Director's Report to the National Advisory Council on Drug Abuse - February, 2009

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Director's Report to the National Advisory Council on Drug Abuse - February, 2009

Research Findings - Basic Neuroscience Research

AMPA Glutamate Receptors Mediate Time Dependent Cue-Induced Craving for Cocaine

Increased time dependent craving for cocaine is frequently seen among cocaine addicts following abstinence and may account for relapse after periods of abstinence. This can be modeled in rats. Rats are trained for 10 days to nose poke to self-administer cocaine when a light cue is presented. 1 or 45 days are allowed to pass before placing the rat back into the chamber where the rat had learned to self-administer cocaine in the presence of the light cue. After the 1 or 45 period of abstinence the light is presented but the rat is no longer rewarded for nose poking with a cocaine injection, a process called extinction. Conrad and colleagues report that rats after 45 days of abstinence made more nose pokes in the presence of the cue as compared to rats after 1 day of abstinence even though no cocaine was delivered showing a time-dependent increase in cue-induced cocaine seeking. Conrad and colleagues then examined whether glutamate synaptic transmission is altered in the nucleus accumbens, a subcortical structure involved in reward that receives input from dopamine neurons and neurons in prefrontal cortex and limbic regions of the brain. Glutamate can act on three classes of receptors: NMDA, AMPA, and metabotropic receptors. The NMDA and AMPA receptors excite the neuron upon sensing the release of glutamate from an adjacent neuron by allowing ions to pass through while metabotropic receptors change neuronal excitability by activating enzymes. Conrad and colleagues report that number of GluR1 and GluR3 receptors, but not GluR2 AMPA receptors are increased in the shell and core of the nucleus accumbens. Naspm, a blocker of GluR1 and GluR3 receptors, inhibited the enhanced cue-induced cocaine seeking after prolonged withdrawal from cocaine withdrawal after injections into the nucleus accumbens on the test withdrawal days. These results suggest that prolonged withdrawal from cocaine produces increases in the number of GluR1 and GluR3 receptors leading to time dependent increased responding for cocaine associated cues and may be responsible for cocaine craving in human addicts. Conrad, K.L., Tseng, K.Y., Uejima, J.L., Reimers, J.M., Heng, L.J., Shaham, Y., Marinelli, M., and Wolf, M.E. Formation of Accumbens GluR2-lacking AMPA Receptors Mediates Incubation of Cocaine Craving. Nature, 454(7200), pp. 118-121, 2008.

Phosphorylation Dependent Trafficking of GluR2 Receptors in the Nucleus Accumbens Play a Key Role in Drug-Induced Reinstatement of Drug Seeking Behavior

Previous work suggests that AMPA glutamategic transmission plays a key role in reinstatement of drug seeking behavior when drug seeking is primed by a drug such as cocaine. In this paradigm animals are trained to press a lever for

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cocaine. The behavior is then extinguished by no longer administering cocaine after a lever press. A week later, the rats are given an injection of cocaine which primes the animal to press the lever again. Injections of AMPA receptor agonists reinstate drug seeking behavior after it has been extinguished and AMPA antagonists injected into the nucleus accumbens block cocaine seeking behavior following a priming injection of cocaine. In the October 22, 2008 issue of the Journal of Neuroscience Dr. Chris Pierce and his colleagues report that the injection of the AMPA receptor antagonist CNQX into the nucleus accumbens shell or core, injected just before a priming dose of cocaine, attenuated cocaine seeking behavior. Dr. Pierce and his colleagues then showed that reinstatement of cocaine seeking behavior by a priming dose of cocaine is mediated by phosphorylation of the GluR2 receptor at serine 880 in the nucleus accumbens shell but not core. The effect on phosphorylation of the GluR2 receptor is specific because phosphorylation of the receptor is not observed for animals receiving a priming dose that were not receiving contingent cocaine. Phosphorylation of GluR2 at serine 880 is required for association of GluR2 to Pick1 and subsequent internalization of the receptor. To test whether phosphorylation of the GluR2 receptor is causally involved in drug reinstatement, Dr. Pierce and his colleagues injected Pep2-EVKI, a peptide that blocks GluR2 trafficking by preventing the phosphorylation of GluR2 and subsequent association of GluR2 with the gene, PICK1, into the nucleus accumbens an hour before the priming dose of cocaine. The Pep2-EVKI but not a control peptide, Pep2-SVKE, attenuated drug induced reinstatement of cocaine seeking behavior. These results suggest that the phosphorylation of GluR2 receptor and its internalization promote drug seeking behavior. Famous, K.R., Kumaresan, V., Sadri-Vakili, G., Schmidt, H.D., Mierke, D.F., Cha, J.H., and Pierce, R.C. Phosphorylation-Dependent Trafficking of GluR2-Containing AMPA Receptors in the Nucleus Accumbens Plays a Critical Role in the Reinstatement of Cocaine Seeking J. Neurosci. 28(43), pp. 11061-11070, 2008.

The Nicotinic Acetylcholine Receptor β2 Subunit (CHRNB2) Gene is Implicated in Smoking Cessation: A Genetic Marker for Bupropion Treatment And Relapse Risk?

It is well-documented that there is substantial variability among individuals in response to bupropion treatment for tobacco dependence. David Conti and his colleagues performed a systems-based candidate gene study of 1295 single nucleotide polymorphisms (SNPs) in 58 genes within the neuronal nicotinic receptor and dopamine systems to investigate their role in smoking cessation in a bupropion placebo-controlled randomized clinical trial. In global tests of main effects and treatment interactions, a SNP (rs2072661) in the 3' UTR region of the β2 nicotinic acetylcholine receptor subunit (CHRNB2) has an impact on abstinence rates at the end of treatment (adjusted P= 0.01) and after a 6-month follow-up period (adjusted P = 0.0002). Independent of treatment at 6-month follow-up, individuals carrying the minor allele have substantially decreased the odds of quitting (OR = 0.31; 95% CI 0.18-0.55). Effect of estimates indicate that the treatment is more effective for individuals with the wild-type (OR = 2.14, 95% CI 1.20-3.81) compared with individuals carrying the minor allele (OR = 0.83, 95% CI 0.32-2.19), although this difference is only suggestive (P = 0.10). Furthermore, this SNP demonstrated a role in the time to relapse (P = 0.0002) and an impact on withdrawal symptoms at target quit date (TQD) (P = 0.0009). Overall, while the results indicate strong evidence for CHRNB2 in ability to quit smoking, these results require replication in an independent sample. Conti, D.V., Lee, W., Li, D., Liu, J., Van Den Berg, D., Thomas, P.D., Bergen, A.W., Swan, G.E., Tyndale, R.F., Benowitz, N.L., and Lerman, C. for the Pharmacogenetics of Nicotine Addiction and Treatment Consortium. Nicotinic Acetylcholine Receptor β2 Subunit Gene Implicated in a Systems-based Candidate Gene Study of Smoking Cessation. Hum. Mol. Genetics, 17, pp. 2834-2848, 2008.

Dopamine, Norepinephrine and Serotonin Modulate Monoamine Transporter Function via TAAR1

The trace amine-associated receptor 1 (TAAR1) is expressed in brain monoaminergic systems and activated by dopamine, norepinephrine and serotonin. This study used transfected HEK293 cells and brain synaptosomes to evaluate the interaction of these monoamines with TAAR1 and with monoamine autoreceptors to explore their modulatory effects on monoamine transporters. The researchers demonstrated that TAAR1 signaling was attenuated by monoamine autoreceptors following exposure to dopamine, norepinephrine or serotonin. In transfected cells, TAAR1 in response to dopamine, norepinephrine or serotonin significantly inhibited uptake and promoted efflux of dopamine, [norepinephrine or serotonin, respectively, whereas the monoamine autoreceptors, D2s, alpha (2A) and 5-HT(1B), enhanced the uptake function under the same condition. In brain synaptosomes, dopamine, norepinephrine or serotonin significantly altered the uptake and efflux of dopamine, norepinephrine or serotonin, respectively, when the monoamine autoreceptors were blocked. By comparing the effects of dopamine, norepinephrine and serotonin in non human primate and wild-type mouse synaptosomes to their effects in TAAR1 knockout mouse synaptosomes, they deduced that TAAR1 activity inhibited uptake and promoted efflux by monoamine transporters and that monoamine autoreceptors exerted opposite effects. These data provide the first evidence that common biogenic amines modulate monoamine transporter function via both TAAR1 and monoamine autoreceptors, which may balance their activity. In this regard, the data reveal that TAAR1 functions as a monoamine autoreceptor in monoaminergic neurons. Xie, Z., Westmoreland, S.V., and Miller, G.M. Modulation of Monoamine Transporters by Common Biogenic Amines via Trace Amine-Associated Receptor 1 and Monoamine Autoreceptors in Human Embryonic Kidney 293 Cells and Brain Synaptosomes. J. Pharm. Exp. Ther., 325, pp. 629-640, 2008.

Cocaine Preferentially Enhances Firing and Evokes Release of Dopamine in the Shell of the Nucleus Accumbens

In this study, characterization of electrophysiological transients (firing of neurons) was accomplished by pharmacologically blocking dopamine autoreceptors, one of the regulatory elements of neurotransmission. Comparisons of real-time measurements using in vivo voltammetry after cocaine administration and systemic manipulation of dopamine autoreceptors provided reliable resolution between increases in the frequency of dopamine release events and the concentration of dopamine released. Wightman and his colleagues showed that the preferential enhancement of dopamine transmission within the NAc shell that is evoked by cocaine is attributable to a greater number of phasic release events originating from midbrain dopaminergic neuron activity. This subregion difference was abolished by autoreceptor blockade before cocaine administration. Finally, cocaine administration in the absence of autoregulation resulted in a synergistic increase in [DA], describing one mechanism by which cocaine induces burst firing from dopaminergic neurons. This study provides novel characterization of the distinct processes that encompass extracellular dopamine transmission, shows the first evidence that cocaine directly increases dopamine release events in a temporally and regionally specific manner, and demonstrates the significance of autoregulation in cocaine-evoked dopamine transmission. Aragona, B.J., Cleaveland, N.A., Stuber, G.D., Day, J.J., Carelli, R.M., and Wightman, R.M. Preferential Enhancement of Dopamine Transmission within the Nucleus Accumbens Shell by Cocaine Is Attributable to a Direct Increase in Phasic Dopamine Release Events. J. Neuroscience, 28, pp. 8821-8831, 2008.

β-Catenin is Required for Memory Consolidation

Recent work by Magaschuk and Ressler suggests that β-catenin, a molecule that governs some of the structural changes in synaptic morphology at excitatory synapses, has a role in long-term memory formation. β-catenin is highly expressed in the adult mouse amygdala and is dynamically regulated at both the transcriptional and post-translational levels with fear learning. Pharmacological stabilization of β-catenin with LiCl resulted in enhanced learning, whereas genetic deletion of its gene, Ctnnb1, in the amygdala resulted in deficient learning. By studying the effects of Ctnnb1 deletion in adult mice, these researchers have identified a role for β-catenin in learning and memory that is distinct from its role in development. Their data suggest that β-catenin is required for the consolidation, but not the acquisition, of fear memory. However, once memory consolidation has occurred, β-catenin is no longer needed to express the memory. During this consolidation period, the interaction between β-catenin and cadherin, a cell adhesion protein, is dynamically regulated, suggesting that β-catenin is involved in the structural conversion of short-term labile to long-term stable memory traces and that this effect was specific to the basal lateral amygdala. This mechanism may also prove to be important in memory consolidation processes associated with drug addiction. Magaschak, K.A. and Ressler, K.J. β-catenin is Required for Memory Consolidation. Nature Neurosci., 11, pp. 1319-1326, 2008.

Pharmacotherapies Targeted at Alpha 6 Nicotinic Acetylcholine Receptors May Be Useful in Treating Human Disorders Involving Changes in Dopamine

Nicotinic acetylcholine receptors (nAChRs) modulate dopaminergic transmission within the nervous system. One subtype of nAChR, the alpha6-containing (alpha6*) nAChR, is selectively expressed in dopamine neurons. Previous studies using gene knockouts (alpha6 knockout mice) or pharmacological inhibition of alpha6 nAChRs have identified behavioral and physiological responses that are regulated by alpha6 nAChR function. This recent study takes these previous results further by generating and studying mice with gain-of-function alpha6* nAChRs that amplify rather than inhibit cholinergic control of dopaminergic transmission. These gain-of-function mice show increased dopamine neuron excitability and dopamine release. And intriguingly, these mice display behavioral phenotypes consistent with increased dopaminergic transmission. Alpha6 gain-of-function mice exhibited locomotor hyperactivity in their home cage and failed to habituate to a novel environment. Selective activation of alpha6* nAChRs with low doses of nicotine, thereby stimulating dopamine but not GABA neurons, exaggerated these phenotypes and produced a hyper-dopaminergic state in vivo. Experiments with additional nicotinic drugs showed that altering agonist efficacy at alpha6* receptors provided fine tuning of dopamine release and locomotor responses. Thus, alpha6*-specific agonists or antagonists may, by targeting endogenous cholinergic mechanisms in midbrain or striatum, provide a method for treating neural disorders that result from aberrant dopaminergic transmission. Drenan, R.M., Grady, S.R., Whiteaker, P., McClure-Begley, T., McKinney, S., Miwa, J.M., Bupp, S., Heintz, N., McIntosh, J.M., Bencherif, M., Marks, M.J., and Lester, H.A. In Vivo Activation of Midbrain Dopamine Neurons Via Sensitized, High-affinity alpha 6 Nicotinic Acetylcholine Receptors. Neuron. 60(1), pp. 123-136, 2008.

Tolerance to Short-Term Repeated Morphine Administration is Associated with Increased, As Well As Decreased, Potency of Opioid Agonists

Tolerance to the pain-relieving effects of opiates limits their clinical use. Morphine tolerance is associated with desensitization of mu-opioid receptors.

However, one problem with the desensitization hypothesis is that acute morphine does not readily desensitize mu-opioid receptors. Thus, studies of opioid tolerance have been typically performed after prolonged, continuous opioid pretreatment. These studies have routinely shown that continuous opioid pretreatment decreases opioid activation of G-protein-mediated inwardly rectifying potassium (GIRK) currents, subsequently altering neuronal activity within the periaqueductal gray region that then contributes to the expression of antinociceptive tolerance. The paper cited here sought to determine whether similar changes occurred with short-term repeated morphine exposure. Using this exposure paradigm, it was found that short-term repeated exposure to opioids produced a biphasic effect on GIRK currents in morphine tolerant rats. Unexpectedly, opioid activation of GIRK currents was initially potentiated in morphine compared to saline pretreated rats. These currents were inhibited by the mu-opioid receptor antagonist beta-funaltrexamine suggesting that short-term repeated morphine administration enhances agonist stimulation of mu-opioid receptor coupling to G-proteins. Longer application of opioids produced mu-opioid receptor desensitization consistent with results obtained with continuous opioid exposure. However, peak GIRK currents from short-term repeated exposure and tolerant rats desensitized more than currents from saline pretreated rats. These data indicate that antinociceptive tolerance due to short-term repeated opioid exposure may be triggered by enhanced agonist potency followed by an increased desensitization of mu-opioid receptors. Thus, this paper may have uncovered a novel action of opioids at mu-opioid receptors. Ingram, S.L., Macey, T.A., Fossum, E.N., and Morgan, M.M. Tolerance to Repeated Morphine Administration is Associated with Increased Potency of Opioid Agonists. Neuropsychopharmacology, 33(10), pp. 2494-504, 2008.

