and (3) ensuring that there is a process for peer-review of the research [Institute would be authorized to use existing peer-review processes used by entities with which the Institute contracts]. Provisions would also establish a Board of Governors comprising 21 members, including the Secretary of HHS, the Director of AHRQ and the Director of NIH, to oversee the Institute's activities. The legislation would create the Comparative Effectiveness Research Trust Fund in the U.S. Treasury. The Trust Fund would be financed through fees on Medicare and private health insurance plans, in addition to transferring CER funds in ARRA (P.L. 111-5) not already obligated or expended. Funding for the Institute would sunset after 10 years. H.R. 2502 was jointly referred to the House Committees on Energy and Commerce and Ways and Means. (Note: many of these provisions were adopted as part of the new health reform law.)

H.R. 2835 - On June 11, Representative Barney Frank (D-MA) introduced the Medical Marijuana Patient Protection Act, to provide for the medical use of marijuana in accordance with the laws of the various States. The bill was referred to the Energy and Commerce Committee.

H.R. 2818 - On June 11, Representative Jerry McNerney (D-CA) introduced the Methamphetamine Education, Treatment, and Hope Act of 2009, to amend the Public Health Service Act to provide for the establishment of a drug-free workplace information clearinghouse, to support residential methamphetamine treatment programs for pregnant and parenting women, to improve the prevention and treatment of methamphetamine addiction, and for other purposes. The bill was referred to the Energy and Commerce Committee.

H.R. 2855 - On June 12, 2009, Representative Donna Edwards (D-MD) introduced the Drug Overdose Reduction Act, to reduce deaths occurring from drug overdoses. The bill was referred to the Committee on Energy and Commerce.

H.R. 2906 - On June 16, Representative Jim Moran (D-VA) introduced the Comprehensive Problem Gambling Act of 2009, to amend the Public Health Service Act to specifically include problem and pathological gambling in programs of the Substance Abuse and Mental Health Services Administration and to establish a national program to address the harmful consequences of problem gambling. The bill includes a new advisory commission that would coordinate research by several agencies, including NIH. The bill was referred to the Energy and Commerce Committee.

H.R. 2943 - On June 18, Representative Barney Frank (D-MA) introduced the Personal Use of Marijuana by Responsible Adults Act of 2009, to eliminate most federal penalties for possession of marijuana for personal use, and for other purposes. The bill was referred to the Judiciary and Energy and Commerce Committees.

H.R. 3001 - On June 23, Representative Tammy Baldwin (D-WI) introduced the Ending LGBT Health Disparities Act. H.R. 3001 would require the collection of sexual and gender minority data from each health related program operated by or that receives funding from the Department of Health and Human Services. The bill also would require the Secretary, acting through the Secretary of LGBT Health (a position that would be established by the bill), and the Directors of the Agency for Health Quality and Research and the NIH, to develop plans to expand existing research into health disparities to include those experienced by sexual and gender minority populations. H.R. 3001 was referred to the House Committees on Energy and Commerce, Armed Services, Judiciary, Ways and Means, Oversight and Government Reform, House Administration, Veterans' Affairs, Transportation and Infrastructure, Intelligence and Foreign Affairs.

H.R. 3002 - On June 23, Representative John Boehner (R-OH) introduced the Preserving Access to Targeted, Individualized, and Effective new Treatments and Services (PATIENTS) Act of 2009. The bill would prohibit the Secretary of HHS from using data obtained from comparative effectiveness research (CER), including CER research funded by P.L. 111-5, the American Recovery and Reinvestment Act (ARRA), to deny coverage under a Federal health care program. The Secretary would also be tasked with ensuring that CER conducted or supported by the Federal Government accounts for factors contributing to differences in the treatment response and treatment preferences of patients, including patient-reported outcomes, genomics and personalized medicine, the unique needs of health disparity populations, and indirect patient benefits. The bill was jointly referred to the House Committees on Energy and Commerce and Ways and Means. See S. 1259

H.R. 3065 - On June 26, Representative Jan Schakowsky introduced the Mental Illness Chronic Care Improvement Act of 2009, to establish a chronic care improvement demonstration program for Medicaid beneficiaries with severe mental illnesses, including co-occurring substance use disorders. The bill was referred to the Energy and Commerce Committee. See S.1136

H.R. 3075 - On June 26, Representative John Lewis (D-GA) introduced the National Parents Corps Act of 2009, to establish a National Parents Corps Program, and for other purposes. The bill was referred to the Education and Labor Committee.

H.R. 3245 - On July 16, Representative Bobby Scott (D-VA) introduced the Fairness in Cocaine Sentencing Act of 2009, to amend the Controlled Substances Act and the Controlled Substances Import and Export Act regarding penalties for cocaine offences. This bill would effectively equalize federal cocaine sentencing for crack vs. powdered cocaine. The bill was reported out by the Judiciary Committee and is pending in the Energy and Commerce Committee. See H.R. 1459

H.R. 3400 - On July 30, Representative Tom Price (R-GA) introduced the Empowering Patients First Act. Section 801 would (1) prohibit the Secretary of HHS from using data obtained from CER, including research conducted or supported using funds appropriated under ARRA, to deny coverage of an item or service under a Federal health care program; (2) require the Secretary to ensure that CER conducted or supported by the Federal Government accounts for factors contributing to differences in the treatment response and treatment preferences of patients, including patient-reported outcomes, genomics and personalized medicine, the unique needs of health disparity populations, and indirect patient benefits; and (3) prohibit the Federal Coordinating Council for Comparative Effectiveness Research findings from being released in final form until after consultation with and approval by relevant physician specialty organizations. H.R. 3400 was jointly referred to the House Committees on Energy and Commerce; Ways and Means; Education and Labor; Oversight and Government Reform; Judiciary; Rules; Budget; and Appropriations.

H.R. 3420 - On July 30, Representative Patrick Kennedy (D-RI) introduced the SUPPORT for Substance Use Disorders Act, to improve and enhance substance use disorder programs for members of the armed forces, and for other purposes. The bill was referred to the Armed Services Committee.

H.R. 3475 - On July 31, Representative Randy Forbes (R-VA) introduced H.R. 3475, the Accelerate Cures for Patients Act of 2009. The bill would amend the PHS Act to authorize to be appropriated (in addition to amounts authorized to NIH under Section 402A of the PHS Act) an equal amount for medical research that has the greatest potential for near-term clinical benefit in human patients. H.R. 3475 was referred to the House Committee on Energy and Commerce.

H.R. 3939 - On October 27, 2009, Representative Sam Farr (D-CA) introduced the Truth in Trials Act, to amend Title 18 of the United States Code to provide an affirmative defense for the medical use of marijuana in accordance with the laws of the various states. The bill was referred to the Committee on the Judiciary.

H.R. 4055 - On November 6, 2009, Representative Adam Schiff (D-CA) introduced the Honest Opportunity Probation with Enforcement (HOPE) Initiative Act of 2009, to authorize a national HOPE program to reduce drug use, crime, and costs of incarceration. The bill was referred to the House Judiciary Committee.

H.R. 4748 - On March 3, 2010, Representative Bill Owens (D-NY) introduced the Northern Border Counternarcotics Strategy Act of 2010, to amend the Office of National Drug Control Policy Reauthorization Act of 2006 to require a northern border counternarcotics strategy, and for other purposes. The bill was referred to the House Judiciary and Homeland Security Committees.

S. 77 - On January 6, Senator John Kerry (D-MA) introduced the Children's Mental Health Parity Act, to amend Title XXI of the Social Security Act to provide for equal coverage of mental health services under the State Children's Health Insurance Program. The bill was referred to the Committee on Finance.

S. 114 - On January 6, Senator Daniel Inouye (D-HI) introduced the National Center for Social Work Research Act, to amend the Public Health Service Act to provide for the establishment of a National Center for Social Work Research within the National Institutes of Health. The bill was referred to the Committee on Health, Education, Labor, and Pensions.

S. 132 - On January 6, Senator Diane Feinstein (D-CA) introduced the Gang Abatement and Prevention Act of 2009, to increase and enhance law enforcement resources committed to investigation and prosecution of violent gangs, to deter and punish violent gang crime, to protect law-abiding citizens and communities from violent criminals, to revise and enhance criminal

penalties for violent crimes, to expand and improve gang prevention programs, and for other purposes. Section 313 of the bill establishes a National Youth Anti-Heroin Media Campaign at the Office of National Drug Control Policy. The bill was referred to the Committee on the Judiciary.

S. 177 - On January 8, Senator Russ Feingold (D-WI) introduced S. 177, the Strengthening Our Economy Through Small Business Innovation Act of 2009. The measure would extend the SBIR program through 2022 and the STTR program through 2023. Additionally, S. 177 would increase SBIR set-aside allocations to 5 percent by 2010, 7.5 percent by 2011, and 10 percent by 2012. The set-aside levels for the STTR program would also double by 2010, and then increase to 0.8 percent by 2011 and to 1.0 percent by 2012. The measure also proposes to increase the SBIR and STTR award levels for phase 1 and 2 grants to $300,000 and $2.2 million, respectively. Finally, the bill would give greater priority consideration to research areas, including those related to energy, security, transportation, and water. S. 177 currently has no co-sponsors and was referred to the Senate Committee on Small Business and Entrepreneurship.

S. 353 - On January 29, Senator Sherrod Brown (D-OH) introduced the Pediatric Research Consortia Establishment Act to amend Title IV of the PHS Act to provide for the establishment of pediatric research consortia. The bill was referred to the House Committee on Energy and Commerce. See H.R. 758

S. 459 - On February 24, Senator Claire McCaskill (D-MO) introduced the SUPPORT for Substance Use Disorders Act, to improve and enhance substance use disorder programs for members of the armed forces, and for other purposes. The bill was referred to the Committee on Armed Services.

S. 487 - On February 26, Senator Tom Harkin (D-IA) introduced the Stem Cell Research Enhancement Act of 2009, which was referred to the Committee on Health, Education, Labor and Pensions. See H.R. 873

S. 586 - On March 12, Senator Patty Murray (D-WA) introduced the National Neurotechnology Initiative Act, to direct the Secretary of HHS to implement a National Neurotechnology Initiative, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions. See H.R. 1483

S. 660 - On March 19, Senator Orrin Hatch (R-UT), introduced S. 660, the National Pain Care Policy Act. The NIH provisions in S. 660 are identical to H.R. 756, described above. S. 660 was referred to the Senate Committee on Health, Education, Labor and Pensions.

S. 714 - On March 26, Senator James Webb (D-VA) introduced the National Criminal Justice Commission Act of 2009, a bill to establish the National Criminal Justice Commission. On January 21, 2010, the bill was amended and reported favorably from the Committee on the Judiciary. It is pending on the calendar.

S. 754 - On March 31, Senator Jay Rockefeller (D-WV) introduced the Methadone Treatment and Protection Act of 2009, to provide for increased federal oversight of methadone treatment. The bill was referred to the Committee on Health, Education, Labor and Pensions.

S. 902 - On April 27, Senator John Kerry (D-MA) introduced the Services, Education and Rehabilitation for Veterans (SERV) Act, to provide grants to establish veterans treatment courts. The bill was referred to the Committee on the Judiciary. See H.R. 2138

S. 914 - On April 28, Senator Arlen Specter (D-PA) introduced S. 914, the Cures Acceleration Network and National Institutes of Health Reauthorization Act of 2009. This legislation would (1) establish the Cures Acceleration

Network, an independent agency that would make awards to accelerate the development of cures and treatment of diseases, (2) elevate NCMHD to institute status, (3) increase NIH's authorization of appropriations section to $40 billion for FY 2010 and such sums as may be necessary for each of the FYs 2011 to 2012, and (4) require the Director of NIH to develop and enforce conflict of interest policies. S. 914 was referred to the Senate Committee on Health, Education, Labor and Pensions (HELP). (NOTE: many provisions of this bill were included in the new health reform law.)