Striatal Misregulation of Cdk5 Alters Locomotor Responses to Cocaine, Motor Learning, and Dendritic Morphology

Cyclin dependent kinase 5 (Cdk5), an enzyme expressed primarily in neural cells, regulates dopamine (DA) neurotransmission and striatal neuron excitability and may play a role in mediating synaptic plasticity and learning. In the striatum, medium spiny neurons (MSNs) receive midbrain dopaminergic and cortical glutamergic inputs which influence reward and motor learning pathways. Recently, James Bibb and colleagues investigated the effects of Cdk5 misregulation on striatal-mediated behavior and learning. Cdk5 regulation of DA signaling alters behavioral and biochemical responses to stimulants such as cocaine. Cleavage of the Cdk5 cofactor p35 to form a Cdk5/p25 complex results in abnormal Cdk5 activity and, in turn, neurotoxicity and neurodegeneration. In this study, the investigators generated a transgenic mouse in which p25 could be selectively overexpressed. Using this mouse strain, Bibb and colleagues demonstrated that overexpression of p25 and the resultant misregulation of Cdk5 leads to reduced locomotor sensitization to cocaine over a five day exposure period. In addition, these mice displayed decreased motor coordination, which further indicates that p25-mediated Cdk5 misregulation results in abnormal DA- and striatal-dependent motor behavior. Histological evaluation of p25 overexpression in striatum revealed elevated amounts of glial fibrillary acidic protein (GFAP) and altered cellular morphology, including abnormally shaped cell bodies and decreased dendritic spine density. GFAP is a marker of activated astrocytes and astrogliosis, which accompanies excitotoxic neuronal cell loss. However, in the case of p25 overexpression-dependent Cdk5 misregulation within the striatum, MSNs remained alive, although with significant loss of function. The above findings show that abnormal Cdk5 regulation results in impaired function of this brain region without the neurodegeneration and neuronal cell loss normally associated with p25 overexpression and, as a result, may prove useful for investigation of non-neurodegenerative neurological disorders. Meyer, D.A., Richer, E., Benkovic, S.A., Hayashi, K., Kansy, J.W., Hale, C.F., Moy, L.Y., Kim, Y., O'Callaghan, J.P.,

Tsai, L.H., Greengard, P., Nairn, A.C., Cowan, C.W., Miller, D.B., Antich, P., and Bibb, J.A. Striatal Dysregulation of Cdk5 Alters Locomotor Responses to Cocaine, Motor Learning, and Dendritic Morphology. Proc. Natl. Acad. Sci. U S A., 105, pp. 18561-18566. Epub, 2008.

Cdk5 Regulates Neurogenesis in Adult Hippocampus

Many substances of abuse affect the dopaminergic neural circuits by inducing specific gene expression. One of the genes substantially affected by substances of abuse, such as cocaine and nicotine, is Cdk5, as it is immediately downstream of several upregulated transcription factors, and is significantly upregulated. During brain development, Cdk5 plays a role in neuronal differentiation and migration, but its role in the adult brain, is not clear. A group of NIDA researchers at University of Texas Southwestern, led by Dr. Amelia Eisch, report that Cdk5 has an essential role in the survival of adult-generated neurons in hippocampus. These researchers assessed the role of Cdk5 in the generation of dentate gyrus (DG) granule cell neurons in adult mice. They demonstrate that Cre recombinase- mediated conditional knockout (KO) of Cdk5 from stem cells and their progeny in the DG subgranular zone (SGZ) prevented maturation of new neurons. In addition, selective KO of Cdk5 from mature neurons throughout the hippocampus reduced the number of immature neurons. Furthermore, Cdk5 gene deletion specifically from DG granule neurons via viral-mediated gene transfer also resulted in fewer immature neurons. In each case, the total number of proliferating cells was unaffected, indicating that Cdk5 is necessary for progression of adult-generated neurons to maturity. In addition, they found that the role for Cdk5 in neurogenesis was activating-cofactor specific, as p35 KO but not p39 KO mice also had fewer immature neurons. These findings suggest that abnormal regulation of Cdk5, induced by substances of abuse, may result in abnormal neurogenesis in hippocampus, with consequences in learning and memory.
Lagace, D.C., Benavides, D.R., Kansy, J.W., Mapelli, M., Greengard, P., Bibb, J.A., and Eisch, A.J. Cdk5 is Essential for Adult Hippocampal Neurogenesis. PNAS 105, pp. 18567-18571, 2008.

Cocaine Binge Alters Cellular Signaling Through Akt-GSK3

The mechanism of cocaine addiction, initiated through blocking dopamine transporters in the dopaminergic neural circuits in the brain, is well known. However, the cellular signaling pathways inside the cell membrane upon cocaine exposure and challenge are not well understood. Ikeda et al (2006), showed, that Akt, also called Protein kinase B, is involved in the cellular mechanisms of addiction. Akt negatively regulates GSK3 activity. Typically, following dopamine receptor activation, a time-dependent decrease in phosphorylated Akt in striatum is observed which leads to increased GSK3 activity (by decreasing phosphorylated GSK3) and subsequent increase in gene transcription. Whether cocaine initiates the same signaling pathway, and where such signaling events occur in the dopaminergic circuits are not known. Dr. Ellen Unterwald, at Temple University, reports that cocaine induces a spatially restricted pattern of phosphorylation of Akt and GSK3, wherein the nucleus accumbens and amygdala but not caudate putamen and hippocampus are affected. Regulation of these signaling molecules is also dependent on the length of cocaine exposure. In their study, rats were injected with cocaine (15 mg/kg) or saline (1 mL/kg) in a binge-pattern (three injections at 1 h intervals beginning at 9 AM) for 1, 3, or 14 days. After the last injection, brains were dissected, and the phosphorylation level of Akt and GSK3 in amygdala, nucleus accumbens, caudate putamen, and hippocampus were decided in protein assay. The team found that phosphorylation of Akt on the threonine-308 (Thr308) residue was significantly reduced in the nucleus accumbens and increased in the amygdala after 1 day of cocaine treatment; however, these effects were not accompanied by a significant decrease in GSK3

phosphorylation. Phosphorylation of Akt and GSK3 was significantly reduced after 14 days of cocaine administration, an effect that was only observed in the amygdala. Cocaine did not alter Akt or GSK3 phosphorylation in the caudate putamen or hippocampus. The researchers suggest that these findings in nucleus accumbens may reflect dopaminergic motor-stimulant activity caused by acute cocaine, whereas the effects in amygdala may be associated with changes in emotional state that occur after acute and chronic cocaine exposure. Since GSK3 is downstream of the gene Wnt and catenin which are involved in axonal growth, dendritic remodeling and synaptic regulation, this study may also suggest roles for Wnt signaling pathway in substance abuse. Perrine, S.A., Miller, J.S., and Unterwald, E.M. Cocaine Regulates Protein Kinase B and Glycogen Synthase kinase-3 Activity in Selective Regions of Rat Brain. J. Neurochem. 107, pp. 570-577, 2008.

Translational Profiling Approach for the Analysis of CNS Cell Types

In the November 14th issue of Cell Dr. Paul Greengard, in collaboration with Dr. Nat Heintz, report the development of a method to identify cell types in the nervous system based on a molecular phenotype. This method, called, translating ribosome affinity purification (TRAP), overcomes the problems associated with isolating the highly heterogenous and highly intermixed cell types in the nervous system. Dissocation of neuron induces changes in gene express resulting from mechanical stress and the properties of neurons may change when not in contact with their local environment. To overcome this problem the Greengard and Heintz laboratory have invented a rapid isolation strategy for isolation of polysomal RNA from genetically targeted cell types. In this method an enhanced green fluorescent protein is fused to the N terminus of the large-subunit ribosomal protein L10a (EGFP-L10a). This protein is incorporated into the polysomes where mRNA is translated into protein. An EGFP-L10a antibody attached to magnetic beads is used to isolate and purify the polysomes and the message is then profiled on a silicon chip or sequenced. This method eliminates the expression profiling of RNAs that are not translated into cells. The reporter, EGFP-L10a, is genetically targeted to neurons by inserting the reporter into a large piece of mouse genomic DNA in a bacterial artificial chromosome. The elements inside the BAC that control expression of the gene direct EGFP-L10a to be expressed in specific cell types. To profile striatalnigal cells and striatalpallidal cells, two different populations in the striatum, EGP-L10a was inserted into a Drd1a and Drd2 receptor BACs, respectively. Striatalnigral and striatalpallidal neurons could be distinguished from one another on the basis of expression with translation of Eya1, Isl1, Gng2, and Crym in striatonigral neurons and Gpr6, Lhx8, Gpr88, Trpc4, and Tpm2 in striatopallidal neurons. Mice were then chronically treated with cocaine and gene expression profiling was performed on striatopallidal (Drd2) and striatalnigral cells (Drd1). The GABA signaling pathway (Gabrb3, Gabra1, Cacnb4, and Gabra4) was observed to be significantly increased in striatalnigral cells but not in striatalpallidal neurons. This change in the expression of these GABA receptors was associated with an increase in the frequency of small-amplitude GABAergic mIPSCs in striatalnigral neurons but not in striatalpallidal neurons. To show that the approach can be generalized to other cell types in the nervous system, the Greengard and Heintz labs used the translating ribosome affinity purification (TRAP) technique to profile 24 CNS populations. They report the identification of thousands of cell specific mRNAs not detected by whole tissue gene expression profiling experiments. Gene expression obtained from these cells using TRAP matched the expression of known genes using other methods. Hierarchial clustering, a statistical method, suggests that gene expression of cortical projection neurons are more similar than cortical interneurons, motorneurons, and Purkinje cells. Similarly, gene expression of astroglial from different regions of the brain show greater similarity in pattern of gene expression than other types of glia. This suggests that cells with similar functions share similar gene expression patterns. They also show that much of

the diversity of cell types is marked by cell surface proteins. This method provides a means by which cells in the nervous system can be defined by a molecular phenotype. This method provides the basis by which investigators can induce human induced pleuripotent stem (iPS) cells derived from fibroblast to become defined cell types in the nervous system. These neuronal derived human iPS cells can be used for studies of human cell in culture or used for restoring function in the nervous system. Furthermore, the effects of mutations on the expression of genes in single cells can now be studied by crossing the TRAP transgene into the genetic background of the mutant. Doyle, J.P., Dougherty, J.D., Heiman, M., Schmidt, E.F., Stevens, T.R,, Ma, G., Bupp, S., Shrestha, P., Shah, R.D., Doughty, M.L., Gong, S., Greengard, P., and Heintz, N. Application of a Translational Profiling Approach for the Comparative Analysis of CNS Cell Types. Cell. 135(4), pp. 749-762, 2008; Heiman, M., Schaefer, A., Gong, S., Peterson, J.D., Day, M., Ramsey, K.E., Suarez-Farinas, M., Schwarz, C., Stephan, D.A., Surmeier, D.J., Greengard, P., and Heintz, N. A Translational Profiling Approach for the Molecular Characterization of CNS Cell Types. Cell, 135(4), pp. 738-748, 2008.

A Radiolabeled Alpha7 nAChR Antagonist Probe

Occurrence of the alpha7 subtype of nicotinic acetylcholine receptors has been documented in brain hippocampus and cortex, and further reported in keratinocytes, lymphocytes, macrophage, astrocytes, microglia, and retinal neurons. Besides the use of alpha7 subunit-detecting antibodies, the most commonly used probes are the peptide alpha-bungarotoxin (alpha-Bgt) and the non-peptide methyllycaconitine (MLA). These antagonists have some limitations: MLA also binds to alpha6-containing subtpyes, while alpha-Bgt also binds to other non-alpha7 subtypes (alpha1, alpha 8, and alpha 9/10), and displays a rather slow rate of dissociation from the receptors, which makes it difficult to determine equilibrium binding. Previous work by Drs. Paul Whiteaker and J. Michael McIntosh has produced two modified c. arenatus conotoxin peptide antagonists, with high selectivity for the alpha7 nAChR subtype. These researchers now report that one of these conotoxins has been modified at the single histidine residue with one or two iodine atoms (either I-127 or I-125), and the association/dissociation kinetics, saturation binding, and autoradiographic properties examined. In mouse hippocampal membranes, the monoiodo and diiodo nonradioactive ligands (I-127) had inhibition of I-125 alpha-Bgt greater than that of their parent peptide (low nM Ki values), and their radioactive counterparts produced association (specific binding) with the hippocampal membranes which was complete in about 120-180 minutes, and with reversible dissociation of this binding complete in 180 minutes at 22 degrees Celcius. The binding density (Bmax at saturation) of both the mono-iodo-125 and di-iodo-125 ligands was approximately equal to that of iodo-125 alpha-Bgt. Autoradiographic results for both iodinated ligands showed labeling of wild-type mouse brain in the hippocampus, amygdala, and cortex regions, with only background labeling in the alpha 7 null mouse brain. In terms of stability, the monoiodinatedq I-125 derivative displayed only slight decay over a twelve week period, based on its value of Kd, Bmax, and signal/noise ratio. Both iodinated derivatives showed a selectivity of more than 100-fold for alpha7 compared to alpha6beta2* and alpha9alpha10 subtypes, using a 1 nM concentration of iodinated peptide, displacing appropriate tritiated standards in various membranes. Whiteaker, P., Marks, M.J., Christensen, S., Dowell, C., Collins, A.C., and McIntosh, J.M. Synthesis and Characterization of I-125-alpha-Conotoxin ArIB[V11L;V16A], a Selective alpha7 Nicotinic Acetylcholine Receptor Antagonist. The Journal of Pharmacology and Experimental Therapeutics, 325(3), pp. 910-919, 2008.

Isolation and Characterization of New Cannabis Constituents

Cannabis sativa L., one of the oldest plants known in medicine, is the most

widely used illicit drug in the world today. A total of almost 500 natural constituents have been isolated and/or identified from Cannabis, with 9-THC as the main biologically active component. The availability of high potency marijuana on the illicit market with unprecedented 9-THC concentrations (>20% by dry weight) has led researchers to discover new constituents from Cannabis. This publication reports the isolation and structure elucidation of six new metabolites, (+/-)-6,7-trans-epoxy-cannabigerolic acid, (+/-)-6,7-cis-epoxycannabigerolic acid, (+/-)-6,7-cis-epoxycannabigerol, (+/-)-6,7-trans-epoxy-cannabigerol, 5'-methyl-4-phenylbiphenyl-2,2',6-triol, and 7-methoxycannabispirone along with seven known compounds namely, cannabigerolic acid, 5'-methoxycannabigerolic acid, cannabispirone, ss-cannabispiranol, dehydrocannabifuran, cannflavin B, and cannabigerol. Their antimicrobial, as well as the antileishmanial activities, were also investigated. Radawan, M.M., Ross, S.R., Slade, D., Ahmed, S.A., Zulfiqar, F., and ElSohly, M.A. Isolation and Characteri-zation of New Cannabis Constituents from a High Potency Variety. Planta Med.,74(3), pp. 267-272, 2008.

Selective Blockade of 2-Arachidonoylglycerol Hydrolysis Produces Cannabinoid Behavioral Effects

2-Arachidonoylglycerol (2-AG) and anandamide are endocannabinoids that activate the cannabinoid receptors CB1 and CB2. Endocannabinoid signaling is terminated by enzymatic hydrolysis; for anandamide this process is mediated by fatty acid amide hydrolase (FAAH), and for 2-AG is thought to involve monoacylglycerol lipase (MAGL). FAAH inhibitors have been shown to generate a subset of the behavioral effects observed with CB1 agonists, which suggests a functional segregation of endocannabinoid signaling pathways in vivo. Testing this hypothesis, however, requires specific tools to independently block anandamide and 2-AG metabolism. Dr. Cravatt and his colleagues describe a potent and selective inhibitor of MAGL (JZL184) that raises brain 2-AG by eight-fold without altering anandamide. JZL184-treated mice exhibited a broad array of CB1-dependent behavioral effects, including analgesia, hypothermia and hypomotility. These findings indicate that 2-AG endogenously modulates several behavioral processes classically associated with the pharmacology of cannabinoids and suggest overlapping and distinctive functions for 2-AG and anandamide in vivo. Long, J.Z., Li, W., Booker, L., Burston, J.J., Kinsey, S.G., Schlosburg, J.E., Pavon, F.J., Serrano, A.M., Selley, D.E., Parsons, L.H., Lichtman, A.H., and Cravatt, B.F. Selective Blockade of 2-arachidonoylglycerol Hydrolysis Produces Cannabinoid Behavioral Effects. Nature Chem. Bio., Published online 23 November 2008.

Nicotinic Acetylcholine Receptors Contribute to Neural Processing of Sensory Stimuli and Sensory-Cognitive Behaviors

Dr. Raju Metherate and his colleagues at the University of California, Irvine, have continued their studies on the role of nicotinic acetylcholine receptors (nAChRs) in modulating tone-evoked responses in auditory cortex. In this study they sought to test the prediction that nicotinic enhancement of sensory physiology had a direct relation to behavioral performance. They trained adult rats in an auditory-cued, active avoidance task and classified their performance as good, intermediate, or poor. Next, they anesthetized the animals and recorded tone-evoked local field potentials in layer 4 of the auditory cortex, before and after a test dose of nicotine or saline. The investigators found that nicotine enhanced the amplitude and decreased the threshold of responses of neurons to the smallest sound intensities in rats classified as good performers, but not in rats considered as intermediate or poor performers. Interestingly, nicotine had the opposite effects on responses to spectrally distant stimuli, in effect showing that cortical receptive fields became more selective to the appropriate stimuli, but once more only in the good performers. Nicotine did reduce onset latencies in all three groups, which the investigators interpreted

as evidence that the drug did attain appropriate dose levels. These findings do not answer the questions of whether or not poor learning is associated with nonfunctional AChRs, whether higher doses of nicotine would be effective in poor performers, or whether robust learning results from or produces improved nAChR expression. These findings do, however, suggest that nicotine-enhanced receptive field selectivity in auditory cortex may contribute to improved cognitive function by enhanced responses to relevant stimuli and suppression of distracters. Liang, K. Poytress, B. Weinberger, N. and Metherate, R. Nicotinic Modulation of Tone-Evoked Responses in Auditory Cortex Reflects the Strength of Prior Auditory Learning. Neurobiology of Learning and Memory, 90, pp. 138-146, 2008.

Director's Report to the National Advisory Council on Drug Abuse - February, 2009

Research Findings - Basic Behavioral Research

Exercise Decreases the Motivation for Cocaine in an Animal Model of Self-Administration

Much is now known about the neurobiological effects of exercise, at the systems and cellular level. Exercise has positive 'psychological' effects, produces interoceptive effects that are phenomenologically similar to those produced by addictive drugs and activates the same central dopamine neurotransmitter systems that are stimulated by drugs of abuse. Adolescents who participate in physical fitness programs have a lower incidence of tobacco and substance abuse, suggesting that exercise should be incorporated in prevention and treatment programs where it might serve as a form of alternative reinforcement. However, until recently, the causal relationship between aerobic exercise and the vulnerability for engaging in drug abuse behaviors had not been investigated. Dr. Mark Smith recently gave female rats 24 h access to running wheels and compared them to sedentary counterparts on measures of drug reward and motivation. Exercise was available for six weeks prior to training for i.v. self-administration of cocaine. All animals were first trained on a fixed ratio schedule of reinforcement and then assessed for their "willingness to work" for cocaine using a progressive ratio (PR) schedule to generate individual break-points (i.e., the maximum number of responses an animal is willing to make for cocaine). Animals in the exercise group continued to have access to running wheels during the self-administration training and testing in this study. Group comparisons revealed no difference between exercising and sedentary rats on the rate of acquisition for self-administration, but PR break-points were greater in sedentary rats. Interestingly, the investigator found significant differences for both low, and high, doses of i.v. cocaine (0.3 and 1.0 mg/kg/infusion). He also reports a positive correlation ($r^2=.462$) between the number of wheel revolutions per day (i.e., exercise output) in the day proceeding access to cocaine and breakpoints for 1.0 mg/kg cocaine, suggesting a protective effect of exercise with high dose availability. These observations suggest that prior, and concurrent, exercise may reduce the motivation for drugs of abuse without changing the vulnerability to acquire self-administration. Smith, M.A., Schmidt, K.T., Iordanou, J.C. and Mustroph, M.L. Aerobic Exercise Decreases the Positive-reinforcing Effects of Cocaine. Drug and Alc. Dep., 98, pp. 129-135, 2008.

Initial Behavioral Response to Cocaine Predicts Sensitization of Reward

Initial "high" or "low" locomotor response to acute cocaine in the rat predicts the development of sensitization produced by repeated psychostimulant administration - that is, low responders (LRs), but not high responders (HRs), develop cocaine-induced behavioral sensitization. LRs are also more likely to

develop cocaine conditioned place preference. In a recent study, male rats were habituated to a test environment and then treated with 10 mg/kg cocaine to assess acute locomotor response. They were divided into LR and HR groups on the basis of a median split. Half of the LR and half of the HR groups then received 10 mg/kg cocaine for four days (repeated exposure group, RE), while the other half received only one cocaine injection (single exposure group, SE). After acquisition training for cocaine self-administration, animals were tested on a progressive ratio (PR) schedule to assess "willingness to work" for cocaine. Break-points, determined for each rat, measured the greatest number of responses made to receive a single drug infusion. Findings revealed that initial differences in acute locomotor activation (LRs versus HRs) were eliminated by four daily injections of cocaine (the RE condition), attributed to behavioral sensitization in the LR group only. RE enhanced acquisition in both LR and HR groups. In addition to this escalated acquisition the researchers also found that RE animals took more drug during the PR schedule (measured as "break-point associated infusions") than animals who received only a single cocaine injection (SE) prior to catheter implantation. Furthermore, LR rats self-administered more cocaine, at all doses tested, than did HR animals during the PR testing (i.e., significant main effects for both exposure, and for initial response), with no significant interactions between these variables. Overall results indicate (1) initial response to the acute cocaine's locomotor effects predicts development of chronic neuroadapations (i.e., only the LR group showed sensitization, as previously reported); and (2) repeated exposure to cocaine (RE) sensitizes animals to acquire self-administration and increases the motivation to work for drug during the maintenance phase of drug intake (in both LR and HR animals). Moreover, animals with an initial insensitivity to the behaviorally stimulating effects of cocaine (LR) administer more drug on a PR schedule, suggesting that they are more motivated to work for the drug. These findings implicate a differential role for initial drug sensitivity in the initiation of drug intake versus the motivation to work for drug, once a pattern of abuse has begun. Furthermore, they also underscore powerful pharmacokinetic and/or pharmacodynamic effects of repeated drug exposure, which can overshadow individual differences in vulnerability. Mandt, B.H., Schenk, S., Zahniser, N.R. and Allen, R.M. Individual Differences in Cocaine-induced Locomotor Activity in Male Sprague-Dawley Rats and Their Acquisition of and Motivation to Self-administer Cocaine. Psychopharmacol., 201, pp. 195-202, 2008.

Impulsivity as a Two-Dimensional Construct: Differences in Vulnerability Phenotypes with an Animal Model

Dr. Marilyn Carroll and her colleagues have been using rodent models to examine vulnerability phenotypes in the acquisition, maintenance, escalation and relapse to drug seeking and drug taking behaviors. As animals that prefer sucrose rich foods also self-administer more cocaine, alcohol and morphine, sweet preference may be an important vulnerability phenotype that contributes to the co-morbidity of obesity and drug addiction. Previous research by this group also reveals that animals bred for high or low saccharin preference (HiS versus LoS) differ on measures of behavioral impulsivity. Thus, sweet preference and impulsivity may be traits shared by a common intermediate phenotype for drug abuse vulnerability. Impulsivity is not a unitary construct, however, and previous studies have compared HiS versus LoS animals on measures of impulsive choice using delay discounting procedures. In a new study, the authors examined aspects of impulsivity that reflect impaired response inhibition with a Go/No-Go task to examine response inhibition. Male and female rats, selectively bred for HiS or LoS preference, were trained to administer i.v. cocaine under several different reinforcement schedules. The schedules included a signaled Go component where responding was reinforced with a drug infusion, alternating with two No-Go components where responses

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were without consequence. Responses made on the previously reinforced lever, during No-Go components, were taken as a measure of impaired response inhibition. Similar testing was conducted using food as the reward, instead of cocaine. Results from the Go component resemble those from previous studies, showing that: (1) female animals make more responses and infuse more drug than males, and (2) HiS rats make more responses for the self-infusion of cocaine. Of interest for the analysis of impulsivity as a vulnerability phenotype is the finding that similar profiles were seen during No-Go components, suggesting effects of sex and the ability to withhold responses contribute to greater drug intake seen by female and HiS animals. Since females and HiS animals responded significantly more during No-Go components than males and LoS animals, the authors suggested that impulsivity is an identifiable phenotype that characterizes female and HiS animals, implicating both phenotype and sex differences in impaired inhibition. By contrast, no group differences were seen on responding during No-Go periods of food reinforced operant schedules; (with the exception of males > females at high fixed ratio requirements). Therefore, sex and impulsivity selectively enhanced the vulnerability for cocaine intake in this study. In a previous experiment, these researchers found no effect for sex and sucrose preference on impulsive choice using delayed discount procedures, suggesting that different aspects of this trait may contribute selectively to vulnerability phenotypes for psychostimulant abuse. Anker, J.J., Gliddon, L.A. and Carroll, M.E. Impulsivity on a Go/No-go Task for Intravenous Cocaine or Food in Male and Female Rats Selectively Bred for High and Low Saccharin Intake. Behav. Pharmacol., 19, pp. 615-629, 2008.

Long-Access Cocaine Self-Administration Induces Sustained Cognitive Impairment in Rats

Animal models provide an opportunity to examine cognitive effects of repeated cocaine and characterize the neurobiological processes responsible for these effects. Recently, Dr. Terry Robinson and colleagues conducted a series of experiments to study cognitive deficits induced by psychostimulant self-administration in a rodent model. Rats in this study were trained on a sustained attention task prior to i.v. cocaine self-administration. The task required animals to discriminate a (1 sec) signaled versus non-signaled trial for food reinforcement. Responses on one lever were reinforced if they followed a signal, while responses on the other lever were reinforced if made during a non-signaled trial. Illumination of the house light designated the beginning of each trial and served to focus the animal's attention toward the intelligence panel. Length of the signal was changed from 1 sec, to vary from 25 to 500 msec, randomly across trials. Rats self-administering cocaine were matched for amount of drug taken during i.v. training, and for performance on the attention task. They were divided into groups given short- (1 hr/day=SA) versus long- (6 hr/day=LA) access to cocaine for four weeks, and then were retested on the sustained attention task. In study two, additional groups of animals were tested on this task at one day, or one month, following six weeks of drug administration and post-mortem tissue collected for in situ hybridization of mRNA was collected as well. In a third study, on day 3 or day 30 after the final self-administration session, rats were sacrificed to quantify D1 and D2 receptor proteins in brain. Results from the first study reveal that LA rats showed escalated drug intake over sessions (as typically reported) and were markedly impaired on the sustained attention task 24 hr after the last self-administration session, using an overall index of performance known as VI (vigilance index). The SA rats, however, showed stable self-administration rates over the six weeks and also did not differ from sham operated controls on VI measures. The LA group was still significantly impaired on a VI measure 14 days after the last drug session. This prolonged deficit was due to increased false alarms on signal detection. Measures of mRNA expression for dopamine receptors in brain revealed decreases for D2 mRNA in the medial prefrontal cortex and the orbitofrontal cortex, at 4 and 33 days after the last drug session, for LA

animals only. Interestingly, D2 receptor mRNA levels in the prefrontal region was positively correlated with VI scores for this group. In study three, analysis of D2 receptor protein in the prefrontal cortex revealed that the LA group, only, had a small, but statistically significant decrease of D2 protein. Differences in D1 mRNA or proteins were not detected in any area. These findings suggest that extended exposure to cocaine, in an animal model that mimics the progressive, compulsive escalation of drug intake seen in human addiction, can induce impairment of attention processes that are important for executive functions. Furthermore, it appears that cocaine induces this effect, in part, by perturbing D2 receptor function in cortical regions that subserve these functions. Briand, L.A., Flagel, S.B., Garcia-Fuster, M.J., Watson, S.J., Akil, H., Sarter, M. and Robinson, T.E. Persistent Alterations in Cognitive Function and Prefrontal Dopamine D2 Receptors Following Extended, but not Limited, Access to Self-administered Cocaine. Neuropyschopharmacol., 33, pp. 2269-2980, 2008.

Nicotine Taken During Adolescence Decreases Aversive Effects of Nicotine as Adults

Although adolescence has been reported to be a period of enhanced vulnerability to tobacco dependence, little is known about what explains this relationship. Dr. Laura O'Dell at the University of Texas, El Paso, used the conditioned place preference paradigm to examine rewarding and aversive effects of nicotine across different stages of development. In two studies, male rats were conditioned to associate one environmental compartment with drug (either nicotine or d-amphetamine), and to associate another environmental compartment with saline. There were 4 conditioning sessions for each environmental compartment, for a total of 8 counter-balanced conditioning sessions. On the test day, undrugged rats were able to choose between the two environments, indicating their conditioned place preference (CPP) for the drug-paired environment. Since adolescence for rats is typically between postnatal days 28 through 45, the initial conditioning session for adolescent rats took place on postnatal day 34, with the preference test taking place on postnatal day 42. For adult rats, the conditioning sessions started on postnatal day 66, with the preference test taking place on postnatal day 74. The first study compared drug-naive adolescent and adult rats who received one of several doses of nicotine or d-amphetamine during the conditioning sessions. The second study compared nicotine-induced CPP in adult rats that were exposed to nicotine during adolescence (postnatal days 28 through 42) with drug-naive adult rats. In study one, nicotine produced an inverted U-shaped dose response curve, with lower doses producing conditioned place preference, and higher doses producing conditioned place aversion. That is, the environment associated with the lower doses of nicotine was preferred on test day whereas it was avoided (e.g., the non-drug side was preferred) when the environment was associated with higher doses of nicotine. Adolescent rats displayed enhanced positive shifts in preference such that they displayed greater CPP over a wider range of nicotine doses. The high dose that produced aversion in adults still produced preference, albeit a small one, in adolescents. Conditioning with d-amphetamine produced a similar inverted U-shaped dose response curve, but there were no differences between the adolescent and adult groups. In study 2, adults who were pre-exposed to nicotine during adolescence failed to show the aversive effects produced by the highest dose of nicotine. They also showed a smaller preference for the nicotine-paired environment. That is, the dose-response curve for the pre-exposed rats was relatively flat, and lacked the preference peak and aversion drop seen in the naive adults. These findings suggest that not only do adolescents show enhanced CPP - and thus are more sensitive to nicotine's rewarding effects or less sensitive to its aversive properties, but exposure during adolescence reduces the aversion to high-dose nicotine typically seen in naive adult animals. Torres, O.V., Tejeda, H.A., Natividad, L.A., and O'Dell. L.E. Enhanced

Vulnerability to the Rewarding Effects of Nicotine During the Adolescent Period of Development. Pharmacol. Biochem. Behav., 90, pp. 658-663, 2008.

Daily Smokers, But Not Chippers, More Likely to be Alcohol Dependent

People with alcohol-use disorders (AUD) and anxiety disorders (ANX) are more likely to use tobacco than the general population. Dr. Sandra Morissette and colleagues therefore evaluated the contribution of tobacco use to the co-occurrence of AUD and ANX disorders by investigating differences between daily smokers, chippers (non-daily smokers), and non-smokers that might affect alcohol or anxiety symptoms. All subjects had co-occurring AUD-ANX disorders and reported their smoking status. Each subject completed several measures, including a TimeLine-Follow-Back to gather retrospective accounts of daily drinking over the past 90 days, the alcohol dependence scale, anxiety sensitivity index, depression anxiety stress scales, Albany phobia and panic questionnaire, social interaction anxiety scale and the Penn State Worry questionnaire. Some subject characteristic differences were noted, including that nonsmokers were older than chippers and that, unlike the gender breakdown in the anxiety literature that leans towards women, this sample was 80% male. Although there were no differences in emotional characteristics reported, there were significant differences in alcohol dependence, average drinks per drinking occasion, percent days alcohol-abstinent and highest and second-highest blood alcohol concentrations in a day. Nonsmokers reported lower alcohol symptoms as compared with daily smokers, with chippers falling between these two groups. It was unexpected that there were no differences with respect to percent heavy drinking days, and no difference in emotional characteristics. The authors suggest that these negative findings may be due to the small, mostly male sample. Despite these caveats, the data have potential treatment implications. Since smoking status is associated with differences in alcohol dependence, smoking status should be considered when treating patients with co-occurring AUD-ANX. Morissette, S.B., Gulliver, S.B., Kamholtz, B.W., Duade, J., Farchione, T., Devine, E., Brown, T.A., Barlow, D.H., and Circaulo, D. Differences Between Daily Smokers, Chippers, and Nonsmokers With Co-Occurring Anxiety and Alcohol-Use Disorders. Addictive Behav., 33, pp. 1425-1431, 2008.