S. 1001 - On May 7, Senator Richard Lugar (R-IN) introduced the Health Promotion Funding Integrated Research, Synthesis, and Training Act or the Health Promotion FIRST Act. Provisions relevant to NIH would require the Director of NIH, acting through OBSSR, to develop a plan on how to best develop the science of health promotion at the agency. The plan must provide for the allocation of resources for the research. The bill would also require the Director of NIH, acting through OBSSR, to conduct or support early research programs and research training regarding health promotion. The bill was referred to the Senate HELP Committee.

S. 1058 - On May 14, Senator Mark Udall (D-CO) introduced the Brewers Excise and Economic Relief (BEER) Act of 2009, to amend the Internal Revenue Code of 1986 to reduce the tax on beer to its pre-1991 level, and for other purposes. The bill was referred to the Committee on Finance. See H.R. 836

S. 1136 - On May 21, Senator Debbie Stabenow (D-MI) introduced the Mental Illness Chronic Care Improvement Act of 2009, to establish a chronic care improvement demonstration program for Medicaid beneficiaries with severe mental illnesses, including co-occurring substance use disorders. The bill was referred to the Committee on Finance. See H.R. 3065.

S. 1188 - On June 4, Senator Jack Reed (D-RI) introduced the Community Mental Health Services Improvement Act, to amend the Public Health Service Act with respect to mental health services. The bill was referred to the Committee on Health, Education, Labor and Pensions. See H.R. 1011

S. 1259 - On June 15, Senator John Kyl (R-AZ) introduced the Preserving Access to Targeted, Individualized, and Effective new Treatments and Services (PATIENTS) Act of 2009. The bill would prohibit the Secretary of HHS from using data obtained from comparative effectiveness research (CER), including CER research funded by P.L. 111-5, the American Recovery and Reinvestment Act (ARRA), to deny coverage under a Federal health care program. The Secretary would also be tasked with ensuring that CER conducted or supported by the Federal Government accounts for factors contributing to differences in the treatment response and treatment preferences of patients, including patient-reported outcomes, genomics and 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. See H.R. 3002

S. 1373 - On June 25, Senators Joseph Lieberman (I-CT) and John Cornyn (R-TX) introduced the Federal Research Public Access Act (FRPAA), to require every federal department and agency with an annual extramural research budget of $100 million or more to make their research available to the public within six months of publication. Senators Cornyn and Lieberman first introduced this legislation in the 109th Congress. The NIH Public Access Policy was established statutorily with the passage of the Consolidated Appropriations Act of 2008, (P.L. 110-161), and became permanent upon passage of the Fiscal 2009 Omnibus Appropriations (P.L. 111-8). The NIH policy requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central (PMC) upon acceptance for publication, and be accessible to the public on PubMed Central no later than 12 months after publication.

Specifically, the FRPAA would:

- Require every researcher with an annual extramural research budget of $100 million or more, whether funded totally or partially by a government department or agency, to submit an electronic copy of the final manuscript that has been accepted for publication in a peer-reviewed journal.
- Ensure that the manuscript is preserved in a stable digital repository maintained by that agency or in another suitable repository that permits free public access, interoperability, and long-term preservation.
- Require that each taxpayer-funded manuscript be made available to the public online and without cost, no later than six months after the article has been published in a peer-reviewed journal. The bill has been referred to the Senate Committee on Homeland Security and Governmental Affairs.

S. 1789 - On October 15, 2009, Senator Richard Durbin (D-IL) introduced the Fair Sentencing Act of 2009, to restore fairness to Federal cocaine sentencing. The bill passed the Senate as amended on 3/17/2010, and was referred to the House Judiciary and Energy and Commerce Committees. See H.R. 265

S. 3011 - On February 11, 2009, Senator Kirsten Gillibrand (D-NY) introduced S. 3011, the National Black Clergy for the Elimination of HIV/AIDS Act of 2009, to address HIV/AIDS in the African-American community. Research provisions would (1) authorize the Secretary, DHHS, acting through the Director, NIH, to conduct or support culturally competent research to develop evidence-based behavioral strategies to reduce the transmission of HIV/AIDS within this community, and (2) require the Secretary to prioritize research that focuses on populations within the African-American community that are at increased risk for HIV/AIDS. Authorized to be appropriated would be $10 million for Fiscal Year (FY) 2010, and such sums as may be necessary for FYs 2011 through 2014. In addition, the Secretary, acting through the Director, NCMHD, would be authorized to make grants for studies of biological and behavioral factors that lead to increased prevalence and that are conducted by researchers with a history and tradition of service to African-American communities; and behavioral and structural network research and interventions, in collaboration with other NIH institutes and centers, faith- and community-based organizations and others. Authorized to be appropriated would be $100,000,000 for FY 2010, and such sums as may be necessary for FYs 2011 through 2014. S. 3011 was referred to the Senate Committee on Health, Education, Labor and Pensions.

S. 3031 - On February 24, 2010, Senator Leahy (D-VT) introduced the Drug Free Communities Enhancement act of 2010, to authorize Drug Free Communities enhancement grants to address major emerging drug issues or local drug crises. The bill was amended and reported favorably by the Judiciary Committee, and is now pending on the Senate calendar.

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

International Activities

Funding Initiatives

International Training Grant Program Receives U.S. Economic Stimulus Funds

The Fogarty International Center (FIC) will commit up to $2.7 million that it received in U.S. economic stimulus funds in FY 2010 for 6 to10 awards that will provide short-term support to U.S. universities and their partners. The purpose of the awards is to create infrastructure, resources, and opportunities for training postdoctoral investigators to carry out innovative, multidisciplinary team research in global health. The initiative emphasizes problem-solving, collaborative, and hands-on approaches and may require the development of new training models and new partnerships within and beyond the university community. The NIH Resource-Related Research Project (R24) will award up to $250,000 in direct costs for a single academic institution or $400,000 in direct costs for a consortium. Because U.S. economic stimulus funds had been made available for international research projects for the first time and the period for submitting letters of intent was unusually short, NIDA IP personally notified potentially eligible grantees about the opportunity.

Binational Agreement

U.S., Mexico Issue Joint Declaration on Demand Reduction

The United States and Mexico issued a joint declaration of cooperation on drug demand reduction efforts that underscored a commitment to reduce illicit drug consumption and the need to work collaboratively with each other and additional partners in the region. The declaration emphasized the importance of both countries intensifying efforts to prevent and treat substance abuse disorders. The two nations agreed to address six areas of improvement within the next 12 months: developing strong families and communities that resist criminal organizations and promote a culture of lawfulness; providing more and better addiction treatment by integrating it into mainstream medicine; expanding screening, brief intervention, and referral to substance abuse treatment; implementing evidence-based practices; bolstering accreditation and licensing programs; and promoting innovations in criminal justice to reduce recidivism and interrupt the cycle of drug use and crime. Both nations pledged to continue domestic initiatives to reduce the demand for drugs through the United States' National Drug Control Strategy and Mexico's Action Program for Prevention and Treatment of Addictions. The joint declaration, which is available online at http://www.ondcp.gov/international/jointdeclaration.pdf, was issued at the conclusion of the 8th U.S.-Mexico Bi-National Drug Demand Reduction Policy Meeting, which was held at the U.S. Department of State in Washington, D.C., on February 23-25, 2010. NIDA Director Dr. Nora D. Volkow and Dr. Mar'a

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Elena Medina Mora, Mexican National Institute of Psychiatry, spoke about scientific advances in a session entitled "How Science has Revolutionized the Understanding of Drug Addiction" that was moderated by NIDA Deputy Director Dr. Timothy P. Condon. IP Director Dr. Steven W. Gust and Dr. Armando Patr—n, CONADIC, co-chaired a session on "Collaborative Research Activities in Treatment and Prevention" that featured presentations by Dr. Betty Tai, CTN, and Dr. Jacqueline Lloyd, DESPR, as well as several NIDA grantees. NIDA IP supported the travel of Dr. Melanie Domenech Rodr'guez, Utah State University, who spoke about adapting a NIDA-supported prevention intervention and implementing it in Mexico.

NIDA Offers Tuition Waiver to Dutch Addiction Program Summer Institute

NIDA IP will provide one tuition waiver to a U.S. participant, and the Netherlands Organization for Health Research and Development (ZonMw) will provide five tuition waivers for participants from new European Union countries at the Dutch Summer Institute on Alcohol, Drugs and Addiction. The Summer Institute is a joint initiative of ZonMw and the University of Amsterdam Graduate School of Social Sciences, which will host the program from July 4-16, 2010. The intensive, multidisciplinary program offers graduate-level and continuing professional development training in addiction research, while promoting opportunities for international networking. Course credits from the University of Amsterdam and continuing education credits for most disciplines are available.

Research Results

INVEST Fellow Validates Noninvasive Drug-Testing Methods

Dr. Marta Concheiro Guis‡n of Spain successfully used her recent INVEST fellowship to develop and validate two new, noninvasive methods of quantifying the level of licit and illicit drugs in biological samples from opiate-dependent patients. The new methods developed by Dr. Concheiro and her mentor, Dr. Marilyn Huestis, NIDA IRP, allow researchers to quantify quickly and simultaneously 16 drugs and their metabolites in oral fluid or 14 drugs and their metabolites in sweat patches. Dr. Concheiro and colleagues validated the methods using specimens from a group of pregnant women who were receiving buprenorphine therapy for opioid dependence within a joint Johns Hopkins University/NIDA IRP clinical trial comparing methadone versus buprenorphine treatment. Drs. Concheiro, Heustis, and their colleagues published several articles describing their innovation, including articles in Analytical and Bioanalytical Chemistry (2009) 394(2):513-522; Forensic Science International (2009) 188(1-3):144-145; Clinical Chemistry (2009) 55(6):1177-1187; Journal of Analytical Toxicology (2009) 33(5):243-252; and Journal of Chromatography B (2009) 877(27):3065-3071. Dr. Concheiro also presented her research at 2009 meetings of the Society of Forensic Toxicologists, International Association of Therapeutic Drug Monitoring and Clinical Toxicology, College on Problems of Drug Dependence, and NIDA International Forum. Dr. Concheiro, who is planning future collaborations with Dr. Huestis, has returned to research and teaching in the Forensic Toxicology Service at the University of Santiago de Compostela Faculty of Medicine.

NIH-Supported Meetings

Fogarty International Tobacco Research and Capacity Building Network Meeting

The 2010 meeting of the FIC International Tobacco Research and Capacity Building Network brought together FIC and other NIH grantees who conduct international tobacco research and/or research capacity building. Participants met February 23-24, 2010, on the NIH Campus to exchange information, share experiences on project management and research/training collaborations

between domestic and foreign investigators, and foster connections between NIH grantees and other U.S. Government and international tobacco research initiatives and activities. Ms. Dale Weiss, IP, chaired a session that featured presentations by three NIDA grantees: Dr. Eliseo Perez-Stable, University of California San Francisco, Tobacco Control Research and Training in South America; Dr. Wasim Maziak, University of Memphis, Responding To the Changing Tobacco Epidemic in the Eastern Mediterranean Region; Dr. Isabel Scarinci, University of Alabama at Birmingham, Network for Tobacco Control Among Women in Parana, Brazil; and one FIC grantee: Dr. Jonathan M. Samet, Johns Hopkins University, Epidemiology and Intervention Research for Tobacco Control in China. Ms. Weiss also introduced Joe Perpich, M.D., J.D., and Jeff McAllister of JGPerpich, LLC, who presented on the NIDA International Virtual Collaboratory (NIVC), its available tools, Collaboration Matching Service, and various working group activities.