Nutritional Changes Produce Significant Alterations in Dopamine Neurotransmission and Response to Dopaminergic Drugs

Since there is high co-morbidity between eating disorders and substance abuse, NIDA Grantee Dr. Charles France and colleagues investigated whether nutritional status impacts vulnerability to drug abuse as measured by dopamine neurotransmission. Rats were food restricted by being placed on a 10 g/day diet. This resulted in significant weight loss, but no change in blood glucose levels. Dopamine neurotransmission and behavior of food-restricted rats were compared to free-feeding rats. The first experiment examined the effects of food restriction on dopamine agonist (amphetamine) induced locomotion and reinforcing properties measured using conditioned place preference (CPP), and on dopamine clearance as measured by in vivo chronoamperometric recordings. Food-restriction did not affect amphetamine induced locomotion or CPP. However, it did reduce dopamine clearance, suggesting a reduction in dopamine transporter activity. Reductions in dopamine clearance were reversed by amphetamine treatment and by a return to free-feeding schedules. The second experiment examined effects of food restriction on dopamine receptor sensitivity by measuring raclopride (a dopamine antagonist) induced cataplexy and quinpirole (a dopamine agonist) induced yawning behavior. Food restriction reduced quinpirole-induced yawning and raclopride-induced catalepsy. Thus, the food-restricted rats were less sensitive to the behavioral effects of both drugs. Although animals remained

hyposensitive to these drug challenges when amphetamine was administered, normal sensitivity was restored once food-restricted rats were again provided with unrestricted access. Taken together, food restriction reduced dopamine neurotransmission, accompanied by relatively modest changes in behavioral responses to dopaminergic drugs. While the mechanisms responsible for these changes remain to be uncovered, understanding the effects of food restriction on central dopaminergic systems may identify biological risk factors for co-morbid drug abuse and eating disorders. Sevak, R.J., Koek, W., Owens, W.A., Galli, A., Daws, L.C., and France, C.P. Feeding Conditions Differentially Affect the Neurochemical and Behavioral Effects of Dopaminergic Drugs in Male Rats. Eur. J. Pharm. 592, pp. 109-115. 2008.

Deletion of the Type 1 Cannabinoid Receptor (CB1) Enhances Preference for Cocaine in Mice

NIDA-grantee Dr. Linda Dykstra and colleagues (University of North Carolina, Chapel Hill) have been examining the role of cannabinoid signaling via the CB1 receptor in the behavioral response to stressors and to drugs of abuse. In a recent report, they examined the effects of exposure to chronic unpredictable stress (CUS) in CB1 receptor knockout (CB1 KO) mice and their wild-type (WT) littermates, on cocaine conditioned place preference (CPP). Mice were either untreated or exposed to two weeks of CUS. After this period, the acquisition of cocaine CPP was examined. Untreated CB1 KO and WT mice both acquired cocaine CPP; however, exposure to CUS enhanced acquisition of cocaine CPP in the CB1 KO mice. These findings support a role for CB1 receptors in the responses to stress as well as in the subjective effects of cocaine. Miller, L.L., Ward, S. J., and Dykstra, L.A., Behav. Pharm., 19, pp. 575-581, 2008.

Peripheral Activation of Either Cannabinoid 1 and 2 Receptors (CB1 and CB2) Attenuate Mechanical Hyperalgesia in a Rat Model of Bone Cancer Pain

NIDA-grantee Dr. Donald Simone and colleagues (University of Minnesota) have been examining the ability of peripherally administered cannabinoids to attenuate tumor-evoked mechanical hyperalgesia. Unilateral injection of osteolytic fibrosarcoma cells into and around the calcaneus bone of the hind paw of rats resulted in tumor formation and mechanical hyperalgesia. WIN 55, 212-2 injected subcutaneously into the tumor-bearing hind paw produced a dose-dependent decrease in paw withdrawal to painful mechanical stimulation without measurable side effects. Administration into the contralateral paws was ineffective. Co-administration of WIN 55,212-2 with either CB1 or CB2 receptor antagonists attenuated the antihyperalgesic effects of WIN 55, 212-2. Thus, peripherally administered WIN 55,212-2 attenuated tumor-evoked mechanical hyperalgesia by activation of both peripheral CB1 and CB2 receptors, suggesting that peripherally administering cannabinoids may be an effective approach in attenuating cancer pain in humans. Potenzieri, C., Harding-Rose, C., and Simone, D.A., Brain Res., 1215, pp. 69 -75, 2008.

Two Studies Show That Calcium Calmodulin-Dependent Kinase II (Camkii) Plays a Critical Role in Drug Seeking Behavior

Two recent reports elucidate important roles for CaMKII in the long-term effects of previous exposure to psychostimulants. CaMKII has been proposed as a candidate molecule for the long-term storage of information because it can remain phosphorylated in the absence of calmodulin. In the first study, Dr. R. Chris Pierce and his colleagues used reinstatement as an animal model of relapse to cocaine seeking. They hypothesized that CaMKII is a biochemical bridge between stimulation of D1-like dopamine receptors and increases in glutamate transmission in the nucleus accumbens shell, known to

independently promote reinstatement of cocaine-seeking. To test this hypothesis, they used numerous approaches, including focal injections of agonists, antagonists, and biochemical inhibitors; viral vectors to inhibit cell-surface expression of AMPA glutamate receptors; and cross-linking followed by immunoblotting to assess surface AMPA receptor levels. They found that stimulation of D1-like receptors in the nucleus accumbens shell reinstated cocaine seeking by activating L-type calcium channels and CaMKII. Reinstatement was associated with D1-like receptor-dependent increases in phosphorylation of CaMKII and of the glutamate receptor 1, which was phosphorylated on a known CaMKII target site. In addition, there was an increase in cell-surface expression of GluR1-containing AMPA receptors in the accumbens shell, and reinstatement was attenuated by administration of a viral vector that impairs the transport of GluR1-containing AMPA receptors. The results support their hypothesis that CaMKII serves as an essential link between accumbens shell dopamine and glutamate systems involved in neuronal plasticity underlying cocaine craving and relapse. The second, complementary study from Dr. Paul Vezina's laboratory used a different animal model -- repeated exposure to amphetamine (AMPH), which enhances the ability of AMPH to produce locomotor activation and dopamine overflow in the accumbens, and also leads to enhanced AMPH self administration. In previous work, Dr. Vezina demonstrated that this enhanced behavioral and neurochemical sensitivity to AMPH is impaired by microinjecting a CaMKII inhibitor into the accumbens shell. In the current study, he investigated the effect of this inhibitor on enhanced AMPH self-administration in rats that were trained to self-administer drug on a progressive ratio (PR) schedule to measure the number of responses an animal emits to receive AMPH. Rats received either 5 injections of AMPH or saline, remained abstinent from drug for 14 days, and then were tested for self-administration with PR. Results show that the AMPH-exposed rats worked harder and obtained significantly more drug infusions than saline-exposed rats. After 4 days of stable responding, a CaMKII inhibitor was injected bilaterally into the accumbens shell just before self-administration. Inhibition of CaMKII reduced the enhanced drug intake in AMPH-exposed rats to levels no different from those of saline-exposed rats. Together, these two studies identify CaMKII, or L-type calcium channels, as potential targets for treating psychostimulant addiction. Anderson, S.M., Famous, K.R., Sadri-Vakili, G., Kumaresan, V., Schmidt, H.D., Bass, C.E., Terwilliger, E.F., Cha, J.H., and Pierce, R.C. CaMKII: A Biochemical Bridge Linking Accumbens Dopamine and Glutamate Systems in Cocaine Seeking. Nature Neuroscience, 11, pp. 344-353, 2008; Loweth, J.A., Baker, L.K., Guptaa, T., Guillory, A.M., and Vezina, P. Inhibition of CaMKII in the Nucleus Accumbens Shell Decreases Enhanced Amphetamine Intake in Sensitized Rats. Neurosci. Lett., 444, pp. 157-160, 2008.

Enhanced Methamphetamine Self-Administration in a Rat Model of Schizophrenia

The high prevalence of dual-diagnosis drug abuse and other mental disorders is well established, but the biological basis for this co-morbidity is not well understood. Animal models of mental disorders can be used to test, for example, the self medication hypothesis versus a hypothesis of shared vulnerability and etiology. Although animal models cannot capture the full spectrum of mental disorders, they can replicate some of the symptoms of these diseases. One such model is the neonatal ventral hippocampal lesion (NVHL), which reproduces several behavioral abnormalities observed in schizophrenia, including hypersensitivity to stimulants, hyperactivity, reduced social interactions, and impaired working memory. With respect to comorbidity, NVHL rats exhibit enhanced reinstatement of cocaine-seeking behavior and enhanced sensitization to cocaine and nicotine. The current study investigated drug-seeking behavior in the NVHL model by assessing methamphetamine (METH) self-administration. Rats received excitotoxic lesions of the ventral

hippocampus, or sham lesions, when they were 7 days old and were then trained as adults to self-administer METH or to respond for natural reinforcers (water or food). NVHL rats were faster than shams to learn to respond for both drug and natural rewards, but after stable responding was acquired, both groups performed similarly for the two types of reward on a fixed ratio schedule and were equally sensitive to METH dose changes. However, when tested under a progressive-ratio schedule, the NVHL animals had significantly higher break points compared to the shams for METH, but not for food reinforcement. This result suggests that the motivation of NVHL rats to acquire the drug was enhanced (they were willing to work harder for it) specifically for the drug reinforcer. The result supports the hypothesis that schizophrenia and drug abuse arise from neuropathology that confers vulnerability for both disorders, which also appear to be characterized by similar dysfunctions in corticolimbic dopamine and glutamate systems. Brady, A.M., McCallum, S.E., Glick, S.D., and O'Donnell, P. Enhanced Methamphetamine Self-administration in a Neurodevelopmental Rat Model of Schizophrenia. Psychopharm (Berlin), 200, pp. 205-215, 2008.

Deep Brain Stimulation Successfully Attenuates Reinstatement of Cocaine Self-Administration

Deep brain stimulation (DBS), originally developed as a therapy for Parkinson's disease, has recently shown promise in treating psychiatric disorders, including a case study indicating that DBS of the nucleus accumbens reduced alcohol consumption in an alcohol-dependent patient. Thus, DBS is being considered as a potential treatment in cases of extreme cocaine addiction. This study in rats was designed to examine the effect of DBS of the accumbens shell on cocaine priming-induced reinstatement of drug seeking. Rats were trained to self-administer cocaine for 21 days and then cocaine-seeking behavior was extinguished by replacing cocaine with saline. In the reinstatement phase of the study, rats were given small priming doses of cocaine. Reinstatement was assessed by number of lever presses on the lever previously associated with drug delivery (although responses during reinstatement testing do not produce a drug infusion). They also investigated several doses of cocaine used to prime reinstatement in this paradigm, (0, 5, 10 or 20 mg/kg). DBS was delivered to assess its ability to reduce the number of presses during reinstatement at different doses of cocaine priming. DBS was administered bilaterally to the accumbens shell after the priming injection. The two higher doses of cocaine both produced robust reinstatement, and DBS significantly attenuated this reinstatement of cocaine seeking at both doses. A separate experiment on animals trained to respond for sucrose pellets showed that DBS had no effect on reinstatement of food seeking. Additionally, DBS of the dorsal striatum had no effect on cocaine reinstatement. Thus, the DBS in this study was both anatomically and reinforcer specific. These results suggest that DBS of the accumbens shell could be a therapeutic option in the treatment of severe cocaine addiction. Vassoler, F.M., Schmidt, H.D., Gerard, M.E., Famous, K.R., Ciraulo, D.A., Kornetsky, C., Knapp, C.M., and Pierce, R.C. Deep Brain Stimulation of the Nucleus Accumbens Shell Attenuates Cocaine Priming-induced Reinstatement of Drug Seeking in Rats. J. Neurosci., 28, pp. 8735-8739, 2008.

Single Neurons in the Amygdala Track the Moment-to-Moment Value of the Animal's Current State

Neuroimaging studies in humans and animals have shown that the amygdala is part of a distributed neural network that functions abnormally in addiction and underlies altered decision-making, the processing of emotional information, and the experience of "craving." Dr. C.D. Salzman and his colleagues are interested in understanding how the brain encodes information about the value of an organism's current state. In ordinary language, how does the brain

monitor whether things are OK, or not OK, or sort of OK? They examined how the brain mediates this process by recording the activity of neurons in the amygdala while monkeys performed a trace-conditioning task during which the presentation of different stimuli induced state transitions. The stimuli were both unconditioned stimuli (USs) -- liquid rewards of two magnitudes, and a mildly aversive airpuff -- and visual conditioned stimuli (CSs) that signaled which US would follow. In each session, new arbitrary CSs were used. After the initial values of the CS-US associations were learned in each session, values for the large reward and the airpuff were reversed. In addition, they also monitored neural activity in response to the fixation stimulus that started the trial, which was considered to always induce a positive value state because the monkey chose when to start the trial by fixating and two thirds of the trials produced positive rewards. The complicated design and analysis of the neural responses was necessary to answer the question of whether amygdala neurons reflect the value of states induced by sensory events independent of the specific stimulus properties of the events. About half of the 145 neurons recorded in 3 monkeys showed differential responses indicating that they encoded value, with about two thirds of these encoding positive value and one third encoding negative value. Importantly, these neurons were not simply associated with rewarding vs. aversive USs and the CSs that predicted them. Rather, they showed graded responses indicating the relative value of the stimuli. As an example, a negative value neuron would be most excited by the CS predicting the airpuff and not fire much or at all when the large-reward CS was presented, but the neuron would fire a modest amount in response to the small-reward CS. This representation of state value could underlie how the amygdala helps coordinate cognitive, emotional, and behavioral responses depending on the value of an organism's state. Knowing the normal function of the amygdala will help us understand how specific alterations of the amygdala in drug abuse contribute to addiction. Belova, M.A., Paton, J.J., and Salzman, C.D. Moment-to-moment Tracking of State Value in the Amygdala. J. Neurosci., 28, pp. 10023-10030, 2008.

Allopregnanolone Decreases Cocaine-Primed Reinstatement of Cocaine-Seeking Behavior in Female But Not Male Rats

Recent studies by Marilyn Carroll, Justin Anker, Erin Larson and their colleagues at the University of Minnesota have highlighted the influence of gonadal hormones, and especially progesterone and its metabolite allopregnanolone (ALLO), on cocaine self-administration in rodent models. Using an escalation of cocaine self-administration procedure, which is commonly used to model the transition from moderate drug use to addiction, they found that progesterone prevented escalation, whereas estrogen facilitated escalation, in ovariectomized female rats, (Larson et al., 2007). They also found that progesterone has an inhibitory effect on reinstatement of cocaine-seeking behavior in females (Anker et al., 2007). In a recently published follow up to that study, they investigated the effects of both progesterone and its metabolite allopregnanolone (ALLO) on cocaine reinstatement in both females and males (Anker et al., 2008). They also tested progesterone in combination with finasteride which is a 5-alpha reductase inhibitor that prevents the metabolism of progesterone into ALLO. Following acquisition and extinction of cocaine self-administration and prior to testing of cocaine-primed reinstatement of responding, separate groups of rats were administered either ALLO, progesterone, progesterone plus finasteride, or saline. As the researchers had previously reported, progesterone suppressed cocaine reinstatement of responding (measured in a paradigm proposed to mimic human relapse); however, greater suppression was produced with ALLO. The combination of progesterone + finasteride (to inhibit progesterone's conversion to ALLO) failed to suppress reinstatement, thus suggesting that progesterone's suppressive effects may be mediated by its conversion to ALLO. In contrast to ALLO's strong suppression of reinstatement in females, ALLO

failed to suppress reinstatement in males. The authors discuss possible neurobiological mechanisms for these suppressive effects of progesterone and ALLO including their modulation of GABA-A receptors to inhibit cocaine-induced dopamine release and their interaction with the HPA-axis to dampen the stress response. The results of this study complements recent work from other NIDA-supported investigators who have shown that cocaine cue-induced craving is inversely related to circulating plasma progesterone levels in women (Sinha et al., 2007) and that experimentally administered progesterone decreases the positive subjective effects cocaine (Evans & Foltin, 2007) in women but not men. The present results are also consistent with recent preclinical NIDA-support research showing an inverse relationship between cocaine-primed reinstatement and plasma progesterone levels in freely cycling female rats across the estrous cycle (Feltenstein and See, 2007). This line of research points to the potential clinical use of progesterone, ALLO or related compounds in the treatment of cocaine use and addiction. Anker, J.J., Holz, N.A., Zlebnik, N., and Carroll, M.E. Effects of Allopregnanolone on the Reinstatement of Cocaine-Seeking Behavior in Male and Female Rats. Psychopharm. [Epub ahead of print], 2008.