Fellowships

DISCA and USDISCA Awards Support Research Collaborations

Senior drug abuse researchers from Taiwan and the United States have been named Distinguished International Scientists, receiving NIDA I P support to advance their collaborations with colleagues in the United States and Russia, respectively:

- **Hwei-Hsien Chen**, Ph.D., a pharmacologist and toxicologist at Tzu Chi University, Taiwan, will work with Athina Markou, Ph.D., University of California, San Diego, to investigate whether the reward-enhancing effects of the abused inhalant toluene occur in mice. Drs. Chen and Markou also will investigate how glutamatergic pharmacological manipulations that are available to treat humans may affect toluene-induced facilitation of brain reward function, an approach that could suggest eventual pharmacotherapies to prevent toluene abuse. Dr. Chen, who visited Dr. Markou's laboratory in San Diego, will concentrate on mastering the mouse intracranial self-stimulation procedure, which currently is unavailable in Taiwan.
- **Kenneth W. Griffin**, Ph.D., M.P.H., Cornell University, will prepare a grant application with Irina Pervova, Ph.D., St. Petersburg State University, Russia, to propose a systematic program of NIH-funded research projects designed to export and adapt evidence-based U.S. prevention programs for Russian youth. Drs. Griffin and Pervova will propose to examine the etiology of substance abuse and HIV risk behavior among Russian youth, identify a U.S. prevention program for implementation in Russia, and implement and evaluate the adapted program in efficacy and effectiveness trials in St. Petersburg. Their collaboration grew out of a 2006 NIDA-funded conference where Dr. Pervova chaired the local organizing committee and Dr. Griffin helped plan the meeting and participated in it.

WHO/NIDA/CPDD Select International Traveling Fellows

NIDA has joined the World Health Organization (WHO) and the College on Problems of Drug Dependence (CPDD) in selecting two drug abuse scientists from developing countries as recipients of International Traveling Fellowship Awards. The awards will support a 1-week research visit with a NIDA-supported research grantee and participation in the NIDA International Forum and the CPDD Annual Scientific Meeting in June 2010. The two International Traveling Fellows are:

- **Irma Kirtadze**, M.D., Georgia, focuses on HIV prevention among drug users, particularly inhalant users, stimulant injectors, and needle exchange program clients. She currently is leading a country wide HIV/AIDS prevention program among injecting drug users (IDUs) in Georgia. Dr. Kirtadze has had numerous papers published in peer-review journals and

conference proceedings, including proceedings of the last three NIDA International Forums. She has been the recipient of a NIDA grant to study engaging non-treatment seeking drug abusing Georgian men as well as other NIDA travel awards. Dr. Kirtadze will visit Dr. Hendree Jones of Johns Hopkins University (JHU) and Dr. Wendee Wechsberg of RTI International, with whom she will study comprehensive approaches to HIV prevention and treatment with the goal of applying these methods to drug using women in Georgia.

- **Sun Hongqiang**, M.D., M.S., China, has conducted research in the field of alcohol and drug dependence, including a published a study on the efficacy of nicotine sublingual tablets for nicotine dependent patients in China. He currently is exploring the effects of acute tyrosine, tryptophan, and phenylalanine depletion treatment on cue-induced alcohol urging in alcoholics. Under his travel fellowship, Dr. Sun plans to visit Dr. Thomas Kosten's laboratory and clinical programs at Baylor College of Medicine, Veterans Affairs (VA) Medical Center, and MD Anderson Cancer Prevention Center in Houston, Texas. He will work with Drs. Thomas F. Newton and Richard De La Garza at Baylor and the VA Medical Center to learn more about basic research on alcohol dependence and its treatment, especially detoxification and relapse prevention. At MD Anderson under Dr. Paul Cinciripini's tutelage, he will learn about pharmacogenetics within the larger clinical smoking cessation trials being conducted in Houston.

Fellowship Orientation Brings Researchers from 13 Nations to NIDA

HHH Fellows from Virginia Commonwealth University (VCU), JHU, and Emory University joined NIDA INVEST and INVEST/CTN Fellows for an orientation program. Sixteen fellows from 12 nations, along with a Vietnamese graduate student at Emory University, participated in the orientation. NIDA IP Director Dr. Steven W. Gust and Associate Director Dale Weiss hosted the program to introduce the fellows to the Institute's international research priorities, NIDA and NIH resources for fellows, and collaboration and training tools developed by the NIDA IP. Participants also were introduced to a webinar series designed to help international researchers improve their scientific communication skills, the NIVC, and the Humphrey Fellowship Professional Affiliation Directory. Representatives from NIDA divisions and the Substance Abuse and Mental Health Services Administration talked with the fellows about their offices' international research priorities and opportunities for collaborative international research. Fellows visited NIDA's IRP in Baltimore, where they met with key IRP staff and toured various facilities, including a laboratory, clinic, magnetic resonance imaging suite, and nicotine addiction and cognition outpatient testing rooms. Fellows also toured the National Library of Medicine and met with staff at the FIC.

Former NIDA Humphrey Fellow Directs Brazilian Integrated Prevention and Treatment Project

The Brazilian Ministry of Justice and the Brazilian Secretariat for Drug and Alcohol Policies has awarded a large grant to the Center for Drug and Alcohol Research at the Federal University of Rio Grande do Sul, Porto Alegre, Brazil, to integrate drug abuse treatment and prevention programs in 60 counties in the states of Porto Alegre, Rio de Janeiro, Salvador, Vitoria, and Brasilia. Former NIDA HHH Fellow Flavio Pechansky, M.D., Ph.D., M.Sc., Director of the Center for Drug and Alcohol Research, will coordinate the project. Researchers will identify and evaluate public, community, and private programs that already exist in these localities, mapping and georeferencing services to improve referral systems. The project will develop specialty training courses for approximately 6,000 health care and social work professionals in treatment and social rehabilitation of individuals with drug and alcohol abuse problems, particularly juveniles. The project also will educate more than 3,000 law enforcement officers and judiciary professionals about drug and alcohol issues. Researchers will conduct a wide array of studies aimed specifically at crack users and at-risk pregnant women and their newborns.

Former NIDA Humphrey Fellow Receives Alumni Professional Development Grant

The Institute of International Education awarded a Hubert H. Humphrey Alumni Professional Development Grant that enabled former NIDA Humphrey Fellow Dr. Peter Kenneth Ndege, Kenya, to attend the International Harm Reduction Association 21st conference, Harm Reduction 2010, held April 25-29, 2010, in Liverpool, England. Currently a lecturer at Kenya Methodist University, Dr. Ndege was a 2006-2007 HHH fellow at Virginia Commonwealth University. He used the skills and experience gained during his fellowship to form the non-government organization Center for Addiction Studies in Africa, which trained 70 primary healthcare clinicians in the diagnosis and management of drug use disorders. He also established Eastern Medical Consultants Limited, which is committed to providing specialized medical services to rural areas in Kenya at minimal charge. Dr. Ndege currently is working with the United Nations Office on Drugs and Crime on the best way to introduce opiate substitution therapy and other harm reduction measures in Kenya, particularly among vulnerable populations such as IDUs, prisoners, and commercial sex workers. He expects to use the information gained from Harm Reduction 2010 not only to update his knowledge in this field but also to acquire skill and contacts in the area of policy making, so that he can help draft a policy paper on harm reduction in Kenya.

Online Initiatives

Newest Virtual Seminar Lecture Focuses on Neurobiology of Inhalant Misuse

The fourth in a series of Volatile Substance Abuse Virtual Seminars is ready for viewing. Silvia Cruz, Ph.D., a neuroscientist at Cinvestav in Mexico, describes preclinical studies that have identified the effects of inhalants on behavior, the central nervous system, and cellular and molecular functions. She also briefly discusses the epidemiology of inhalant abuse in Mexico and the implications of preclinical research findings for treatment and prevention interventions. The seminars, which are available on the NIDA International Virtual Collaboratory and the NIDA International Program Web site, are being developed by a multinational working group of inhalant abuse researchers funded by the Social Sciences and Humanities Research Council of Canada and supported by NIDA. Dr. Cruz's lecture is available here: http://www.screencast.com/t/MDE4MjQ2YzYt. Two additional lectures, one each from researchers in Canada and the United States, are being prepared.

Travel Support

American Society of Addiction Medicine (ASAM)

NIDA IP provided partial travel support for the following individuals attending a meeting of the ASAM in San Francisco, California, on April 15-18, 2010.

- **Paul Haber**, M.D., Australia, is Medical Director of the Drug Health Service at Sydney South West Area Health Services.
- **Felice Nava**, M.D., Ph.D., Scientific Committee Director for the Italian Society of Addiction Medicine and a consultant physician at the Department of Addiction Medicine, Hospital of Castelfranco Veneto.

ASAM covered the registration and room expenses for Drs. Haber and Nava.

Meeting on Drugged Driving

NIDA IP supported the participation of Dr. Inger Marie Bernhoft, from the Technical University of Denmark, at a one-day workshop on research needs related to drugs and driving, held on March 19, 2010, at the NIH campus. NIDA hosted the meeting to gain expert advice on the current state of the science

and knowledge gaps in the field of drugged driving, which it will use to guide future research efforts. NIDA IP paid the travel expenses of Dr. Bernhoft, who described ongoing research being conducted under the Epidemiology Work Package of the Driving under the Influence of Drugs, Alcohol and Medicines (DRUID) project.

Kasr Al-Ainy Annual International Psychiatry Conference
NIDA IP supported the participation of Dr. Inger Marie Bernhoft, from the Technical University of Denmark, at a one-day workshop on research needs related to drugs and driving, held on March 19, 2010, at the NIH campus. NIDA hosted the meeting to gain expert advice on the current state of the science and knowledge gaps in the field of drugged driving, which it will use to guide future research efforts. NIDA IP paid the travel expenses of Dr. Bernhoft, who described ongoing research being conducted under the Epidemiology Work Package of the Driving under the Influence of Drugs, Alcohol and Medicines (DRUID) project.

Kasr Al-Ainy Annual International Psychiatry Conference
NIDA IP supported the travel of Dr. Robert P. Schwartz of the Friends Research Institute to the Kasr Al-Ainy Annual International Psychiatry Conference, held in Cairo, Egypt, on February 24-25, 2010. Dr. Schwartz spoke on Pharmacotherapy for Opiate Addiction in Prison, during which he presented findings from his recently completed randomized clinical trial of methadone in prison and an early report from an ongoing clinical trial of buprenorphine for opiate-addicted prisoners.

The National Institute on Drug Abuse awarded three CTN INVEST fellowships:

- Suzanne Nielsen, Australia / Mentor Walter Ling, UCLA
- Meera Vaswani, India / Mentor Wade Berrettini, Univ of Pennsylvania
- Felipe Vallejo Reyes, Chile / Mentor Eugene Somoza, Univ of Cincinnati

Current CTN INVEST fellows presented reports to the CTN on January 29, 2010:

- Dr. Mario Zapata, CES University, Medellin, Colombia (sponsor: Michael Robbins, University of Miami) presented a progress report on his fellowship.
- Leonardo Estacio Jr., Philippines (Mentor: Dr. Dennis Donovan, University of Washington, Seattle, WA) presented his goals for the fellowship.

Other International Activities

Two visitors from Kazakhstan visited NIDA on February 18, 2010. Mr. Madiyar Kozhakhmet, Deputy Director, Youth Department, Ministry of Education and Science and Ms. Zhanar Rakysbayeva, Chief Inspector in Special Affairs, Prevention Service Department, Ministry of Interior Arrairs were on a tour sponsored by the Department of State's International Visitor Leadership Program. Meeting with the visitors from NIDA were Dale Weiss, IP and Drs. Aria Crump, Rich Jenkins and Tom Brady, DESPR.

Dr. Ivan Montoya, DPMCDA and Cora Lee Wetherington, DBNBR participated in the 3rd International Conference of Women Mental Health in Medellin, Colombia on March 2-6, 2010.

Dr. Cora Lee Wetherington, DBNBR, gave two invited talks, "Gender Differences in Tobacco Addiction" and "Gender Aspects in Research on Drug Abuse" at the International Women's Medicine and Mental Health International Congress, Medelin, Colombia, March 2-7, 2010.

Dr. Wilson M. Compton, Director, DESPR, participated in the Binational US-Mexico Meeting on Demand Reduction, Washington, DC, February 23-25, 2010.

Dr. Wilson M. Compton chaired two panels and presented on "Setting the Stage for Prevention: Epidemiology of Illicit Drug Abuse" and "Understanding Addiction as a Brain Disease: Implications for the Drug-Crime Nexus", Abu Dhabi, United Arab Emirates, February 7-8, 2010.

Drs. Wilson Compton and Eve Reider of DESPR and Mr. Kevin Haggerty of the University of Washington presented at a meeting on January 8, 2010 on "Evidence Based Prevention" that was held by the Emirate of Abu Dhabi National Rehabilitation Centre at the Emirates Palace Hotel, in Abu Dhabi, United Arab Emirates. The objectives of the meeting were: 1) to understand the drug disease burden and need for monitoring in developing addiction response; 2) to advocate policy makers on the importance of developing prevention programs integral to drug response; 3) to understand prevention principles and educate on Ôgood practices' in prevention, and 4) to mobilize decision makers and opinion leaders toward endorsing evidence based prevention programs. Dr. Compton presented on "Setting the Stage for Prevention: The Burden of Drug Abuse and Drug Abuse Surveillance and Monitoring, Dr. Reider presented on "Fundamentals of Drug Abuse Prevention: A Research Based Guide," and Mr. Haggerty presented on "Implementing School Based and Family Based Prevention."

Jan R. Anderson, Member of the Swedish Parliament, met with the Prevention Research Branch at NIDA on February 2, 2010, to discuss drug abuse prevention research.

Dr. Farida Allaghi, Executive Director of Mentor Arabia, and Trustee of the Mentor Foundation, visited with the Prevention Research Branch at NIDA on October 27, 2009. Mentor Arabia is a regional non-governmental organization which advocates for drug prevention and implements awareness-raising and training programs among Arab youth. The Mentor Foundation is an international non-government not for profit organization with a focus on the prevention of drug misuse and the promotion of health and well-being of young people. Mentor seeks to identify, support and share information on effective practice that will protect young people from the harm that drugs can cause.

Dr. Peter Hartsock participated in the Center for Strategic and International Studies (CSIS) consultation on "Global Health in the 21st Century: Identifying the Big Priorities," October 14, 2009, Washington, D.C. Dr. Hartsock covered the use of applied epidemiology and advanced modeling to more accurately determine coming public health needs.

Dr. Peter Hartsock participated in the Council on Foreign Relations' Global Health Program's consultation meeting, "AID for AIDS: Considering the Future of PEPFAR, December 3, 2009, Washington, D.C.

Dr. Peter Hartsock participated in the Center for Strategic and International Studies (CSIS) consultation meeting on "The Future of Global HIV Treatment and Prevention," December 14, 2009, Washington, D.C.

Dr. Peter Hartsock participated with Dr. Volkow and OAR/NIH in a teleconference with the Medical Research Council of South Africa on surging methamphetamine use in that country, December 15, 2009, Bethesda, MD.

Dr. Peter Hartsock participated in a meeting of representatives of the Russian government and NIAID concerning HIV vaccine development and drug users, January 8, 2010, Bethesda, MD.

Dr. Peter Hartsock participated in the Center for Strategic and International Studies (CSIS) consultation meeting on "Opportunities for Improving U.S.-Cuba Engagement in Health Policy," January 22, 2010, Washington, D.C.

Dr. Peter Hartsock served in the Center for Strategic and International Studies' (CSIS) Working Group on Health, Demography, and the HIV Epidemic, and in

the group on Borders, Biases, and Bio-Threats: Public Health Concerns and International Migration in the Russian Federation, February 16, 2010, Washington, D.C.

Dr. Roy Wise, IRP, presented a seminar entitled "Some anatomical substrates of reward prediction and relapse to addiction" at the Neurobiological Studies and Perspectives on Drug Addictions Symposium, April 15-18, 2010, Mexico City, Mexico.

Dr. Jonathan Katz, IRP, presented an invited seminar entitled "Atypical Dopamine Transport Inhibitors: Mechanisms Underlying Their Potential As Treatments For Cocaine Abuse." The talk was sponsored by the Centre for Advanced Research on Logic and Sensibility at Keio University, Mita Campus, Tokyo, March 14, 2010.

Dr. Jonathan Katz presented an invited seminar entitled "Behavior Analysis in the Age of Cognitive Neuroscience." The talk was invited by the Department of Psychology, Teikyo University, Tokyo, Japan, March 13, 2010.

Dr. Jonathan Katz was invited to participate in a symposium held at the 83rd Annual Meeting of the Japanese Pharmacological Society, March 16, 2010, Osaka, Japan. The symposium was chaired by Drs. Kohji Takada and Shigeru Watanebe and was entitled: "Cognitive Safety: A New Approach to Drug Safety."

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Meetings/Conferences

NIDA convened the 8th Blending Conference on April 22-23, 2010, in Albuquerque, New Mexico in partnership with the University of New Mexico, the University of Arizona, and the University of California, San Francisco. The Conference, titled: **Blending Addiction Science and Practice: Evidence-Based Treatment and Prevention in Diverse Populations and Settings**, provided an opportunity for over 1,300 clinicians and researchers to collectively learn about innovative, science-based approaches that have been proven to be effective in the prevention and treatment of drug abuse and addiction. This two-day event has evolved into NIDA's signature conference and is designed to narrow the "translational gap" by disseminating science-based findings to treatment providers. The Blending Conference Planning Committee included NIDA's Deputy Director, Dr. Timothy P. Condon, who oversaw all conference planning activities, Drs. Cindy Miner (OSPC), Denise Pintello (OD), Carol Cushing and Harold Perl (CCTN), as well as Dr. Susan Storti and Roxanne Kibben, who worked closely with the two CTN Node PIs co-hosting the Blending Conference: Drs. James Sorenson (California-Arizona Node) and Michael Bogenschutz (Southwest Node).

The National CTN Steering Committee Meetings were held April 19-21, 2010 in conjunction with the NIDA Blending Conference in Albuquerque, New Mexico.

- CTP and PI Caucuses
- Invest Fellow Meeting
- Executive Committee
- Research Utilization Committee
- Research Development Committee
- Node Coordinator Workgroup
- Steering Committee
- CTN 10th Anniversary Symposium
- Psychology Special Interest Group
- Pharmacotherapy Special Interest Group
- CTN 0015 Women's Treatment for Trauma and SUD
- CTN 0037 STRIDE Study Team
- CTN 0046 S-CAST Study Team
- CTN 0047 SMART ED Study Team

On April 21, 2010, the CTN convened a **Celebration and Symposium in Honor of the 10th Anniversary of the National Drug Abuse Treatment Clinical Trials Network**. This celebrated 10 years of research and clinical

trials in the CTN and focused both on past findings and potential future directions. The symposium included 3 panels on pharmacological research findings, psychosocial research findings, and the implications on clinical practice and policy yielded by the dissemination and implementation of CTN research findings. Six additional speakers addressed topics such as: the past, present, and future of the CTN following the original 1998 IOM report on "Bridging the Gap;" HIV/AIDS research; community expectations of CTN research; impact of psychological research; international collaborations; and smoking cessation research. The symposium concluded with closing remarks by Dr. Nora Volkow.

On January 13th and 14th, 2010 NIDA held a meeting entitled **Exploring Interconnections: A Network Dynamics Workshop for Understanding and Preventing Adolescent and Young Adult Substance Abuse** at Natcher Conference Center, Balcony B, and NIH Main Campus. The National Institutes on Drug Abuse (Co-chairs: Drs. Bethany Deeds, Elizabeth Ginexi and Thomas Brady) collaborated with the NIH's Office of Behavioral and Social Sciences Research (OBSSR), the Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD) and the National Institute of Alcohol Abuse and Alcoholism (NIAAA) to develop and implement this successful workshop. The workshop's objectives were to describe state-of-the-art methodological advances in the field of social network research; identify and discuss obstacles and opportunities for stimulating and integrating scientific advancements in social network analysis for epidemiology, prevention, and services research in adolescents and young adult substance use; and discuss strategies for promoting the translation of social network research findings to improve prevention and treatment of substance use among adolescents and young adults, including the support of ongoing recovery.

On March 19, 2010 Drs. Jeff Schulden and Aria Crump of DESPR chaired a meeting entitled **Drugged Driving: Future Research Directions** to develop a research agenda for future efforts to reduce injuries and deaths related to drug impaired driving. This meeting involved private sector and federal participants including representatives from the National Highway Traffic Safety Administration, the Office of National Drug Control Policy, and the National Institute on Alcohol Abuse and Alcoholism.

Dr. Jonathan D. Pollock, DBNBR, organized and chaired the **Consortium on the Genetic Analysis of Smoking Phenotypes (CGASP) meeting**, held February 23, 2010 at the Inner Harbor Sheraton Hotel, Baltimore, MD. The Consortium on the Genetic Analysis of Smoking Phenotypes (CGASP) was established in June 2010 to conduct meta-analysis of the genetics of smoking phenotypes and to integrate primary genetic and phenotypic data on smoking phenotypes. The CGASP consortium has four analytic groups. These are analysis of ch15q125 for smoking phenotypes; a group for analyzing smoking initiation; a group for smoking cessation, and a group for biomarkers. Groups of investigators from more than 37 institutions participate in CGASP. As a result of this effort a manuscript describing a meta-analysis of smoking phenotypes associated with chr15q25 is in preparation.

On February 22-23, 2010, the Special Populations Office hosted a two-day **Research Development Seminar Series workshop** in Bethesda, Maryland. Chaired by Flair Lindsey, Program Analyst, the workshop was geared to trainee investigators interested in becoming funded through NIDA and the NIH. During the two-day session, trainee investigators met with funded NIDA investigators and senior NIDA program officials, received feedback on research concept papers and learned about the NIH grants submission and review processes.

On April 12-13, 2010, the Special Populations Office, in conjunction with the Association of Black Psychologists (ABPsi), hosted a two-day **Research Development Seminar Series workshop** in Bethesda, Maryland. Chaired by Flair Lindsey, Program Analyst, the workshop was attended by 15 trainee

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investigators interested in becoming funded through NIDA and the NIH. The workshop provided participants with an opportunity to meet with NIDA funded investigators and senior NIDA program officials, receive feedback on research concept papers, learn of NIDA/NIH program interests and priority areas and learn about the NIH grants submission and review processes.

CCTN staff organized a NIDA Science Meeting titled **Clinically Meaningful Substance Abuse Treatment Outcome Measures for Effectiveness Trials**. It was held on December 15-16, 2009, in Bethesda, MD, and was sponsored by NIDA's Office of Science Policy and Communications.

Dr. Timothy P. Condon, Deputy Director, NIDA, delivered the keynote presentation, "Addiction Fact & Fiction" and served as a panelist at the Writer's Guild of America West Panel on Addiction in Los Angeles, California on January 14, 2010.

Dr. Timothy P. Condon chaired the Blending Planning Meeting at the Hyatt Regency in Albuquerque, New Mexico on January 22, 2010.

Dr. Timothy P. Condon chaired the NIDA Meeting on Funding Scientists/Organizations that accept Tobacco Monies in Bethesda, Maryland on January 26, 2010.

Dr. Timothy P. Condon presented opening welcome remarks at the NIDA POP Workgroup cross-agency Workshop on Pain Measurement, Pain Measurement Scales: Current Issues and Future Direction in Bethesda, Maryland on January 27, 2010.