Director's Report to the National Advisory Council on Drug Abuse - February, 2009

Research Findings - Behavioral and Brain Development Research

Children's Cognitive Ability from 4 to 9 years old as a Function of Prenatal Cocaine Exposure, Gender, Environmental Risk, and Maternal Verbal Intelligence

This study investigated the effects of prenatal cocaine exposure on children's cognitive ability in a large sample of 231 children (91 cocaine exposed, 140 unexposed). The children were administered the Stanford-Binet IV Intelligence test at ages 4, 6, and 9 years. The sample consisted of 120 boys and 111 girls. Gender and age were used as potential moderators of the effects of cocaine exposure. An interaction was observed between gender and prenatal exposure; cocaine-exposed boys had lower composite IQ scores. This gender-specific effect on IQ remained after controlling for covariates such as prenatal exposure to other drugs, neonatal medical risk, environmental risk and maternal verbal intelligence. Age at assessment did not moderate this relationship in that the lower IQs for boys persisted across the age period. In boys exposed to cocaine, lower scores were seen in a number of domains which included the Abstract/Visual Reasoning subscale, as well as trends in lower scores for the Short-Term Memory and Verbal Reasoning subscales of the Stanford-Binet IV. Higher composite IQ scores were also predicted by a stimulating home environment and high maternal verbal IQ. It is unclear the reasons for the gender-specific effects; however, the results are consistent with prior research that show the central nervous system in male fetuses may be more susceptible to the influence of intrauterine factors. The findings of this study highlight the importance of examining gender as a potential moderator of prenatal exposure to cocaine. Bennett, D., Bendersky, M., and Lewis, M. Children's Cognitive Ability from 4 to 9 years old as a Function of Prenatal Cocaine Exposure, Environmental Risk, and Maternal Verbal Intelligence. Developmental Psychology, 44(4), pp. 919-928, 2008.

Body Size and Intelligence in 6-year-olds Exposed to Drugs of Abuse In Utero: Are Offspring of Teenage Mothers at Risk?

Prior research has indicated that the offspring born to adolescent mothers have lower birthweight and shorter gestational age. However, little is known about growth outcomes in older children and whether cognitive deficits in the offspring of adolescent mothers can be solely attributed to young maternal age. The purpose of this study was to examine differences in size and intelligence between two cohorts of offspring born to adolescent (n = 357) and adult (n = 668) mothers enrolled in prospective longitudinal studies of prenatal substance exposure and developmental outcomes. Both cohorts were of low socio-economic status and were assessed from gestation to 6 years of age. The teen cohort was evaluated in the mid-1990s and the adult cohorts were studied

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in the mid-1980s. After adjusting for covariates, including exposure to prenatal tobacco, alcohol, and marijuana, the results indicated that the offspring of adolescent mothers scored significantly lower on the Stanford-Binet composite score, as well as the quantitative, verbal reasoning and short-term memory scores. These children of adolescent mothers also had significantly smaller head circumference and higher weight to height ratio than the offspring of adult mothers. Further studies should follow these children to determine if additional problems are detected as the offspring of adolescent mothers mature and whether early interventions such as parenting support, nutritional information and enriched home environments may be beneficial to these children. Cornelius, M., Goldschmidt, L., Willford, J., Leech, S., Larkby, C., and Day, N. Body Size and Intelligence in 6-year-olds: Are Offspring of Teenage Mothers at Risk? Maternal and Child Health Journal, Aug 6, 2008; DOI 10.1007/s10995-008-0399-0 (Epub ahead of print).

Using Umbilical Cord Tissue to Detect Fetal Exposure to Illicit Drugs

The purpose of this study was to determine the utility of using an enzyme-linked immunosorbent assay (ELISA)-based screening test to analyze drugs in umbilical cord samples. The umbilical cord tissues were collected in a multicenter study in Utah and New Jersey when high-risk criteria were met for maternal illicit drug ingestion. The deidentified umbilical cord specimens were analyzed for five drug classes: methamphetamine, opiates, cocaine, cannabinoids and phencyclidine. A total of 498 umbilical cord samples were analyzed using the ELISA, as well a 'gold standard' test, consisting of gas or liquid chromatography tandem mass spectrometry. The mass spectrometric testing revealed that thirty two percent of the umbilical cord samples were positive for drugs. The sensitivity and specificity of the ELISA-based test for each class of drugs tested were as follows: methamphetamine 97 and 97%, opiates 90 and 98%, cocaine 90 and 100%, cannabinoids 96 and 98% and phencyclidine (only 1 of the 498 umbilical cord sample was positive for phencyclidine) 100 and 100%. These results reveal that the ELISA-based tests on umbilical cord tissue are sufficient to detect fetal exposure to illicit drugs and because of the rapid send-off time, may be more suitable than meconium or hair-based methods. Montgomery, D., Plate, C., Jones, M., Jones, J., Rios, R., Lambert, D., Schumtz, N., Wiedmeier, S., Burnett, J., Ail, S., Brandel, D., Maichuck, G., Durham, C., Henry, E., and Christensen, R. Using Umbilical Cord Tissue to Detect Fetal Exposure to Illicit Drugs: A Multicenter Study in Utah and New Jersey. Journal of Perinatology, 28(11), pp. 750-753, 2008.

Pregnancy Smoking in Context: The Influence of Multiple Levels of Stress

Although smoking has steadily declined during the past 15 years, approximately 10.2% of pregnant women smoke cigarettes during pregnancy. Smoking during pregnancy is associated with numerous adverse perinatal outcomes including low birth weight, premature delivery, infant mortality and long-term behavioral sequelae. The current study utilized data from the Family Health and Development Project which is a longitudinal study that examines the effects of maternal smoking during pregnancy on infant behavioral vulnerability. The purpose of the current project was to examine predictors of persistent smoking and smoking intensity during the third trimester in a sample of 113 pregnant women with a mean age of 29.7 years. Using a single comprehensive structural equation model, latent variables comprised of indicators of stress and resources were derived for three contextual levels: intimate social context, broader social context and socioeconomic context. The results revealed that the probability of being a persistent pregnancy smoker was positively associated with a stressful socioeconomic context (probit

regression coefficient = .70, p< .05). Smoking rate was predicted by the broader social context with greater stress and fewer resources associated with a greater number of cigarettes smoked during the third trimester (standardized regression coefficient = .81, p< .05). Results suggest that pregnancy smoking may be influenced by psychosocial context at multiple levels. Elucidating the differences between pregnancy smokers and nonsmokers or quitters may inform smoking cessation and reduction interventions with this population. Weaver, K., Campbell, R., Mermelstein, R., and Wakschlag, L. Pregnancy Smoking in Context: The Influence of Multiple Levels of Stress. Nicotine & Tobacco Research, 10(6), pp. 1065-1073, 2008.

Neurodevelopmental Changes in Verbal Working Memory Load-Dependency: An fMRI Investigation

Prior behavioral research has indicated that the development of working memory (transient storage and manipulation of information) follows a protracted course of maturation reaching adult-like levels around middle adolescence. Structural changes in frontal-parietal association cortices are important for performance on working memory (WM) aptitude. Also in support of the postulated phonological loop of verbal working memory is the cerebellum whose function along with the frontal and parietal cortices, has been shown to exhibit linear WM load-dependent activation in adults. It remains unclear; however, whether WM load-dependent relationships exist for cerebro-cerebellar networks in developmental populations. The purpose of the present study was to investigate developmental changes in WM load-dependent cerebro-cerebellar activation using fMRI and a verbal Sternberg WM task. The sample consisted of 30 typically developing children, adolescents, and young adults between the ages of 7 and 28. The results demonstrated that the extent to which cerebro-cerebellar verbal working memory networks are activated in response to increasing task difficulty changes significantly between childhood and adolescence. In both adolescents and adults, increasing WM load was associated with increasing activation in frontal, parietal and cerebellar regions. In contrast, only the left ventral prefrontal cortex was recruited in response to increasing WM load in children. O'Hare, E., Lu, L., Houston, S., Bookheimer, S. and Sowell, E. Neurodevelopmental Changes in Verbal Working Memory Load-Dependency: An fMRI Investigation. Neuroimage, 42(4), pp. 1678-1685, 2008.

Environmental Stimulation, Parental Nurturance and Cognitive Development in Humans

Although animal models exist that examine the effects of environmental stimulation and parental nurturance on brain development, little is known about the relations between cognitive development and childhood experience in humans. The current project utilized a sample that consisted of 110 African American middle school-aged children (mean age 11.7 years) to identify the human counterparts of early life experience studied in animals, environmental enrichment and stress-buffering maternal behaviors. These children had been recruited at birth for a longitudinal study that examined the effects of gestational cocaine exposure utilizing ecologically valid in-home measures of childhood experience and measures of cognitive ability assessed later in the laboratory. The subjects were born of mothers receiving public assistance and were at or near term. None of the children had Fetal Alcohol Syndrome or any chromosomal disorder known to be associated with developmental delay. The analyses conducted indicated that there was a relationship between parental nurturance and memory development which is in agreement with the animal literature on maternal buffering of stress hormone effects on hippocampal development. However, language development was shown to selectively relate to environmental stimulation and not to parental nurturance. Although it is uncertain whether the results obtained with this sample would generalize to children of a different ethnicity or socioeconomic background, the findings

provide a strong scientific incentive to better understand the complex relations among socioeconomic class, life experience and cognitive development. Farah, M., Betancourt L., Shera, D., Savage J., Giannetta J., Brodsky N., Malmud, E., and Hurt H. Environmental Stimulation, Parental Nurturance and Cognitive Development in Humans. Developmental Science, 11(5), pp. 793-801, 2008.

Neighborhood Disorganization, Substance Use, and Violence Among Adolescents in Puerto Rico

The current project utilized data from a larger longitudinal project which was designed to examine risk and resilience to HIV/AIDS in adolescents' ages 12 to 15 years in San Juan, Puerto Rico. The purpose of the current study was to determine how neighborhoods influence adolescent violence in poor communities. Using a cross-sectional design, the incidence of violent behaviors among participants was obtained via a self-completed questionnaire, as well as an interviewer questionnaire. Demographics, characteristics and neighborhood social disorganization using the concepts of both physical disorders (i.e. environmental deterioration of urban landscapes) and social disorders (threatening behaviors by individuals in social spaces) were utilized. The results indicated that social disorder in the neighborhood was positively associated with adolescent violence. The display of adult violence may lead adolescents to view violence as an accepted behavior. It is also possible that social support and resources are limited in socially disorganized neighborhoods which might lead to the failure to organize on their own behalf. Reyes, J., Robles, R., Colon, H., Negron, J., Matos, T., Calderon, J., and Perez, O. Neighborhood Disorganization, Substance Use, and Violence Among Adolescents in Puerto Rico. Journal of Interpersonal Violence, 23(11), pp. 1499-1512, November, 2008.

Towards an Explanation of Subjective Ketamine Experiences among Young Injection Drug Users

This study explored factors that shape or influence the reported subjective experiences of the drug ketamine which has powerful sedative and hallucinogenic properties. The data were collected as part of a study examining health risks associated with injecting ketamine. Two hundred and thirteen injection drug users between the ages of 16 and 29 years of age who had injected ketamine at least once within the past two years were recruited from New York, Los Angeles and New Orleans between 2004 and 2006. In depth interviews were conducted that focused on specific ketamine events such as first injection of ketamine, most recent injection of ketamine and most recent experience sniffing ketamine. The results of these interviews revealed that both positive and negative subjective experiences during any given ketamine event were shaped by two or more of the following six factors: polydrug use, drug using history, mode of administration, quantity and quality of ketamine, user group, and setting. Subjective ketamine experiences were also influenced by a lifestyle characterized by homelessness and traveling. Although these findings may not generalize to all ketamine users, the model used in this study may inform future studies seeking to examine the subjective experiences on ketamine or other drug use. Lankenau, S., Sanders, B., Bloom, J., and Hathazi, D. Towards an Explanation of Subjective Ketamine Experiences among Young Injection Drug Users. Addiction Research and Theory, 16(3), pp. 273-287, 2008.

The Effects of Low Literacy and Cognitive Impairment on Medication Adherence in HIV-Positive Injecting Drug Users

This study utilized two factors (low literacy and cognitive impairment) in combination to examine the effects on non-adherence to medications for

HIV/AIDS. The sample included 57 HIV-positive injecting drug users who were community-recruited. Performance on a reading test and a brief neuropsychological battery classified the participants into one of four groups: high literacy/high cognition, low literacy/high cognition, high literacy/low cognition and low literacy/low cognition. The results obtained from chi-square and bivariate analyses characterized the literacy and cognitive skills of the overall sample. After controlling for recent cocaine use, the relationship of the four groups to non-adherence (<95%) was tested using a logistic regression analysis. Severe deficits were noted in psychomotor functioning and performance on measures of literacy and cognitive functioning were below average. Those individuals who were classified as low literate/low cognition were nine times more likely to be non-adherent than the referent high literate/high cognition group. The findings from this study suggest that interventions designed to improve cognitive deficits in drug users diagnosed with HIV would help to improve adherence to HIV medications. Waldrop-Valverde, D., Jones, D., Weiss, S., Kumar, M., and Metsch, L. The Effects of Low Literacy and Cognitive Impairment on Medication Adherence in HIV-Positive Injecting Drug Users. AIDS Care, 20(10), pp. 1202-1210, 2008.

Director's Report to the National Advisory Council on Drug Abuse - February, 2009

Research Findings - Clinical Neuroscience Research

Cortical Recruitment by The Stroop Task at Baseline is Predictive of Abstinence Following Treatment for Cocaine Addiction

Dr. M. Potenza and colleagues at Yale University administered the Stroop task to cocaine-dependent patients during functional magnetic resonance imaging at treatment baseline. During Stroop performance, individuals activated brain regions similar to those reported in nonaddicted individuals, including the anterior cingulate cortex, dorsolateral prefrontal cortex, parietal lobule, insula, and striatum. Longer duration of self-reported abstinence at follow-up correlated with activation of ventromedial prefrontal cortex, left posterior cingulate cortex, and right striatum; percent drug-free urine screens correlated with striatal activation; and treatment retention correlated with diminished activation of dorsolateral prefrontal cortex. A modest correlation between Stroop effect and treatment retention was found. These findings implicate neurocircuitry underlying cognitive control in behavioral treatment outcome and provide insight into the mechanisms of behavioral therapies for cocaine dependence. They also suggest that neural activation patterns during cognitive control tasks are more sensitive predictors of treatment response than behavioral measures. Brewer, J.A., Worhunsky, P.D., Carroll, K.M., Rounsaville, B.J., and Potenza, M.N. Pretreatment Brain Activation During Stroop Task is Associated With Outcomes in Cocaine-Dependent Patients. Biological Psychiatry, 64(11), pp. 998-1004, 2008.

Recovery of Brain Glutamate/Glutamine during Abstinence from Chronic Methamphetamine Use

Dr. Linda Chang and colleagues at the University of Hawaii used proton magnetic resonance spectroscopy (MRS) to asses alterations in the glutamatergic system altered following prolonged methamphetamine (METH) exposure. While overall glutamine concentrations at baseline were similar between METH and control subjects, glutamine concentrations correlated positively with time of abstinence of METH in frontal gray and white matter. Reduced glutamine concentrations in frontal gray matter during early abstinence of METH recovered by the second month and showed a trend of compensatory increase after the fifth month. Subjects with craving symptoms had lower frontal gray matter glutamine than those without craving. These findings suggest dynamic abnormalities in brain glutamine in recently abstinent METH users, with depletion of the glutamatergic system in METH users within the first 2 months of abstinence followed by partial normalization during prolonged abstinence. Ernst, T., and Chang, L. Adaptation of Brain Glutamate Plus Glutamine during Abstinence from Chronic Methamphetamine Use. Journal of Neuroimmune Pharmacology, 3(3), pp. 1157-1890, 2008.