Dr. Timothy P. Condon participated as a panelist for the CADCA Federal Town Hall on Substance Use Disorders: Health and Healthcare Reform and co-chaired a workshop on "How to Implement Evidence-Based Prevention Programs that Work: Proven Examples to Use in Your Communities" in National Harbor, Maryland on February 9, 2010.

Dr. Timothy P. Condon co-chaired the Blending Team Meeting: MIEDAR 2.0 in Rockville, Maryland on February 23, 2010.

Dr. Timothy P. Condon moderated a panel discussing The Science of Addiction: How Science has Revolutionized the Understanding of Drug Addiction" at the US-Mexico Bi-National Drug Demand Reduction Policy Meeting at the U.S. State Department in Washington, D.C. on February 23, 2010.

Dr. Timothy P. Condon was an expert panelist at the Multijurisdictional Counterdrug Task Force Training broadcast taping in Saint Petersburg, Florida on February 26, 2010.

Dr. Timothy P. Condon spoke at the National Inhalant Prevention Coalition at the National Press Club in Washington, D.C. on March 11, 2010.

Dr. Timothy P. Condon presented a "National Institute on Drug Abuse: Institute Update" at the Washington Circle Expert Panel Meeting: Performance Measurement for Substance Use Disorders: A Research Agenda Meeting in Washington, DC on March 18, 2010.

Dr. Timothy P. Condon participated on a plenary panel at the TERROS 6th Annual Cesar Chavez Behavioral Health Conference "Overcoming Barriers of Health Disparities: Diversity, Civility, and Acceptance in Behavioral Health" at Arizona State University in Glendale, Arizona on March 26, 2010.

Dr. Timothy P. Condon presented and served as a panel chair for the "Dissemination/ Implementation & Policy/Practice Implications Panel" during the Celebration and Symposium in Honor of the 10th Anniversary of the National Drug Abuse Treatment Clinical Trials Network in Albuquerque, New

Mexico on April 19, 2010.

Dr. Timothy P. Condon provided welcoming remarks at the NIDA Blending Conference in Albuquerque, New Mexico on April 22, 2010.

Dr. Cindy Miner, Deputy Director, OSPC, was the ÔScientist On-Site' at the DEA Museum's traveling exhibit Target America: Opening Eyes to the Damage Drugs Cause on March 2-3, 2010 in New Orleans, LA.

Dr. Susan Weiss, Chief, Science Policy Branch, OSPC gave a presentation as part of the DEA Museum Lecture Series on: The Science of Marijuana: What We Know and What We Don't on April 27, 2010.

Dr. Susan Weiss spoke at the IBRO Women in World Neuroscience Event at the Cosmos Club, Washington DC. The topic of her lecture was the Role of Stress in Drug Addiction on March 23, 2010.

Dr. Ruben Baler, Science Policy Branch, OSPC, lectured on "The Neuroscience of Addiction" in the Drug Awareness course at the George Washington School of Public Health on February 2, 2010.

Dr. Lula Beatty, Ph.D., Director, SPO, attended a meeting of the Office of Minority Health's (OMH) Federal Interagency Management Team on January 29, 2010 in Bethesda, Maryland.

Dr. Lula Beatty participated in the sixth annual National African American Drug Policy Coalition (NAADPC) Summit on March 24-26, 2010 in Silver Spring, Maryland.

Dr. Lula Beatty participated on an expert panel at SAMHSA on Treatment Improvement Protocols (TIPS) on March 3, 2010 in Rockville, Maryland.

Dr. Lula Beatty served as a moderator at meeting on African American Marriage and Health, which was sponsored by the Administration for Children and Families (ACF), DHHS, on March 4, 2010 at the Humphrey Building in Washington, D.C.

Dr. Lula Beatty served as Faculty at the Leadership Institute for Women in Psychology (LIWP) meeting on March 18, 2010 in Washington, D.C.

Dr. Lula Beatty attended a meeting of APA's Committee on Women and Psychology on March 19, 2010 in Washington, D.C.

Dr. Lula Beatty attended a meeting on NIH's Clinical Research Education and Career Development (CRECD) program, along with PIs and Program Officials, on April 5, 2010 in Bethesda, Maryland.

Dr. Lula Beatty was a keynote speaker at a conference on addiction at North Carolina A&T State University in Greensboro, North Carolina on April 16, 2010. Her keynote address was centered on Health Disparities and Culturally Based Treatment.

Ana Anders, M.S.W., Public Health Analyst, SPO, participated in the National Hispanic Science Network (NHSN) steering committee meeting on February 15-16, 2010 in Los Angeles, California.

Ana Anders participated in the National Hispanic Medical Association (NHMA) annual conference on March 26-27, 2010 in Washington, D.C.

Dr. Cora Lee Wetherington, DBNBR and Coordinator, Women and Sex/Gender Differences Research Program was an invited session co-chair (with Dace Svikis, VCU) of the paper session, "Sex and Tobacco Use," at the annual meeting of the Society for Research on Nicotine and Tobacco, February 24-27, 2010, Baltimore, MD.

Dr. Samia Noursi, DBNBR and Deputy Coordinator, Women and Sex/Gender Differences Research Program chaired three panel presentations as the National Summit on Interpersonal Violence and Abuse across the Lifespan: Forging A Shared Agenda, February 24-26, 2010, Dallas, TX. The first was a plenary presentation entitled "Intersecting Problems of HIV, Partner Abuse, and Trauma Among Drug-involved Women: Implications for Prevention and Treatment," by Dr. Nabila El- Bassel, Columbia University. The second panel entitled "Violence, Abuse, and Trauma: Are they Risk Factors for Drug Abuse" with the following speakers: Carolyn Smith Cynthia Larkby, and Laura Proctor. The third panel entitled "Gender Issues in Intimate Partner Violence," with Denise Hines, Maureen McHugh and Kenneth Leonard.

Dr. Da-Yu Wu, DBNBR, organized a web-based workshop on rat genetics and rat genomics research for drug addiction held on February 25. The meeting was co-chaired by Drs. Da-Yu Wu, Minda Lynch and Jonathan Pollock, with leading scientists invited nationally and internationally in the areas of behavioral genetics and rat and human genetic and genomics, and was attended by NIH staff from several institutes including NCI, NCRR and NIDA.

Dr. Cora Lee Wetherington represented NIDA at the IOM Neuroscience Forum's Workshop on Sex Differences and Implications for Translational Neuroscience Research in San Francisco, CA, March 8-9, 2010.

Dr. Roger Sorensen, DBNBR, participated in the Interagency Epilepsy Working Group (IEWG) meeting, hosted by the National Institute of Neurological Disorders and Stroke (NINDS) with representation from various federal and epilepsy affiliate agencies held on 23 March in Bethesda, MD.

Dr. Cora Lee Wetherington gave an invited Psychiatry Grand Rounds presentation, "Gender Differences in Drug Abuse," at the University of Miami Miller School of Medicine, March 26, 2010.

Dr. David Shurtleff, Director, DBNBR, gave an invited presentation "Overview of NIDA and NIH Research Funding Opportunities" at the 16th Annual Meeting of the Society on Neuroimmune Pharmacology, held on April 14-18 in Manhattan Beach, CA.

Dr. Yu (Woody) Lin, DCNBR, was invited by the Board of Directors to attend the 26th annual conference of the American Academy of Pain Medicine (AAPM) as a representative of the NIH Pain Consortium. The conference was held on February 4-6, 2010 in San Antonio, TX. Dr. Lin and Dr. David Thomas of DBNBR were introduced to AAPM Board of Directors, presented "an introduction to the NIH" at the AAPM research committee pre-meeting and served at the NIH booth.

Dr. Yu (Woody) Lin organized a seminar presented by Dr. Ajay Wasan of Brigham and Women's Hospital and Harvard Medical School entitled, The Impact of Negative Affect on Chronic Pain Treatment Outcomes, Including Prescription Opioid Misuse, sponsored by the Division of Clinical Neuroscience and Behavior Research held on January 26 at the NIH Neuroscience Building.

Dr. Yu (Woody) Lin participated in the organization of the 2010 Pain Consortium Symposium on "Moving Towards Personalized Pain Management" held on the NIH campus on May 5, 2010.

Dr. Steven Grant, DCNBR, presented a talk on "Translation of Addiction Neuroscience" as part of the 2010 University of Utah Brain Institute March Symposium series. The symposium was held at the University of Utah in Salt Lake City on March 19, 2010.

Dr. Steven Grant represented NIDA at the Dept. of Energy Radiochemistry and Radionuclide Imaging Instrumentation Program Contractor-Grantee Workshop that was held in Rockville, MD on January 5-6, 2010.

Dr. Steven Grant represented NIDA at a conference on Science-Policy-Practice in Addiction: Implications of Policy Work in Early Brain Development & Children's Mental Health for Addiction Research & Policy sponsored by the Norlien Foundation that was held on March 2, 2010 in Washington, DC.

Dr. Wilson M. Compton, Director, DESPR, served as Co-Chair for the Surveillance Subcommittee of the Department of Health and Human Services Tobacco Strategic Planning Workgroup, December, 2009 through March 2010 and ongoing.

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 "Understanding Addiction as a Brain Disease: Implications for Recovery" at the Mississippi Society of Addiction Medicine, Jackson, Mississippi, January 15, 2010.

Dr. Wilson M. Compton participates in the ONDCP Inter-agency Workgroup for Demand Reduction; meetings have been held on an ongoing basis since March 2009.

Dr. Wilson M. Compton served as discussant and participant in the NIDA-sponsored meeting "Exploring Interconnections: A Network Dynamics Workshop for Understanding and Preventing Adolescent and Young Adult Substance Abuse", Bethesda, Maryland, January 13-14, 2010.

Dr. Wilson M. Compton presented on "Understanding Addiction as a Brain Disease: Implications for the Drug-Crime Nexus" at the New York Society of Psychiatry and the Law, New York, New York, January 23, 2010.

Drs. Elizabeth Robertson, Augie Diana and Jacqueline Lloyd of the Prevention Research Branch, DESPR, were on the planning committee for and attended the Phase II SPF SIG Cross-Site Evaluation Kick-Off Meeting on January 7, 2010 at the Westat Conference Center in Rockville, MD.

Drs. Elizabeth Robertson and Aleta Meyer, DESPR, attended a working meeting of the Society for Prevention Research, Type 2 Translational Research Task Force held at The Dupont Hotel in Washington, DC on February 18 -19, 2010.

Dr. Eve Reider, DESPR, represented NIDA as a member of the program planning committee for the 2nd Annual Trauma Spectrum Disorders Conference: A Scientific Conference on the Impact of Military Service on Families and Caregivers. This meeting was held December 10-11, 2009, Natcher Auditorium, NIH, Bethesda, MD.

Dr. Aleta Meyer chaired a session titled "Challenges with Adaptation and Fidelity when Translating Evidence-Based Practices" at the 10th Annual Scientific Meeting of the American Academy of Health Behavior on February 10, 2010, in Clearwater Beach, FL. The title of Dr. Meyer's talk was "Thinking about Adoption, Implementation, and Sustainability on the Front-end of Drug Abuse Prevention Research." Her co-presenter was Dr. Karen BlasŽ of the University of North Carolina-Chapel Hill.

Dr. Belinda Sims, in the Prevention Research Branch, DESPR, co-chaired a session with Dr. Timothy Condon, Deputy Director, NIDA titled "How to Implement Evidence-Based Prevention Programs That Work: Proven Examples to Use in Your Communities" at the 2010 CADCA National Leadership Forum, in National Harbor, MD, on February 9, 2010 Workshop speakers included Dr. Sheppard Kellam, American Institutes for Research, "Improving Behavior in 1st and 2nd Grade Classrooms: One of a Set of Prevention Strategies Over the Life Course"; Dr. Richard Spoth, Iowa State University, "PROSPER'S Formula for Achieving Positive Community-Level Outcomes"; and Dr. David Hawkins, University of Washington, "Coalitions Using The Communities That Care System

to Prevent Drug Misuse and Crime Community-Wide."

Drs. Jacqueline Lloyd, Belinda Sims, and Aria Crump served as mentors for the NIDA Special Populations Office Research Development Seminar Series held in Bethesda on February 22 and 23, 2010. At this meeting, Dr. Crump also presented to the group on research priorities in DESPR.

On March 13, 2010 Dr. Aria Crump chaired two sessions for the Biennial Meeting of the Society for Research on Adolescence held in Philadelphia. The first session was entitled "Prevention of Drug Use and Problem Behavior in Adolescence: Considering the Cultural Context" and the second was entitled "Drug Use during the Transition to Adulthood: Predictors and Prevention in College Students."

Dr. Augusto Diana organized a symposium as part of the CSAP-NIDA Innovations in Prevention Symposium Series in Rockville, MD, February 4, 2010. The speaker was Dr. William Crano, who discussed his NIDA-funded research on the role of persuasion in preventing adolescent drug use.

Drs. Joe Frascella and Laurence Stanford represented NIDA at a conference on Science-Policy-Practice in Addiction: Implications of Policy Work in Early Brain Development & Children's Mental Health for Addiction Research & Policy sponsored by the Norlien Foundation that was held on March 2, 2010 in Washington, DC.

On March 5th 2010, Dr. Lisa Onken gave a presentation to the NIH Behavioral and Social Science Coordinating Committee entitled, "Behavioral Intervention Development: A Bidirectional + Translational Research Process to Develop Potent Interventions where Efficacy = Effectiveness."

Dr. Lisa Onken gave a plenary presentation, Behavioral Treatment Development: Efficacy, Effectiveness, and Community-Friendliness, at the International Conference on the Treatment of Addictive Behaviors in Santa Fe, New Mexico on February 10, 2010. The theme of the international conference was "Evidence-Based Treatment in Real World Systems: Maximizing Service, Value, and Outcome."

Dr. Lisa Onken led a "Roundtable" discussion on Everything You Want to Know about Behavior Therapy Development Grants at the International Conference on the Treatment of Addictive Behaviors in Santa Fe, New Mexico on February 10, 2010.

Dr. Shoshana Kahana and other members of the Behavioral and Integrative Treatment Branch, with Jacques Normand and Lynda Erinoff of NIDA's Office of AIDS Research, organized a 1.5 day meeting (March 4-5, 2010) on the Intersection of Technology, HAART Adherence, and Drug Abuse Treatment whose purpose was to encourage multidisciplinary collaboration between social scientists, medical researchers (doctors and nurses), and technology experts to develop and refine mobile technological instrumentation, e-health technology, and software as interventions to foster adherence to HIV treatment regimens and access to care among substance-abusing populations.

Drs. Jessica Chambers, Cecelia Spitznas, Lisa Onken, and Vince Smeriglio, all of DCNBR, held a NIDA-sponsored meeting on Digital Media & Communication Technologies in Adolescent Drug Abuse Treatment on April 26-27, 2010 in Rockville, MD. A major purpose was to encourage and facilitate research on the integration of digital media and communication technologies into adolescent drug abuse treatment.

Dr. Karen Sirocco, DCNBR, presented a grant-writing workshop at the International Neuropsychological Society, February 5, 2010 in Acapulco, Mexico.

Dr. Nicolette Borek and Dr. Cheryl Anne Boyce, DCNBR, participated in scientific sessions, workshops and technical assistance office hours at the Society for Research on Adolescence Biennial Meeting, March 11-12, 2010 in Philadelphia, PA, along with fellow colleagues Dr. Belinda Sims, Dr. LeShawndra Price, Dr. Aleta Meyer, and Dr. Jacqueline Lloyd, DESPR.

Dr. Ivan Montoya, DPMCDA, gave a lecture on March 26th at the Howard University's Annual Spring Institute (Washington DC) on the topic of Prevalence, Pharmacotherapies and Future Research on Marijuana Addiction.

Dr. Ivan Montoya presented a Webcast to the Department of Psychiatry of the University of Massachusetts entitled "Trends in Pharmacotherapy Research for Drug Addiction".

Dr. Jag Khalsa, DPMCDA, chaired a symposium on: Clinical Implications of Research on Genetics of Drug Addiction at the Annual Meeting of ASAM, April 14-18, 2010. Dr. Khalsa also co-chaired two additional symposia: "The Multiple Seen and Unseen Implications of the Criminal Justice System for Addiction Services" with Dr. Richard Denisco of DESPR, and "Alternatives to Conventional Treatment: A Joint Session with the International Society of Addiction Medicine" with Dr. Marc Galanter of ASAM.

Dr. Teri Levitin, Director, OEA, helped plan and participated in a workshop on grant writing for early career investigators that was held at the Society for Research on Adolescence meeting in Philadelphia in early March. Representatives from several ICs and NSF were on the panel.

Dr. Scott Chen, OEA, presented "Overview of the NIH Peer Review Process and Electronic Submission", NIDA Special Populations Research Development Seminar Series workshop with the Association of Black Psychologists at the Bethesda Doubletree Hotel, Bethesda, Maryland, April 13, 2010.

Dr. Gerald McLaughlin, OEA, presented an education and professional development session entitled "What's New at NIH? An Update on NIH Grants and Contracts Submission Processes." to the National Contract Management Association (NCMA) Bethesda Chapter on February 17, 2010.

Dr. Kristen Huntley, OEA, presented "NIH Training Grants and the Review Process" and co-chaired a workshop titled "Writing a Competitive Training Grant" at the Society for Research on Nicotine and Tobacco, 16th Annual Meeting, Baltimore, MD, February 26, 2010.

Dr. Gerald McLaughlin served as Judge for the Georgetown University School of Medicine graduate schoolÔs 24th annual Student Research Days Competition, March 16, 2010.

On February 9, 2010, Dr. Harold Perl, CCTN, co-chaired a symposium entitled, "Maximizing the Impact of Evidence-Based Treatment through Mutually Beneficial Collaborative Research with AI/AN Communities," and he presented a talk entitled, "Developing the NIDA CTN MOD Projects" at the Twelfth International Conference on Treating Addictive Behaviors in Santa Fe, NM.

Dr. Betty Tai, Director, CCTN, participated in the US-Mexico Bi-National Drug Demand Reduction Policy Meeting at the George Marshall Conference Center, U.S. Department of State February 23-25, 2010 in Washington, DC. She was the U.S. facilitator for one of the breakout sessions: Panel A - Collaborative Research Activities in Treatment and Prevention. Dr. José Szapocznik, Principal Investigator of the Florida Node, was the U.S. speaker for this session.

Dr. Amy Newman, IRP, was invited to participate in a panel entitled "Dopamine Signaling and Disease: Wormholes, Flytraps, Organic Farmers and Mouseketeers in the Pursuit of New Medications" at the 43rd Winter Conference on Brain Research, Breckinridge, CO, in January.

Dr. Amy Newman chaired the Plenary Symposium entitled "Dopamine D3 Receptors and Addiction" and gave the first talk entitled "Evolution of D3 Antagonists" at the Behavior, Biology and Chemistry: Translational Research in Addiction meeting, San Antonio, TX, in March 2010.

Several IRP scientists were members of a workshop at the 2010 Motivational Neuronal Network Conference, April 24-27, 2010, North Carolina. Dr. Roy Wise was a member of a workshop entitled "Extending the circuit, part 1: reemerging regions of the so-called, limbic system: the bed n. of the stria terminalis, extended amygdala, and the hypothalamus" and Dr. Thomas Jhou was a member of a workshop entitled "Extending the circuit, part 2: the emerging caudal areas, the lateral habenula, the PPTG, LDTG, and RMTG network in disappointment and pleasure".

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Media and Education Activities

NIDANews on Twitter

The Press Team designed and launched a NIDA Twitter page, "NIDANews." NIDA will "tweet" about press releases, NewsScans, research findings, conferences, ongoing programs and other news items. To view the page and become a "follower" of NIDANews, go to www.twitter.com/NIDAnews.

Multijurisdictional Counterdrug Task Force Training

Dr. Timothy Condon was a panelist in a webcast titled "This is Your Brain on Drugs," produced by the Multijurisdictional Counterdrug Task Force Training (MCTFT). The webcast was taped February 26, 2010, and other panelists included Dr. Amelia Arria, NIDA grantee and Director of the Center on Young Adult Health and Development at the University of Maryland School of Public Health; and Senta Goudy, Chief of Prevention in the Florida Office of Drug Control in Tallahassee, Florida.

National Inhalant Prevention Coalition

Dr. Timothy P. Condon was a panelist at the National Inhalant Prevention Coalition press conference March 11th in Washington, DC. PILB's press team issued a note to reporters announcing Dr. Condon's participation in the event and provided on-site assistance.

Upcoming Events

OSPC/PILB began planning media and outreach activities for NIDA participation in several upcoming meetings, including the **NIDA Blending Conference** April 22-23 in Albuquerque, NM; the **American Psychiatric Association Meeting** May 22-26 in New Orleans, LA; and the **International AIDS Conference** July 18-23 in Vienna, Austria.

NIDA will once again co-sponsor an addiction science award at the **Intel International Science and Engineering Fair (Intel ISEF)** to be held May 9-14 in San Jose, CA. Intel ISEF is the world's largest international pre-college science competition for students in grades 9-12. Over 1,500 high school students from over 50 countries, regions, and territories showcase their independent research at the annual event. Members of OSPC and NIDA grantees serve as judges for the addiction science award, and Friends of NIDA provide funding for the awards.

Media planning and partnership collaboration is also underway for **National Drug Facts Week (NDFW)** to be held November 8-14, 2010. The event is an

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extension of NIDA's annual Drug Facts Chat Day, which began in 2008 and during which thousands of teens ask questions about drugs via a Web chat. Each year, NIDA gets many more questions than can be answered in a day. In response to this demonstrated interest by teens to get the scientific facts about drugs, NIDA developed NDFW -- asking teens, schools and community groups all over America to hold their own "Q and A" events, with local experts. Throughout the week, teens will participate in a variety of NDFW activities such as hosting movie nights and book club meetings, contacting their members of congress, holding school assemblies and sponsoring music and art contests. NIDA will hold its annual Drug Facts Chat Day on November 9th. A NDFW event page on Facebook, a registration page on NIDA's website, a toolkit and a logo are in development by PILB.

Press Releases & Notes to Reporters

January 7, 2010 - **NIDA Researchers Discover A New Mechanism Underlying Cocaine Addiction.** Researchers have identified a key epigenetic mechanism in the brain that helps explain cocaine's addictiveness. The study, published in the January issue of the journal Science, shows how cocaine affects an epigenetic process (a process capable of influencing gene expression without changing a gene's sequence) called histone methylation. These epigenetic changes in the brain's pleasure circuits, which are also the first impacted by chronic cocaine exposure, likely contribute to an acquired preference for cocaine.

January 13, 2010 - **NIDA Researchers Honored With Presidential Early Career Award.** Two NIDA-funded researchers have been awarded the White House Office of National Science and Technology Council's Presidential Award for Early Career Scientists and Engineers (PECASE). NIDA grantees Dr. Bruce J. Hinds, III and Dr. Gonzalo E. Torres received their awards during a ceremony at the Commerce Building in Washington, DC.

January 19, 2010 - **Leading Medication Development Researcher Phil Skolnick joins NIDA to lead Drug Discovery Efforts.** NIDA announced that Phil Skolnick, Ph.D., D.Sc. (hon.), a leader in the worlds of corporate and academic drug research, has been appointed Director of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMCDA).