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Frontocortical Glucose Metabolism in Methamphetamine Abusers Improves with Abstinence and Correlates with Cognitive Task Improvement

Dr. E. London and colleagues at UCLA used positron emission tomography with [F-18]fluorodeoxyglucose (FDG) to quantify regional cerebral glucose metabolism, an index of brain function, during performance of a vigilance task. A total of 10 methamphetamine-dependent subjects were tested after 5-9 days of abstinence, and after 4 additional weeks of supervised abstinence. A total of 12 healthy control subjects were tested at corresponding times. Global glucose metabolism increased between tests (P=0.01), more in methamphetamine-dependent (10.9%, P=0.02) than in control subjects (1.9%, NS). Glucose metabolism did not change in subcortical regions of methamphetamine-dependent subjects, but increased in neocortex, with maximal increase (>20%) in parietal regions. Changes in reaction time and self-reports of negative affect varied more in methamphetamine-dependent than in control subjects, and correlated both with the increase in parietal glucose metabolism, and decrease in relative activity (after scaling to the global mean) in some regions. Berman, S.M., Voytek, B., Mandelkern, M.A., Hassid, B.D., Isaacson, A., Monterosso, J., Miotto, K., Ling, W., and London, E.D. Changes in Cerebral Glucose Metabolism During Early Abstinence From Chronic Methamphetamine Abuse. Molecular Psychiatry, 13(9), pp. 897-908, 2008.

Changes in Regional Blood Volume During a 28-Day Period of Abstinence in Chronic Cannabis Smokers

Dr. J. Sneider and colleagues at McLean Hospital used dynamic susceptibility contrast MRI (DSCMRI) to determine changes in regional blood volume in the frontal and temporal lobe, and the cerebellum during 28 days of supervised abstinence from cannabis in 15 current, long-term cannabis users. DSCMRI scans were obtained between 6 and 36 h after the subjects' last reported cannabis use (Day 0), and again after 7 and 28 days of abstinence. Resting state CBV images were also acquired on 17 healthy comparison subjects. The present findings demonstrate that at Day 7, cannabis users continued to display increased blood volumes in the right frontal region, the left and right temporal regions, and the cerebellum. However, after 28 days of abstinence, only the left temporal area and cerebellum showed significantly increased CBV values in cannabis users. These findings suggest that while CBV levels begin to normalize with continued abstinence from cannabis, specifically in frontal areas, other temporal and cerebellar brain regions show slower CBV decreases. Sneider, J., Pope, H., Silveri, M., Simpson, N., Gruber, S., and Yurgelun-Todd, D. Differences in Regional Blood Volume During a 28-Day Period of Abstinence in Chronic Cannabis Smokers. European Neuropsychopharmacology, 18(8), pp. 612-619, 2008.

HIV-Associated Deficits in Complex Motor Skills, but not in Procedural Learning Associated with the Performance

Dr. E. Martin and colleagues at the University of. Illinois, Chicago, compared performance across multiple trial blocks of three procedural learning tasks: rotary pursuit, mirror star tracing, and weather prediction. Previous results from this group found HIV+ individuals had a poorer performance on retrospective memory and time-based but not event-based prospective memory. The current study compared HIV seropositive and HIV seronegative participants with history of cocaine and/or heroin dependence who were abstinent from drugs at the time of study and who were well matched on demographic, psychiatric, and substance use parameters. Individuals in the HIV+ group tended to perform worse than those in the HIV- group across all trial blocks of procedural learning tasks with motor demands, especially in the

mirror star tracing task. The rate of improvement of the performance however, was not affected across all three procedural learning tasks. These findings support the observation of HIV-associated deficits in complex motor skills, but not in procedural learning. No associations were evident between serostatus and any of the procedural learning tasks. Gonzalez, R., Jacobus, J., Amatya, A.K., Quartana, P.J., Vassileva, J., and Martin, E.M. Deficits in Complex Motor Functions, Despite no Evidence of Procedural Learning Deficits, among HIV+ Individuals with History of Substance Dependence. Neuropsychology, 22(6), pp. 776-786, 2008.

More Pronounced Changes in Brain Metabolite Indices and Correlation with Mild Cognitive Impairment in HIV+ Individuals

Dr. Robert Paul of the University of Missouri along with the HIV MRS consortium and ACTG 700 team examined relationships between cognitive function, magnetic resonance spectroscopy brain metabolite indices in the basal ganglia, and anatomical magnetic resonance imaging of the caudate nucleus and the putamen in the earliest stages of HIV-related cognitive involvement. HIV+ individuals had poorer performance on several cognitive measures, which were associated with significantly higher choline/creatine ratios and significantly lower N-acetyl aspartate/choline ratios. Although caudate and putamen sizes of HIV+ individuals were smaller, there was no statistical difference from the HIV- subjects. Caudate size was significantly correlated with performances on higher-order thinking tests whereas the putamen size was significantly correlated with performances on motor tests. The results suggest that change in the size of basal ganglia is an important contributor to cognitive status in this population, and that changes in MRS measures are more pronounced than alterations in the size of brain region in mild stages of HIV-related cognitive impairment. Paul, R.H., Ernst, T., Brickman, A.M., Yiannoutsos, C.T., Tate, D.F., Cohen, R.A., and Navia, B.A.; ACTG 301 team; ACTG 700 team; and HIV MRS Consortium. Relative Sensitivity of Magnetic Resonance Spectroscopy and Quantitative Magnetic Resonance Imaging to Cognitive Function among Nondemented Individuals Infected with HIV. J. Intern. Neuropsychological Society, 14(5), pp. 725-733, 2008.

Brain Imaging Evidence of Persistent Disease Progression Correlated with Declined Global Deficit Score of HIV Patients at One Year Follow-up

Dr. Linda Chang and colleagues at the University of Hawaii used Diffusion Tensor Imaging (DTI) MRI to investigate whether there are temporal, greater than normal age-related brain inflammatory changes in HIV patients one year after the infection. Post mortem neuropathological data has previously found ongoing neuron inflammation and premature neurodegeneration in HAART treated drug abusers, indicating HAART does not prevent HIV-associated brain damage. In addition, HIV+ patients exhibit an on-going decline in global cognitive deficit scores relative to the initial evaluation compared to stable cognitive performance seen in HIV- subjects. Using DTI, clinically and cognitively stable HIV+ patients exhibited degradation of the microstructure of white matter underlying the frontal and parietal cortex and genu of the corpus collosum, as well as in putamen. DTI is thought to index neuroinflammation associated with ongoing HIV infection since greater increases in mean diffusivity and decreases in fractional anisotropy are associated with elevation of an inflammatory chemokine, macrophage chemoattractant protein-1. These results are similar to studies in patients with multiple sclerosis or with head trauma where correlations existed between cognitive function and diffusion measures. The changes in the brain diffusion within the 1-year follow-up period were observed without accompanying greater changes on the global deficit score. It suggests that DTI can be more sensitive than global cognitive

measures and may serve as objective surrogate markers for early detection of disease progression in HIV brain infection. Chang, L., Wong, V., Nakama, H., Watters, M., Ramones, D., Miller, E.N., Cloak, C., and Ernst, T. Greater Than Age-related Changes in Brain Diffusion of HIV Patients After 1 Year. J. Neuroimmune Pharm. 3(4), pp. 265-274, 2008.

Decreased Brain Dopamine Transporters Related to Cognitive Deficits in HIV Patients with or without Cocaine Abuse

Dr. Linda Chang and colleagues at the University of Hawaii combined PET ligand imaging and neuropsychological testing to assess how HIV status affects the relationship between striatal dopamine transporter (DAT) and dopamine D2 receptors (D2R) availability and cognitive performance. Compared to seronegative controls, all HIV subjects had lower DAT in putamen but only HIV+ subjects with a history of cocaine dependence showed lower DAT in caudate. Lower D2R in both regions of all HIV+ subjects was accounted for by the greater nicotine use. Lower DAT, but not D2R, in putamen and caudate were associated with poorer performance on several neuropsychological tests, corrected for the effects of age, education, intelligence, mood, and nicotine use. In addition, lower average dopamine function (both DAT and D2R) was related to poorer overall function on neuropsychological tests. The study suggested that reduced dopaminergic function may contribute to cognitive dysfunction in HIV patients with or without additional cocaine abuse. Chang, L., Wang, G.J., Volkow, N.D., Ernst, T., Telang, F., Logan, J., and Fowler, J.S. Decreased Brain Dopamine Transporters are Related to Cognitive Deficits in HIV Patients with or without Cocaine Abuse. Neuroimage, 42(2), pp. 869-878, 2008.

Sociocultural Specificity in the Neurocognitive Effects of HIV as Evidenced in Hispanics

Susan Morgello of New York University and colleagues, using resources of the NIDA-funded Manhattan HIV Brain Bank, characterized neuropsychological (NP) test performance of HIV+ English-speaking Hispanic participants (n = 51) and investigated the combined roles of sociocultural factors (e.g., ethnicity, socioeconomic status [SES] proxy, and reading level) on NP test performance among HIV+ Hispanic and non-Hispanic White participants (n = 49). Hispanic individuals in the U.S. have been disproportionately impacted by HIV/AIDS, yet little is known regarding the neuropsychological sequelae of HIV within the Hispanic population. The pattern of NP impairment in HIV+ Hispanic participants was consistent with the frontal-striatal pattern observed in HIV-associated CNS sequelae, and the overall prevalence of global NP impairment was high compared to previous reports with more ethnically homogeneous, non-Hispanic White cohorts. Multivariate prediction models that considered both sociocultural factors and CD4 count revealed that reading level was the only unique predictor of global NP functioning, learning, and attention/working memory. In contrast, ethnicity was the only unique predictor of abstraction/ executive functioning. This study provides support for the use of neuropsychological evaluation in detecting HIV-associated NP impairment among HIV+ Hispanic participants and adds to the growing literature regarding the importance of considering sociocultural factors in the interpretation of NP test performance. Mindt, M.R., Byrd, D., Ryan, E.L., Robbins, R., Monzones, J., Arentoft, A., Germano, K.K., Morgello, S., and Henniger, D.E. Characterization and Sociocultural Predictors of Neuropsychological Test Performance in HIV+ Hispanic Individuals. Cultural Diversity & Ethnic Minority Psychology, 14(4), pp. 315-325, 2008.

Genotype Patterns are Shown to Contribute to Increased Risk for, or Protection from, Developing Heroin Addiction

M.J. Kreek and colleagues at Rockefeller University did a genome-wide association study in former severe heroin addicts and matched controls (all of Caucasian ancestry) and found several autosomal variants showing strong association with heroin addiction by genotype frequency analysis. They analyzed gene patterns (rather than haplotypes) and found one pattern using strong risk alleles had an odds ratio of 6.25 that explained 27% of the population attributable risk for heroin addiction in their cohort. Another pattern of the same variants was found to be significantly associated with protection from developing heroin addiction with an odds ratio of 0.13 where lacking this genotype pattern explained 83% of the population attributable risk for developing heroin addiction. This approach has identified several new genes potentially associated with heroin addiction. Nielsen, D.A., Ji, F., Yuferov, V., Ho, A., Chen, A. Levran, O., Ott, J., and Kreek, M.J. Genotype Patterns that Contribute to Increased Risk for or Protection from Developing Heroin Addiction. Mol. Psych., 13, pp. 417-428, 2008.

Genetic Variation in Human NPY Expression Affects Stress Response and Emotion

A collaboration among several NIDA researchers, principally J. K. Zubieta, R. Sinha, and D. Mash, among others and their colleagues, describe convergent evidence that haplotype-driven NPY expression predicts brain response to emotional and stress challenges. Using post-mortem tissue differential expression of mRNA was observed for four haplotypes: two with low expression, one with high expression, and one intermediate; diplotypes (i.e., made up of homozygous or heterozygous alleles) divided into three expression groups. Results demonstrated 1) using fMRI in a threat-related facial expression paradigm, amygdala activation in individuals with low NPY expression diplotype was higher than in those with the high expression; reactivity was predicted in a allele-dosage fashion; 2) using PET to determine the availability of mu-opioid receptors during application of a painful stressor, highly expressed NPY diplotypes predicted significantly higher levels of stress-induced mu-opioid system activation in prefrontal cortex, posterior insula, medial and lateral thalamus, ventral basal ganglia and amygdala; 3) using the TPQ (personality questionnaire), NPY expression was inversely correlated with trait anxiety. These results are consistent with the function of NPY as an anxiolytic peptide and help to explain inter-individual variation in resiliency to stress. Zhou, Z., Zhu, G., Hariri, A.R., Enoch, M.A., Scott, D., Sinha, R., Virkkunen, M., Mash, D.C., Lipsky, R.H., Hu, X.-Z, Hodgkinson, C.A., Ku, K., Buzas, B., Yuan, Q., Shen, P.H., Ferrell, R.E., Manuck, S.B., Brown, S.M., Hauger, R.L., Stohler, C.S., Zubieta, J.Z. and Goldman, D. Genetic Variation in Human NPY Expression Effects Stress Response and Emotion. Nature, 452, pp. 997-1002, 2008.

Brain MAO A Activity but not Genotype Variation Predicts Trait Aggression

Drs. R. Goldstein, N. Alia-Klein and colleagues at Brookhaven National Laboratory investigated whether MAO A activity regardless of genotypes differing the number of tandem repeats is related to personality measures assessed with the MPQ. Using PET, significant correlations were found with aggression for several cortical (temporal, occipital, percuneus, and medial PFC) and subcortical (caudate, putamen, amygdala, and thalamus) brain regions for individuals who had either high or low numbers of tandem repeats upstream of the coding region. No other personality measure assessed with the self-report instrument was correlated. To the extent that this aggression is associated with psychopathology including drug abuse makes MAO A activity a target for treatment. Alia-Klein, N., Goldstein, R.Z., Kriplani, A., Logan, J., Tomasi, D., Williams, B., Teland, F., Shumay, E., Biegon, A. Craig, I.W., Henn, F., Wang,

G.-J., Volkow, N.D., and Fowler, J.S. Brain Monoamine Oxidase A Activity Predicts Trait Aggression. Journal of Neuroscience, 28(19), pp. 5099-5104, 2008.

Behavioral and Neurochemical Changes Induced by Oxycodone Differ between Adolescent and Adult Mice

Dr. Y. Zhang in the laboratory of M.J. Kreek at Rockefeller University compared the behavioral and striatal dopamine alterations between adolescent and adult mice after taking oxycodone. Oxycodone is a prescription drug which has seen increased nonmedical use of late. The results demonstrated that pre-exposure to oxycodone during adolescence enhances the ability of oxycodone to increase striatal dopamine levels relative to adult exposure. Assays demonstrated that exposure during adolescence resulted in long-lasting alterations in the nigrostriatal dopamine system, possibly due to over-expression of dopamine receptors and/or enhancement in mu-opioid receptor function. The implication for teenagers is that they may be differentially sensitive to the reinforcing and neurobiological effects thereby encouraging increased use as adults. In other words, teenagers taking the drug for nonprescription use may be at higher risk when becoming adults. Zhang, Y., Picetti, R., Butelman, E.R., Schlussman, S.D., Ho, A., and Kreek, M.J. Behavioral and Neurochemical Changes Induced by Oxycodone Differ between Adolescent and Adult Mice. Neuropsychopharmacology, Sep 10, 2008 [Epub ahead of print; PMID: 18784649; DOI: 10.1038/npp.2008.134].

Limited Abuse-like Effects of Therapeutic Zolpidem in Drug-naive Females: a Pilot Study

Dr. S. Licata and colleagues at the McLean Hospital/Harvard Medical School conducted a double-blind, placebo-controlled, cross over pilot study to investigate the subjective effects of zolpidem (10 mg) in drug-naive females. Over the course of a 5-h period vital signs were monitored and a series of computerized questionnaires was administered. Results indicate that zolpidem engendered subjective effects characteristic of hypnotic drugs, but reduced ratings of drug liking, willing to take again, and willing to pay for, relative to placebo. Thus, a therapeutic dose of zolpidem may have limited potential for misuse among females who have no experience with drugs of abuse. Licata, S.C., Penetar, D.M., Dunlap, S., and Lukas, S.E. A Therapeutic Dose of Zolpidem has Limited Abuse-like Effects in Drug-Naive Females: A Pilot Study. European Journal of Pharmacology, 598(1-3), pp. 64-67, 2008.

Comparison of Methods for Quantification of Self-Reported Caffeine Use

Ms. M. Addicott (a predoctoral candidate) and colleagues, at the Wake Forest University School of Medicine, compared two methods for self-reported caffeine use. The first was a retrospective interview of weekly caffeine use and a 7-day prospective diary. The second was salivary caffeine concentrations in a subset of participants. The estimates of caffeine use (mg/day) from the interview- and diary-based methods correlated with one another ($r = 0.77$) and with salivary caffeine concentrations ($r = 0.61$ and 0.68, respectively). However, almost half of the subjects who reported more than 600 mg/day in the interview reported significantly less caffeine use in the diary. Self-report measures of caffeine use are a valid method of predicting actual caffeine levels. Estimates of high caffeine use levels may need to be corroborated by more than one method. Addicott, M.A., Yang, L.L., Peiffer, A.M., and Laurienti, P.J. Methodological Considerations for the Quantification of Self-Reported Caffeine Use. Psychopharmacology (Berl), 2008 Nov 15 [Epub ahead of print; PMID: 19011837; DOI: 10.1007/s00213-008-1403-5].

Brain Mechanisms of Regulation of Reward Expectancy

Dr. M. Delgado and colleagues at Rutgers University and New York University used fMRI to see if emotion regulation strategies can also efficiently regulate expectations of reward arising from conditioned stimuli. Using a monetary reward-conditioning procedure with cognitive strategies in healthy human volunteers, they observed attenuation in both the physiological (skin conductance) and neural correlates (striatum) of reward expectation as participants engaged in emotion regulation. These findings provide a potential brain basis for studying how cognitive and behavioral therapeutic approaches can lead to increased control by drug abusers of craving and other drug-related expectancies. Delgado, M.R., Gillis, M.M., and Phelps, E.A. Regulating the Expectation of Reward Via Cognitive Strategies. Nature Neuroscience, 11(8), pp. 880-881, 2008.

Frequent Users of Cannabis Exhibit Blunted Psychotomimetic and Amnestics Effects During Acute THC Administration

Dr. C. D'Souza and colleagues at Yale School of Medicine sought to determine whether people who frequently use cannabis are either protected from or are tolerant to the effects of Delta-9-THC, the main psychoactive compound in cannabis. 30 frequent users of cannabis and 22 comparison subjects (infrequent cannabis users) were administered Delta-9-THC (0, 2.5, and 5 mg, i.v.) using a double-blind, randomized, placebo-controlled design. THC (1) produced transient psychotomimetic effects and perceptual alterations; (2) impaired memory and attention; (3) increased subjective effects of 'high'; (4) produced tachycardia; and (5) increased serum cortisol in both groups. However, frequent users showed blunted responses to the psychotomimetic, perceptual altering, cognitive impairing, anxiogenic, and cortisol increasing effects of Delta-9-THC but not to its euphoric effects. These data suggest that frequent users of cannabis are either inherently blunted in their response to, and/or develop tolerance to the many effects of cannabinoids. D'Souza, D.C., Ranganathan, M., Braley, G., Gueorguieva, R., Zimolo, Z., Cooper, T., Perry, E., and Krystal, J. Blunted Psychotomimetic and Amnestic Effects of Delta-9-Tetrahydrocannabinol in Frequent Users of Cannabis. Neuropsychopharmacology, 33(10), pp. 2505-2516, 2008.

DAT Genotype Modulation of Brain and Behavioral Responses To Cigarette Cues

Dr. T. Franklin and colleagues at the University of Pennsylvania combined fMRI brain imaging with a candidate gene approach to investigate the basis of the considerable individual variability in brain and subjective responses to cigarette cues observed in previous studies. As dopamine (DA) is critical for reward and its predictive signals, genetically driven variation in DA transmission may account for the observed differences. They hypothesized that brain and behavioral responses may be enhanced in probands carrying the 9-repeat allele of the DA transporter (DAT) SLC6A3 gene. Perfusion fMRI images were acquired during cue exposure in 19 smokers genotyped for the 40 base pair variable tandem repeat number polymorphism in the SLC6A3 gene. Contrasts between groups revealed that 9-repeat (9-repeats) had a greater response to smoking (vs nonsmoking) cues than smokers homozygous for the 10-repeat allele (10/10-repeats) in the interconnected ventral striatal/pallidal/orbitofrontal cortex regions (bilateral VS/VP/OFC). Activity was increased in 9-repeats and decreased in 10/10-repeats in the VS/VP/OFC. Brain activity and craving was strongly correlated (r-squared of 0.79-0.86) in 10/10-repeats in these regions and others (anterior cingulate, parahippocampal gyrus, and insula). Strikingly, there were no significant correlations between brain and behavior in 9-repeats. There were no differences in cigarette

dependence, demographics, or resting baseline neural activity between groups. These results provide evidence that genetic variation in the DAT gene contributes to the neural and behavioral responses elicited by smoking cues. Franklin, T.R., Lohoff, F.W., Wang, Z., Sciortino, N., Harper, D., Li, Y., Jens, W., Cruz, J., Kampman, K., Ehrman, R., Berrettini, W., Detre, J.A, O'Brien, C.P., and Childress, A.R. DAT Genotype Modulates Brain and Behavioral Responses Elicited by Cigarette Cues. Neuropsychopharmacology advance online publication, 13 August 2008; doi:10.1038/npp.2008.124].

Compromised Sensitivity to Monetary Reward in Current Cocaine Users: An ERP Study

Dr. R. Goldstein and colleagues at Brookhaven National Laboratories studied modulation of the P300 by monetary reward expected to be received on a sustained attention task in 18 individuals with current cocaine use disorders (CUD) and 18 control subjects. Results in the controls revealed sensitivity to changes in monetary outcomes as indexed by P300 amplitude and speed of behavioral response. Furthermore, these measures were intercorrelated. In contrast, despite generally faster P300 waveforms and higher self-reported interest in the task, individuals with CUD did not display changes in responses to money versus nonreward; at the behavioral level, this impairment correlated with frequency of recent cocaine use. These preliminary results suggest a compromised sensitivity to a secondary reinforcer in CUD. This deficit may underlie the compromised ability to advantageously modify behavior in response to changing inner motivations and environmental contingencies. Goldstein, R., Parvaz, M., Maloney, T., Alia-Klein, N., Woicik, P., Telang, F., Wang, G., and Volkow, N. Compromised Sensitivity to Monetary Reward in Current Cocaine Users: An ERP Study. Psychophysiology, 45(5), pp. 705-713, 2008.

Behavioral and Electrophysiological Evidence for Attentional Deficits in Cocaine Abusers

Dr. N. Boutros and colleagues at Wayne State University used behavioral and evoked potential to study attentional performance of cocaine-dependent patients (n=14) compared to healthy control individuals (n=15). Attention was assessed using an auditory oddball event-related task as well as the Continuous Performance Test (CPT, Identical Pairs version). The cocaine-dependent group displayed P300 amplitude reduction compared to controls, but there were no group differences in P300 response latency. The cocaine-dependent patients displayed significantly poorer discriminability and greater errors of commission than the controls. There was a positive correlation between performance on the oddball event-related task and performance on the CPT. This investigation provides converging behavioral and electrophysiological evidence of attentional deficits in cocaine-dependent patients. Gooding, D.C., Burroughs, S. and Boutros, N.N. Attentional Deficits in Cocaine-Dependent Patients: Converging Behavioral and Electrophysiological Evidence. Psychiatry Research, 160(2), pp. 145-154, 2008.

Heavy Smoking is Not a Potential Confound in the fMRI BOLD Responses

In a multi-site study, Dr. L. Leyba and colleagues investigated whether the vascular effects of heavier long-term cigarette use is a confound in fMRI BOLD signals. The blood oxygen level dependent (BOLD) response to a simple sensorimotor task was compared between schizophrenia patients with a smoking history (mean 17 pack years) and carefully matched patient non-smokers and control non-smokers. Group differences in activation magnitude and spatial extent were non-significant. Therefore, typical smoking histories in

schizophrenia patients do not significantly confound fMRI results in simple sensorimotor tasks when patient demographics are carefully controlled. Leyba, L., Mayer, A.R., Gollub, R.L., Andreasen, N.C., and Clark, V.P. Smoking Status as a Potential Confound in the BOLD Response of Patients with Schizophrenia. Schizophrenia Research, 104(1-3), pp. 79-84, 2008.

Gender Related Differences in Subjective Responses and Cardiovascular Effects of Self-Administered Cocaine

Dr. R. Malison and colleagues at Yale School of Medicine examined gender differences in cocaine self-administration and cocaine-induced subjective and cardiovascular measures. Subjects (21 men, 10 women) self-administered cocaine infusions (8, 16 and 32 mg/70 kg) over a 2-hour period under a fixed ratio 1, 5 minute time out schedule in three test sessions. All subjects had a history of either cocaine abuse or dependence and were not currently seeking treatment. Women and men self-administered similar amounts of cocaine. None of the subjective effects measures showed a significant main effect of sex during the cocaine self-administration session. Significant interactions were observed for subjective ratings of 'high' (sex x time) and 'stimulated' (sex x time x dose), with women reporting lower ratings over time/doses than men. Relative to men, cocaine produced dose- and time-dependent increases in feelings of hunger (i.e., reduced appetite suppression) in women. Systolic and diastolic blood pressures showed different patterns of change in men and women, with women showing less robust cocaine-induced increases than men. Taken together, these findings indicate that women and men differ in their subjective and cardiovascular responses to self-administered cocaine. Lynch, W.J., Kalayasiri, R., Sughondhabirom, A., Pittman, B., Coric, V., Morgan, P.T., and Malison, R.T. Subjective Responses and Cardiovascular Effects of Self-Administered Cocaine in Cocaine-Abusing Men and Women. Addiction Biology, 13(3-4), pp. 403-410, 2008.

Error-Specific Medial Cortical and Subcortical Activity During the Stop Signal Task

Dr. R. Li and colleagues at Yale School of Medicine used fMRI in healthy volunteers to investigate how the brain uses error signals specifically to adjust behavior on a moment to moment basis. Subjects performed a version of stop signal task (SST) that was adjusted to elicit errors approximately half of the time in high-conflict trials despite constant behavioral adjustment of the observers. Greater and, sequentially, less activation in the medial cortical regions were observed when observers made an error, compared with when they successfully resolved high-conflict responses. Errors also evoked greater activity in the cuneus, retrosplenial cortex, insula, and subcortical structures including the thalamus and the region of the epithalamus (the habenula). However, error-related medial cortical activities were not correlated with post-error behavioral adjustment, as indexed by post-error slowing (PES) in go trial reaction time. These results delineated an error-specific pattern of brain activation during the SST and suggest that the relationship between error-related activity and post-error behavioral adjustment may be more complicated than proposed in current conceptual frameworks. Li, C.R., Yan, P., Chao, H.H., Sinha, R., Paliwal, P., Constable, R.T., Zhang, S., and Lee, T. Error-Specific Medial Cortical and Subcortical Activity During the Stop Signal Task: A Functional Magnetic Resonance Imaging Study. Neuroscience, 155(4), pp. 1142-1151, 2008.

Different Cortical Thickness Abnormalities in Cocaine Addiction Are Related to Behavioral Performance and Drug Use

Dr. H. Brieiter and colleagues at Massachusetts General Hospital used

advanced morphometric methods to compare the thickness of neocortical and paralimbic brain regions between cocaine-dependent and matched control subjects. Four of 18 a priori regions involved with executive regulation of reward and attention were significantly thinner in addicts. Correlations were significant between thinner prefrontal cortex and reduced key-presses during judgment and decision making of relative preference in addicts, suggesting one basis for restricted behavioral repertoires in drug dependence. Reduced effortful attention performance in addicts also correlated with thinner paralimbic cortices. Some thickness differences in addicts were correlated with cocaine use independent of nicotine and alcohol, but addicts also showed diminished thickness heterogeneity and altered hemispheric thickness asymmetry. These observations suggest that brain structure abnormalities in addicts are related in part to drug use and in part to predisposition toward addiction. Makris, N., Gasic, G., Kennedy, D., Hodge, S., Kaiser, J., Lee, M., Kim, Y. Blood, A., Evins, A., Seidman, L., Iosifescu, D., Lee, S., Baxter, C., Perlis, R., Smoller, J., Fava, M., and Breiter, H. Cortical Thickness Abnormalities in Cocaine Addiction-A Reflection of Both Drug Use and a Pre-Existing Disposition to Drug Abuse? Neuron, 60(1), pp. 174-188, 2008.

Abstinent MDMA ("Ecstasy") Users Exhibit Alterations in Serotonin Transporters that are Related to Cognitive Performance but Not to Changes in Dopamine Transporters

Dr. U. McCann and colleagues at Johns Hopkins University used PET ligand binding brain imaging to determine whether MDMA users exhibit reductions in DA transporter (DAT), in addition to previously demonstrated serotonin transporter (SERT) reductions, and whether there is a relationship between transporter binding and cognitive performance. Of particular interest were MDMA users who take closely spaced sequential doses, which engender high plasma MDMA concentrations. Sixteen abstinent MDMA users with a history of using sequential MDMA doses (two or more doses over a 3- to 12-h period) and 16 age-, gender-, and education-matched controls participated. Subjects underwent positron emission tomography with the DAT and SERT radioligands, [11C]WIN 35,428 and [11C]DASB, respectively. Subjects also underwent formal neuropsychiatric testing. MDMA users had reductions in SERT binding in multiple brain regions but no reductions in striatal DAT binding. Memory performance in the aggregate subject population was correlated with SERT binding in the dorsolateral prefrontal cortex, orbitofrontal cortex, and parietal cortex, brain regions implicated in memory function. Prior exposure to MDMA significantly diminished the strength of this relationship. Use of sequential MDMA doses is associated with lasting decreases in brain SERT, but not DAT. Memory performance is associated with SERT binding in brain regions involved in memory function. Prior MDMA exposure appears to disrupt this relationship. These data are the first to directly relate memory performance to brain SERT density. McCann, U., Szabo, Z., Vranesic, M., Palermo, M., Mathews, W., Ravert, H., Dannals, R., and Ricaurte, G. Positron Emission Tomographic Studies of Brain Dopamine and Serotonin Transporters in Abstinent (+/-)3,4-Methylenedioxymeth-amphetamine ("Ecstasy") Users: Relationship to Cognitive Performance. Psychopharmacology, 200(3), pp. 439-450, 2008.

Association of a Polymorphism Near CREB1 with Aversion Processing in the Insula

Dr. H. Breiter and colleagues at Massachusetts General Hospital combined functional brain imaging with a candidate gene analysis in a study of altered brain processing of and behavioral avoidance responses to angry facial expressions. A polymorphism near the cyclic adenosine monophosphate response element binding protein gene (CREB1) has recently been associated with greater self-reported effort at anger control. Changes in CREB expression have also been linked to administration of cocaine and other drugs of abuse A

total of 28 healthy caucasian participants (mean age, 29.2 years; 13 women) were genotyped for rs4675690, a single- nucleotide polymorphism near CREB1. Changes in BOLD fMRI signals in the amygdala, insula, anterior cingulate, and orbitofrontal cortex were obtained during passive viewing of photographs of faces with emotional expressions. To measure approach and avoidance responses to anger, an off-line key- press task that traded effort for viewing time assessed valuation of angry faces compared with other expressions. The CREB1- linked single- nucleotide polymorphism was associated with significant differential activation in an extended neural network responding to angry and other facial expressions. The CREB1- associated insular activation was coincident with activation associated with behavioral avoidance of angry faces. These results indicated that A polymorphism near CREB1 is associated with responsiveness to angry faces in a brain network implicated in processing aversion. Coincident activation in the left insula is further associated with behavioral avoidance of these stimuli. Perlis, R., Holt, D., Smoller, J., Blood, A. Lee, S., Kim, B., Lee, M., Sun, M., Makris, N., Kennedy, D., Rooney, K., Dougherty, D., Hoge, R., Rosenbaum, J., Fava, M., Gusella, J., Gasic, G., and Breiter, H. Association of a Polymorphism Near CREB1 with Differential Aversion Processing in the Insula of Healthy Participants. Archives of General Psychiatry, 65(8), pp. 882-892, 2008.

Neural Correlates of Voluntary and Involuntary Risk Taking in the Balloon Analog Risk Task (BART)

Dr. J. Detre and colleagues at the University of Pennsylvania used fMRI to investigate the neuronal basis of voluntary choice on risk taking. A modified version of the Balloon Analog Risk Task (BART) was performed during functional magnetic resonance imaging (fMRI) and administered in both an active choice mode and a passive no-choice mode in order to examine the neural correlates of voluntary and involuntary risk taking in the human brain. Voluntary risk in the active choice task was associated with robust activation in mesolimbic-frontal regions (midbrain, ventral and dorsal striatum, anterior insula, dorsal lateral prefrontal cortex (DLPFC), and anterior cingulate/medial frontal cortex (ACC/MFC)), in addition to activation in visual pathway regions. In contrast, these mesolimbic-frontal activation patterns were not observed for involuntary risk in the passive no-choice task. Decision making was associated with neural activity in the right DLPFC. These findings suggest that recruitment of the brain mesolimbic-frontal pathway during risk-taking is contingent upon the agency of the risk taker. Since the performance of the BART has been shown to be an index of impulsitivity and risk for substance abuse, the present paradigm may be extended to pathological populations to determine the specific neural components of their impaired risk behavior. Rao, H., Korczykowski, M., Pluta, J., Hoang, A., and Detre, J. Neural Correlates of Voluntary and Involuntary Risk Taking in the Human Brain: An fMRI Study of the Balloon Analog Risk Task (BART). Neuroimage, 42(2), pp. 902-910, 2008.