March 15, 2010 - **Impulsive-Antisocial Personality Traits Linked to a Hypersensitive Brain Reward System.** Normal individuals who scored high on a measure of impulsive/antisocial traits display a hypersensitive brain reward system, according to a brain imaging study by researchers at Vanderbilt University. The findings provide the first evidence of differences in the brain's reward system that may underlie vulnerability to what's typically referred to as psychopathy. The NIDA-funded study was published in the journal *Nature Neuroscience*.

March 28, 2010 - **Common Mechanisms of Drug Abuse and Obesity.** Some of the same brain mechanisms that fuel drug addiction in humans accompany the emergence of compulsive eating behaviors and the development of obesity in animals, according to research funded by NIDA. When investigators gave rats access to varying levels of high-fat foods, they found unrestricted availability alone can trigger addiction-like responses in the brain, leading to compulsive eating behaviors and the onset of obesity. The study, conducted by researchers at the Scripps Research Institute, was released May 28th in the online version of *Nature Neuroscience* and will also appear in the journal's May 2010 print issue.

Notes to Reporters:

January 14, 2010 - A note was sent to reporters about the publication of the NIDA-funded study *"Impact of the Positive Action program on school-level*

indicators of academic achievement, absenteeism, and disciplinary outcomes: A matched-pair cluster randomized, controlled trial" by Snyder, et al. and published in the *Journal of Research on Educational Effectiveness*.

January 14, 2010 - A note alerted media that NIDA's Virtual Town Hall on Prevention is now available online at https://archives.drugabuse.gov/newsroom/09/townhall.html. The Town Hall, conducted live in September 2009, featured the Communities that Care prevention system.

January 19, 2010 - A note to reporters was sent out about the publication of the NIDA-funded study *"Overdose and Prescribed Opioids: Associations between Prescribed Opioids and Overdose in Patients with Chronic Pain: A Cohort Study"* by Dunn, et al. and published in *Annals of Internal Medicine*.

February 1, 2010 - Reporters were notified about the publication of the NIDA-funded study entitled *"Efficacy of Extended-Duration Transdermal Nicotine Therapy: A Randomized Trial."* The study was conducted by researchers at Penn Medicine, an academic medical center that includes the University of Pennsylvania School of Medicine and the University of Pennsylvania Health System; and published in the *Annals of Internal Medicine*.

February 22, 2010 - A note to reporters alerted the media to the publication of the NIDA-funded study entitled *"Toward discovery science of human brain function."* The research was conducted by investigators at the NYU Langone Medical Center and published in the *Proceedings of the National Academy of Sciences*.

March 1, 2010 - Reporters were alerted to the publication of the NIDA-funded study entitled "The relationship between methamphetamine use and increased dental disease." The article was published in *The Journal of the American Dental Association*, and suggests that dentists should consider severe oral health problems in otherwise young, healthy people as a possible sign of drug addiction.

March 8, 2010 - A note to reporters alerted the media to a NIDA-funded study published in *Nature Neuroscience*, entitled "Methylphenidate facilitates learning-induced amygdala plasticity," by Tye, et al. Methylphenidate (Ritalin or Concerta) has been used for decades to treat ADHD, yet little is known about the precise mechanisms by which it exerts its therapeutic effects. This study uses an animal model to study the mechanisms underlying methylphenidate's effects on learning.

March 8, 2010 - A note to reporters announced that NIDA Deputy Director Timothy Condon would be speaking at a press conference sponsored by the National Inhalant Prevention Coalition (NIPC). The annual press event highlights the risks of inhalant abuse among young people. The event, with support from the Substance Abuse and Mental Health Services Administration (SAMHSA), took place at the National Press Club in Washington, D.C. on March 11th.

Research News

Full NewsScans can be seen at http://www.nida.nih.gov/NIDANews.html#newsscan. Please note the colorful re-design of NIDA's NewsScan, which launched with issue #65.

January 28, 2010 - **NIDA NewsScan #65** - Research News

- Database Created to Supplement Commercial Microarray Coverage of Addiction-Related Genes
- Two Thirds of Injection Drug Users in Tijuana, Mexico Have a Latent

Tuberculosis Infection

- Many School Districts Have Punitive Responses to Positive Results from Random Drug Testing
- Highly Selective Compounds Developed to Target the Brain's Dopamine D3 Receptor
- Increasing Glutamate Transmission Eliminates Cocaine-Induced Place Preference in Rats
- Men with Anabolic-Androgenic Steroid Dependence also Have High Lifetime Prevalence of Opioid Dependence
- Benzotropine Analogs Reduce Cocaine Self-Administration in Rats
- Drug Combinations Contribute to HIV Risk in Gay and Bisexual Men

Highlights of Interviews & Articles of Interest

January 5, 2010 - *Cable News Network (CNN)* — Dr. Nora Volkow was interviewed on-camera about prescription drug abuse and overdose.

January 5, 2010 - *Associated Press (AP)* — Dr. Steven Grant was interviewed about NIDA's khat research.

January 6, 2010 - *Time.com* — Dr. Volkow was interviewed about the effect of cocaine on genes in the brain (regarding a NIDA-funded study published in Science).

January 7, 2010 - *Reuters* — Dr. Volkow was interviewed about the effect of cocaine on genes in the brain (regarding a NIDA-funded study published in Science).

January 13, 2010 - *Teen Vogue* — Dr. Volkow was interviewed about teens and marijuana use.

January 14, 2010 - *Time* — Dr. Volkow was interviewed about levamisole.

January 19, 2010 - *MSNBC* — Dr. Susan Weiss and Jennifer Elcano, of OSPC's Science Policy Branch, were interviewed about prescription drug abuse among women.

February 5, 2010 - *Time.com* — Dr. Volkow was interviewed about opioid abuse.

February 11, 2010 - *Associated Press (AP)* — Dr. Marilyn Huestis was interviewed about fake marijuana substances.

February 15, 2010 - *Reuters London* — Dr. Volkow was interviewed about treatment for addiction.

February 17, 2010 - *Associated Press (AP)* — Dr. Volkow was interviewed about the proposed changes to the DSM-V pertaining to substance abuse and addiction.

February 22, 2010 - *BBC Radio* — Dr. Volkow was interviewed about obesity research.

March 3, 2010 - *Newsweek* — Dr. Volkow was interviewed about the effectiveness of psychosocial therapies for drug abuse compared to pharmacological or immune-based therapies (i.e. vaccines).

March 8, 2010 - *National Public Radio (NPR)* — Dr. Ivan Montoya was interviewed on the Kojo Nnamdi Show about the nicotine vaccine.

March 16, 2010 - *New York Times* — Dr. Wilson Compton was interviewed on how cocaine and marijuana can impact behavior.

March 23, 2010 - *Journal of the American Medical Association (JAMA)* — Dr. Volkow was interviewed about NIDA's comorbidity research.

March 26, 2010 - *Associated Press (AP)* — Dr. Steven Grant was interviewed about the drug mephedrone or "meow meow."

Steven Grant of CNB, DCNBR was interviewed on February 16, 2010 by a reporter for Wired magazine on the topic of brain changes after treatment for substance abuse.

Steven Grant was interviewed on April 1, 2010 by National Public Radio to provide background for a potential story on Mephedrone, an emerging drug of abuse.

Dr. Ivan Montoya, DPMCDA, was interviewed by The Patient Channel on the treatment of nicotine dependence.

Other Educational Activities

On March 11, 2010, Dr. Jay Sanders presented, "Information Technology and the Transformation of Healthcare Delivery: Where We Are and Where We Need to Be." Dr. Sanders is President and CEO of The Global Telemedicine Group, Adjunct Professor of Medicine at Johns Hopkins University School of Medicine and a founding board member and President Emeritus of the American Telemedicine Association. He discussed issues related to "off-the-shelf" eHealth technology that can fundamentally change how healthcare is provided.

On February 25, 2010, Dr. Paul Kessler, provided a presentation on Nicotine Vaccine for Smoking Cessation: Update on NicVAX¨ Development. Dr. Paul Kessler, Senior Vice President, Clinical, Medical and Regulatory Affairs, reviewed preclinical and clinical data for Nabi's Biopharmaceuticals' nicotine conjugate vaccine, NicVAX¨, which is currently undergoing phase III testing for smoking cessation.

On January 14, 2010, Dr. James McKay, presented "Continuing Care for Substance Use Disorders: Old Challenges and New Ideas." Dr. McKay, Professor of Psychology in Psychiatry at the University of Pennsylvania, reviewed findings from continuing care studies, and identified factors associated with positive treatment results. The limitations of the research literature were discussed as well as newer research on disease management approaches that address these limitations. Additionally, trends toward wider use of measurement-based care, adaptive treatment models, and pharmacotherapy in the long-term management of addictive disorders were discussed.

Dr. Mary Kautz, DCNBR, along with other NIDA colleagues, participated in Brain Awareness Week activities held at the National Museum of Health and Medicine, Walter Reed Army Medical Center, on March 17 & 18, 2010. Five institutes from NIH hosted interactive sessions focusing on brain health and neuroscience for Washington, DC area students, grades five through twelve.

Recent and Upcoming Conferences/Exhibits

American Society Addiction Medicine (ASAM) 41st Annual Meeting and Medical-Scientific Conference
April 15-18, 2010 -- San Francisco, CA

National Institute on Drug Abuse Blending Research and Practice Meeting (NIDA)
April 22-23, 2010 -- Albuquerque, NM

American College of Obstetricians and Gynecologists Annual Clinical Meeting (ACOG)
May 15-19, 2010 -- San Francisco, CA

American Psychiatric Association Annual Meeting (APA)
May 22-26, 2010 -- New Orleans, LA

American Academy of Physician Assistants Conference (AAPA)
May 29-June 3, 2010 -- Atlanta, GA

American College Health Association Annual Meeting (ACHA)
June 1-5, 2010 -- Philadelphia, PA

National Association of Drug Court Professionals (NADCP) Annual Training Conference
June 2-5, 2010 -- Boston, MA

National Alliance on Mental Illness (NAMI) Annual Convention
June 30-July 3, 2010 -- Washington, DC

American Psychological Association (APsychA) Annual Convention
August 12-15, 2010 -- San Diego, CA

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Planned Meetings

The National Institute on Drug Abuse (NIDA) is collaborating with the **American Psychiatric Association (APA) to hold a major research based track titled, Neurobiological Circuits of Addiction: Significance for Psychiatric Practice at the APA Annual Meeting in New Orleans, LA, May 22-26, 2010**. NIDA is sponsoring a number of symposia on topics unique to addiction science. This special track will highlight topics ranging from innovative technological advances, such as the use of optogenetics and epigenetic research to elucidate the basic mechanisms underlying addictive behaviors, to the translation of new knowledge into better prevention and treatments for drug use disorders. Special emphasis is given to sessions touching upon circuits in the brain that are involved in both addiction and other mental illness. In addition, symposia and lectures will highlight areas critical to psychiatric practice, including the unique issues facing military personnel and their families, the important clinical overlap of smoking with psychiatric disorders, development of medications for addiction, the commonalities between obesity and addiction, the potential therapeutic effects and abuse of cognitive enhancers, and novel approaches to stop the spread of HIV. NIDA Director, Dr. Nora Volkow will give an invited Frontiers of Science Lecture titled, *Addiction: Conflict between Brain Circuits*.

Drs. Mary Kautz, Woody Lin and Minda Lynch, DBNBR, have organized a symposium entitled **Executive Function as a Brain System for Self-Control: The Neurocircuitry of Psychiatric Disorders and Addiction** which will be held at the American Psychiatric Association Annual Meeting on May 22, 2010 in New Orleans, LA.

Drs. James Bjork and Susan Volman, DBNBR, have organized a symposium entitled **Reward Neurocircuitry in Substance Dependence and Other Psychiatric Disorders: What Does Brain Research Tell Us?** This symposium will be held at the American Psychiatric Association Annual Meeting on May 25, 2010 in New Orleans, LA.

Drs. Steven Grant, DCNBR, and Roger Sorenson, DBNBR, have organized a symposium entitled **How Dysfunction of Learning and Memory Circuits Contribute to Substance Abuse and Other Psychiatric Disorders** which will be held at the American Psychiatric Association Annual Meeting on May 26, 2010 in New Orleans, LA.

The National Institute on Drug Abuse (NIDA) will again sponsor the "Grant Writing Workshop" and the "Tutorials Workshop" at the **College on Problems of Drug Dependence (CPDD) Annual Scientific Meeting**. This year's conference will be held in Scottsdale, Arizona, on June 12-17, 2010. The "Tutorials Workshop" provides junior investigators with fundamental information from a variety of scientific disciplines representing the breadth of drug abuse and addiction research. Speakers for this workshop are selected

from amongst NIDA's T32 Training Directors to each give a presentation on a research topic within their field of expertise. The "Grant Writing Workshop" is designed to orient new research investigators to NIDA and the grant application process. NIDA will also be offering a limited number of travel awards to partially defray the cost of attending this conference.

The National Institute on Drug Abuse (NIDA) is organizing a program at this year's **American Psychological Association (APA) Annual Meeting in San Diego, CA, August 12-15, 2010**. A number of NIDA staff throughout the Institute are involved in organizing and/or presenting on a wide range of session topics. 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.

Dr. Minda Lynch, DBNBR, with Dr. David Shurtleff, DBNBR, as Co-chair, is organizing a half-day NIDA-sponsored satellite symposium at CPDD in June, Scottsdale, AZ. This session, on Genetics Approaches in Drug Abuse and Addiction Research, will highlight recent findings from mouse mutagenesis, human pharmacogenetics, QTL studies and techniques to study micro-RNAs in paradigms relevant for understanding addiction. Presentations, to include both research findings and didactic instruction, will be delivered by Drs. Marilyn Carroll, Abraham Palmer, Caryn Lerman and Paul Kenny.

The **31st Annual Meeting of the Society for Clinical Trials** will take place May 16-19, 2010, in Baltimore, MD. Carmen Rosa is organizing a workshop titled "Considerations in the Design of Clinical Trials for Comparative Effectiveness Research" to be held from 1:00 PM to 5:00 PM on May 16, 2010.

The next **National CTN Steering Committee Meetings** will be held September 21-23, 2010 in Bethesda, MD.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Publications

NIDA Publications

Research Report Series: Marijuana (Revised) NIH Pub. No. 10-3859
This report contains current data based on an extensive review of scientific literature on the scope of marijuana abuse in the United States, as well as its physical and social effects. NIDA addresses the adverse physical, mental, emotional and behavioral changes associated with heavy marijuana use in this publication and presents an overview of study results on health consequences of marijuana abuse.

Drugs, Brains, and Behavior: The Science of Addiction (Rev.) NIH Pub. No. 10-5605
The "Science of Addiction" explains in layman's terms how science has revolutionized our understanding of drug addiction as a brain disease that affects behavior. It uses simple language, diagrams, and graphics to help people understand how drugs change the brain in structure and in function. The booklet explains some of the reasons that people take drugs, helps explain why some people become addicted while others do not, and demonstrates how addiction, like other chronic diseases, may be prevented and treated.

Research Report Series: Cocaine and Addiction (Sp.) NIH Pub. No. 10-4166
This updated version contains scientific information on crack and cocaine. Facts based on the latest technology are used to describe the different effects of this drug; as well as the pathways in the brain that it affects; the medical consequences of use; and some behavioral treatments for cocaine abuse. NIDA also reports on several pharmacological compounds currently being tested for their potential use in treating cocaine addiction.

Research Report Series: Tobacco Addiction (Sp.) NIH Pub. No. 18-4342
This updated version describes what tobacco is, presents current epidemiological research data regarding its use, and reports on the medical consequences of tobacco use. Emphasizes the effects on the brain as well as current research findings about use during pregnancy. It also includes treatment approaches.

Principles of Drug Addiction Treatment: A Research-Based Guide (Revised) (Sp.)
NIH Pub. No. 10-4180
This second edition of the "Blue Book" includes updated principles, new questions, new program information, and expanded references and resources based on the latest findings from NIDA-funded research. Thirteen fundamental principles of effective treatment for addiction are outlined that include defining the disease of addiction to recognizing that it often co-occurs with other health

conditionsÑall of which need to be addressed for the patient to successfully recover. This publication is intended to help patients and their families learn more about what they can expect from drug abuse treatment and how to optimize their results and minimize their difficulties. It also serves as a resource for healthcare providers seeking information about the various drug abuse treatment options.

NIDA NOTES

***NIDA NOTES,* Vol. 23, No. 1**
The lead article in this issue describes how an activity called the Good Behavior Game, which is played in the primary grades, produces a spectrum of long-term benefits in young adults, including reductions in substance abuse, delinquency, and antisocial personality disorder. The issue also reports research findings indicating that youths who abuse opioids benefit from extended treatment with buprenorphine and naloxone. Another feature presents evidence that vouchers can increase the efficacy of smoking abstinence programs for pregnant women and improve fetal growth. The issue also includes a report that for people with both bipolar disorder and substance abuse problems, group counseling that addresses the two conditions is more effective than standard substance abuse group counseling. In the Director's Perspective, Dr. Nora Volkow introduces NIDAMED, the Institute's comprehensive physician-outreach initiative. The issue also reviews the activities of NIDA's Genetics Workgroup in the search for genes that influence addiction.

NIDA IN THE NEWS

Issue #28 of NIDA in the News was distributed to all NIDA HQ, IRP and contractor staff on February 18, 2010.

CTN-Related Publications

Seven 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 22 CTN trials are now available on the CTN Data Sharing Web Site. Over 300 research scientists have downloaded one or more data sets. 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.

International Program-Related Publications

NIDA IP's New Mission Brochure
A new, four-page color brochure highlights NIDA IP's pivotal work in promoting international collaborative drug abuse research, training, and exchange. The brochure briefly describes NIDA IP's efforts to link NIDA to the world through partnerships with countries, organizations, and individual researchers; support research through Program Announcements and Requests for Applications; build capacity through research training and professional development opportunities; and share knowledge through a variety of channels. The back of the brochure spotlights the annual NIDA International Forum and lists the NIDA IP Web site address. A downloadable PDF version of the brochure is available on the International Program's Web site at http://international.drugabuse.gov/whoweare/PDFs/MissionBrochure.pdf.

NIDA IP Fellowships Flyer

Planned Meetings

Publications

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Grantee Honors

NIDA IP has developed a new flyer to provide at-a-glance information on the variety of training fellowships and research exchanges that it offers for all levels of scientists interested in drug abuse research. Arranged by career level, the flyer's concise chart lists nine programs with key information on their respective eligible audiences, application deadlines, and what the fellowships include. A downloadable PDF version of the flyer is available on the International Program's Web site at http://www.international.drugabuse.gov/research/PDFs/FellowshipFlyer.pdf.

HHH Fellowship Flyer

The NIDA Humphrey Drug Abuse Research Fellowship is the focus of a new two-page flyer that promotes this unique component of the HHH Fellowship program. The brochure describes the focus of the fellowship, what it covers, who is eligible, and where and when to apply. In addition to listing resources for more information, the brochure gives an email address to request advice on preparing a competitive application. A downloadable PDF version of the flyer is available on the International Program's Web site at http://www.international.drugabuse.gov/research/PDFs/HHH_Flyer.pdf.

IP E-News

March 2010 - This issue announced the availability of tuition waivers for the Dutch Summer Institute on Alcohol, Drugs and Addiction and training grants made available through the FIC as a result of U.S. economic stimulus funds. The issue also reported on an orientation program for new HHH fellows, the appointment of Dr. Phil Skolnick as the director of DPMCDA, three new INVEST-CTN fellows, new DISCA and USDISCA awardees, and the accomplishments of former INVEST and HHH fellows. This issue is available online at http://international.drugabuse.gov/about-us/news/2010/03/fellowship-orientation-brings-researchers-13-nations-nida.

Other Publications

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Chefer VI, Denoroy L, Zapata A, Shippenberg TS. Mu opioid receptor modulation of somatodendritic dopamine overflow: GABAergic and glutamatergic mechanisms. Eur J Neurosci. 2009 Jul; 30(2): 272-278.

Director's Report to the National Advisory Council on Drug Abuse - May, 2010

Staff Highlights

Staff Honors and Awards

Dr. Wilson M. Compton, Director, DESPR, received the Paul Hoch Award from the American Psychopathological Association and presented on "Criminal Justice Settings: Intersecting Risks of Mental Health, Substance Abuse and High Risk Behaviors, New York, New York, March 4, 2010.

Dr. Bin Wang from the Behavioral Neuroscience Section and **Dr. Toni Shippenberg** from the Integrative Neuroscience Section, IRP won the NIDA Fellow Award from the Women Scientist Advisor Achievement Award.

Dr. Toni Shippenberg, Chief, Integrative Neuroscience Section, IRP, received a Fulbright Senior Specialist Award to aid researchers at the University of Wellington, New Zealand in developing a center of excellence in addiction research.

Staff Changes

Bukeeia Goodson joined the Office of Science Policy and Communications in April 2010. Ms. Goodson will be serving as the new Program Assistant in the Public Information and Liaison Branch. Ms. Goodson joins us from NIH/OD where she served as an Extramural Support Assistant working with scientific review groups for grants dealing a wide variety of biomedical and behavioral diseases and disorders.

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Grantee Honors

Dr. John W. Olney will give a keynote address, in which he will discuss his findings of loss of brain cells in the neonatal primate brain induced by ketamine, at the annual meeting of the International Anesthesiology Research Society (IARS), 20 March 2010, in Honolulu. IARS, in collaboration with the FDA, and largely as a result of Dr. Olney's findings, formed a consortium referred to as the SAFEKIDS (Safety of Key Inhaled and Intravenous Drugs in Pediatrics) initiative, the purpose of which is to make anesthesia and sedation safer for children (http://www.smarttots.org/).

CTN Grantees

Southern Consortium Node

The Medical University of South Carolina (MUSC) Board of Trustees awarded Dr. Kathleen Brady the title of MUSC Distinguished University Professor. This award ". . . has been bestowed upon fewer than thirty individuals in the history of the university. This designation is reserved for individuals who have contributed in substantial ways to their own field of scholarship, and have enriched or enhanced the institution or society in areas outside of their own primary area of scholarship." Dr. Brady's distinguished contributions to the field of clinical psychiatry and to clinical and translational science at MUSC plus her remarkable leadership in obtaining the CTSA proposal have earned her this well-deserved honor.

Oregon/Hawaii (OR/HI) Node

In their annual review of the top doctors in Portland, Portland Monthly Magazine listed Bradley M. Anderson, MD, Chief of Addiction Medicine at Kaiser Permanente Northwest as the top addiction physician in the metropolitan area. Kaiser Permanente Northwest is a program in the OR/HI Node.

New England Node

The National Council for Community Behavioral Healthcare presented its 2010 award for Excellence in Addictions Treatment to The Hartford Dispensary, Paul McLaughlin Executive Director. The Hartford Dispensary is one of the Community Treatment Providers in the New England Node. Fifteen exemplary individuals and organizations were presented with the National Council Awards of Excellence on March 16, 2010, during the 40th Annual Conference of the National Council for Community Behavioral Healthcare in Orlando, FL. The Awards of Excellence honors those who have significantly shaped the mental health and addictions industry and improved the lives of those in need of treatment and support.

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