Cognitive Control is Related to White Matter Alterations in the Corpus Collosum of Methamphetamine-Dependent Subjects

Dr. R. Salo and colleagues at the University of California, Davis used Diffusion Tensor Imaging to determine the relationship of cognitive control and indices of white matter (WM) in the callosal genu and splenium in 37 currently abstinent MA abusers and 17 non-substance abusing control subjects. Cognitive control was indexed by performance of a computerized measure of the Stroop selective attention task. Measurements of fractional anisotropy (FA), apparent diffusion coefficient (ADC) of callosal fibers, and diffusion tensor eigenvalues were obtained in all subjects. The MA abusers exhibited greater Stroop reaction time interference (i.e., reduced cognitive control) ($p = .04$) compared with control subjects. After correcting for multiple comparisons, FA within the genu correlated significantly with measures of cognitive control in the MA abusers (p

= .04, Bonferroni corrected) but not in control subjects (p = .26). Group differences in genu but not splenium FA only exhibited a non-significant trend (p = .09). These results demonstrate that methamphet-amine abuse primarily alters anterior callosal WM microstructure compared to posterior callosal WM microstructure. Furthermore, the DTI indices within the genu but not splenium correlated with measures of cognitive control in chronic MA abusers. Salo, R., Nordahl, T.E., Buonocore, M.H., Natsuaki, Y., Waters, C., Moore, C.D., Galloway, G.P., and Leamon, M.H. Cognitive Control and White Matter Callosal Microstructure in Methamphetamine-Dependent Subjects: A Diffusion Tensor Imaging Study. Biological Psychiatry, [Epub ahead of print; PMID: 18814867; DOI:10.1016/j.biopsych.2008.08.004, 2008].

Neural Correlates of the Processing of Another's Mistakes: A Possible Underpinning for Social and Observational Learning

Dr. M. Shane and colleagues at the MIND Institute at University of New Mexico used fMRI to compare and contrast those regions that show sensitivity to the performance, and to the observation, of committed errors. Healthy volunteers performed a speeded go/no-go task and also observed a video of another person performing the same task. Dorsal anterior cingulate, orbitofrontal cortex, and supplementary motor regions were commonly activated to both performed and observed errors, providing evidence for common neural circuitry underlying the processing of one's own and another's mistakes. In addition, several regions, including inferior parietal cortex and anterorostral and ventral cinguli, did not show activation during performed errors, but were instead uniquely activated by the observation of another's mistakes. The unique nature of these 'observer-related' activations suggests that these regions, while of potential import towards recognition of another's errors, are not core to circuitry underlying error monitoring. Rather, the authors suggest that these regions may represent components of a distributed network important for the representation and interpretation of complex social actions. Shane, M.S., Stevens, M., Harenski, C.L., and Kiehl, K.A., Neural Correlates of the Processing of Another's Mistakes: A Possible Underpinning for Social and Observational Learning. NeuroImage, 42(1), pp. 450-459, 2008.

Comparative Distributions of the Monoamine Transporters in the Rodent, Monkey, and Human Amygdala

Drs. L. Porrino and H. Smith from Wake Forest University reviewed the functional relevance of dopamine, serotonin, and norepinephrine transmission in the amygdala, and compared the distributions of the monoamine transporters in the rodent, monkey, and human brain. The transporters were found to be heterogeneously distributed in the amygdala. The dopamine transporter (DAT) is consistently found to be extremely sparsely distributed, however the various accounts of its subregional topography are inconsistent, making any cross-species comparisons difficult. The serotonin transporter (SERT) had the greatest overall degree of labeling of the three markers, and was characterized by substantial inter-species variability in its relative distribution. The norepinephrine transporter (NET) was shown to possess an intermediate level of labeling, and like the SERT, its distribution is not consistent across the three species. The results of these comparisons indicate that caution should be exercised when using animal models to investigate the complex processes modulated by the monoamines in the amygdala, as their relative contributions to these functions may differ across species. Smith, H., and Porrino, L. The Comparative Distributions of the Monoamine Transporters in the Rodent, Monkey, and Human Amygdala. Brain Structure & Function, 213(1-2), pp. 73-91, 2008.

Distinguishing Expected Negative Outcomes from Preparatory

Control in the Human Orbitofrontal Cortex

Dr. S. Urus and colleagues at the University of California, Davis used BOLD fMRI to determine if subdivisions of the OFC are specifically engaged when negatively valenced outcomes are expected, and to what extent such areas might be involved in preparatory active control of behavior. In order to dissociate these two processes, healthy human participants performed two tasks during fMRI scanning, which either simultaneously or independently manipulated monetary incentives for correct performance, and demands for active preparation of cognitive control. In both experiments, preparation for performance was associated with lateral PFC activity in response to high incentives, regardless of their valence, as well as in response to increased task demands. In contrast, areas of the OFC centered around the lateral orbital sulcus responded maximally to negatively perceived prospects, even when such prospects were associated with decreases in preparatory cognitive control. These results provide direct support for theoretical models which posit that the OFC contributes to behavioral regulation by representing the value of anticipated outcomes, but does not implement active control aimed at avoiding or pursuing outcomes. Furthermore, they provide additional converging evidence that the lateral OFC is involved in representing specifically the affective impact of anticipated negative outcomes. Ursu, S., Clark, K.A., Stenger, V.A., and Carter, C.S., Distinguishing Expected Negative Outcomes from Preparatory Control in the Human Orbitofrontal Cortex. Brain Research, 1227, pp. 110-119, 2008.

Sleep Deprivation Decreases Binding of [11C]Raclopride to Dopamine D2/D3 Receptors in the Human Brain

Dr. Nora Volkow and colleagues used PET ligand brain imaging to test whether one night of sleep deprivation changes dopamine brain activity in 15 healthy human participants. [11C]raclopride was used to probe dopamine D2/D3 receptor radioligand occupany and [11C]cocaine was used to index dopamine transporter levels. Subjects were tested twice: after one night of rested sleep and after one night of sleep deprivation. The specific binding of [11C]raclopride in the striatum and thalamus were significantly reduced after sleep deprivation and the magnitude of this reduction correlated with increases in fatigue (tiredness and sleepiness) and with deterioration in cognitive performance (visual attention and working memory). In contrast, sleep deprivation did not affect the specific binding of [11C]cocaine in the striatum. Because [11C]raclopride competes with endogenous dopamine for binding to D2/D3 receptors, these data suggest that the decreases in binding reflect dopamine increases with sleep deprivation. However, there is the possibility that decreased [11C]raclopride binding reflects decreases in receptor levels or affinity. Sleep deprivation did not affect dopamine transporters (target for most wake-promoting medications) and thus dopamine increases are likely to reflect increases in dopamine cell firing and/or release rather than decreases in dopamine reuptake. Because dopamine-enhancing drugs increase wakefulness, the authors postulate that dopamine increases after sleep deprivation is a mechanism by which the brain maintains arousal as the drive to sleep increases but one that is insufficient to counteract behavioral and cognitive impairment. Volkow, N.D., Wang, G., Telang, F., Fowler, J.S., Logan, J., Wong, C., Ma, J., Pradhan, K., Tomasi, D., Thanos, P.K., Ferre, S., and Jayne, M. Sleep Deprivation Decreases Binding of [11C]Raclopride to Dopamine D2/D3 Receptors in the Human Brain. J. Neuroscience, 28(34), pp. 8454-8461, 2008.

New Method for Measuring White Matter Conductivity Using Diffusion Tensor MRI

Dr. K. Lim and colleagues at the University of Minnesota developed a new

algorithm to derive the anisotropic conductivity of the cerebral white matter (WM) from the diffusion tensor MRI (DT-MRI) data. The new algorithm was applied to the DT-MRI data acquired from two healthy human subjects. The extracted anisotropic conductivity distribution was compared with those obtained by using two existing algorithms, which were based upon a linear conductivity-to-diffusivity relationship and a volume constraint, respectively. The present results suggest that the VF algorithm is capable of incorporating the partial volume effects of the CSF and the intravoxel fiber crossing structure, both of which are not addressed altogether by existing algorithms. Therefore, it holds potential to provide a more accurate estimate of the WM anisotropic conductivity, and may have important applications to clinical neuroscience research. Wang, K., Zhu, S., Mueller, B., Lim, K., Liu, Z., and He, B. A New Method to Derive White Matter Conductivity From Diffusion Tensor MRI. IEEE Transactions on Biomedical Engineering, 55(10), pp. 2481-2486, 2008.

L-Tetrahydropalmatine Reduces Opiate Craving and Increases the Abstinence Rate in Heroin Users

Dr. S. Li and colleagues at Medical College of Wisconsin examined the ability of levotetrahydropalmatine (l-THP) to reduce heroin craving and increase the abstinence rate among heroin-dependent patients (n = 120) using a randomized, double-blinded, and placebo-controlled design. The participants remained in a ward during a 4-week period of l-THP treatment, followed by 4 weeks of observation after treatment. The patients were followed for 3 months after discharge. Outcome measures included the measured severity of the protracted abstinence withdrawal syndrome (PAWS) and the abstinence rate. Four weeks of l-THP treatment significantly ameliorated the severity of PAWS, specifically, somatic syndrome, mood states, insomnia, and drug craving, in comparison to the placebo group. Based on the 3 month follow-up observation, participants who survived the initial 2 weeks of l-THP medication and remained in the trial program had a significantly higher abstinence rate of 47.8% (95% confidence interval [CI]: 33%-67%) than the 15.2% in the placebo group (95% CI: 7%-25%), according to a log-rank test (P < 0.0005). These results support the potential use of l-THP for the treatment of heroin addiction. Yang, Z., Shao, Y., Li, S., Qi, J., Zhang, M., Hao, W., and Jin, G., Medication of L-Tetrahydropalmatine Significantly Ameliorates Opiate Craving and Increases the Abstinence Rate in Heroin Users: A Pilot Study. Acta Pharmacologica Sinica, 29(7), pp. 781-788, 2008.

Director's Report to the National Advisory Council on Drug Abuse - February, 2009

Research Findings - Epidemiology and Etiology Research

Highly Active Antiretroviral Therapy and Survival in HIV-infected Injection Drug Users

Highly active antiretroviral therapy (HAART) is often withheld from injection drug users (IDUs) infected with the human immunodeficiency virus (HIV) based on the belief that their unstable lifestyles may predetermine a markedly inferior outcome with HAART. However, long-term evaluations of HIV treatment outcomes among IDUs in comparison with other risk groups have not yet been available. Researchers compared survival rates among HIV-infected patients initiating HAART with and without a history of injection drug use. They used data from a population-based, prospective cohort study of 3116 antiretroviral-naive HIV-infected patients in a province-wide HIV/AIDS treatment program in British Columbia, Canada. Of the 3116 patients, 915 were IDUs (29.4%), 579 were female (18.6%), and the median age was 39.4 years (interquartile range, 33.3-46.4 years). Treatment with HAART was initiated between August 1, 1996, and June 30, 2006. The median duration of follow-up was 5.3 years (interquartile range, 2.8-8.3 years) for IDUs and 4.3 years (interquartile range, 2.0-7.6 years) for non-IDUs. Patients were followed up until June 30, 2007. Data were analyzed between November 1, 2007, and May 26, 2008. The main outcome measure was all-cause mortality. Overall, 622 individuals died (20.0%) during the study period (232 IDUs and 390 non-IDUs), for a crude mortality rate of 20.0% (95% confidence interval [CI], 18.4%-21.5%). At 84 months after the initiation of HAART, the product limit estimate of the cumulative all-cause mortality rate was similar between the 915 IDUs (26.5%; 95% CI, 23.2%-29.8%) and 2201 non-IDUs (21.6%; 95% CI, 16.9%-26.2%) (Wilcoxon P = .47). In multivariate time-updated Cox regression, the hazard ratio of mortality was similar between IDUs and non-IDUs (1.09; 95% CI, 0.92-1.29). These findings indicate that, in this study population, injection drug use was not associated with decreased survival among HIV-infected patients initiating HAART. Wood, E., Hogg, R., Lima, V., Kerr, T., Yip, B., Marshall, B., and Montaner, J. Highly Active Antiretroviral Therapy and Survival in HIV-Infected Injection Drug Users. JAMA, 300(5), pp. 550-554, 2008.

A Randomized Intervention Trial to Reduce the Lending of Used Injection Equipment among Injection Drug Users Infected with Hepatitis C

Researchers evaluated the efficacy of a peer-mentoring behavioral intervention designed to reduce risky distributive injection practices (e.g., syringe lending, unsafe drug preparation) among injection drug users with hepatitis C virus (HCV) infection. A randomized trial with a time-equivalent attention-control group was conducted among 418 HCV-positive injection drug users aged 18 to 35 years in 3 US cities (n=222 to intervention; n=196 to control). Almost half

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(47%) were recruited in Baltimore and about 1/4th from New York City (28%) and Seattle (25%). Participants reported their injection-related behaviors at baseline and at 3- and 6-month follow-ups. Compared with the control group, intervention-group participants were less likely to report distributive risk behaviors at 3 months (odds ratio [OR]=0.46; 95% confidence interval [CI]=0.27, 0.79) and 6 months (OR=0.51; 95% CI=0.31, 0.83), a 26% relative risk reduction, but were no more likely to cite their HCV-positive status as a reason for refraining from syringe lending. Effects were strongest among intervention-group participants who had known their HCV-positive status for at least 6 months. Peer mentoring and self-efficacy were significantly increased among intervention-group participants, and intervention effects were mediated through improved self-efficacy. This behavioral intervention reduced unsafe injection practices that may propagate HCV among injection drug users. Latka, M., Hagan, H., Kapadia, F., Golub, E., Bonner, S., Campbell, J., Coady, M., Garfein, R., Pu, M., Thomas, D., Thiel, T., and Strathdee, S. A Randomized Intervention Trial to Reduce the Lending of Used Injection Equipment among Injection Drug Users Infected with Hepatitis C. Am. J. Public Health, 98(5), pp. 853-861, 2008.

MAOA Methylation and Substance Dependence in Women

In recent years, the role of epigenetic phenomena, such as methylation, in mediating vulnerability to behavioral illness and in explaining gene-environment interplay have become increasingly appreciated. One prominent locus at which epigenetic phenomena are thought to be in play is the monoamine oxidase A (MAOA) locus. In order to examine the role of methylation at this locus, the authors performed quantitative methylation analysis across the promoter region of this gene in lymphoblast lines derived from 191 subjects (95 male, mean age 42; 96 female, mean age 39) participating in the Iowa Adoption Studies (IAS). They analyzed the resulting data with respect to genotype and lifetime symptom counts for the more common major behavioral disorders in the IAS, antisocial personality disorder (ASPD), and substance use disorders (alcohol (AD) and nicotine dependence (ND)). Methylation status was significantly associated with lifetime symptom counts for ND ($P < 0.001$) and AD ($P < 0.008$) in women, but not men. Furthermore, a trend was found for women homozygous for the 3,3 allele to have a higher degree of overall methylation than women homozygous for the 4,4 allele ($P < 0.10$). The authors conclude that methylation of MAOA may play a significant role in common psychiatric illness and that further examination of epigenetic processes at this locus is in order. Philibert, R., Gunter, T., Beach, S., Brody, G., and Madan, A. MAOA Methylation is Associated with Nicotine and Alcohol Dependence in Women. Am. J. Med. Genet. B Neuropsychiatr. Genet, 147B(5), pp. 565-570, 2008.

Correlates of Smoking Cessation in a Nationally Representative Sample of U.S. Adults

Persistent cigarette smoking is associated with significant morbidity and mortality. Correlates of difficulty quitting smoking include psychopathology, such as major depressive disorder, and problems with other substances, such as alcoholism. In addition, socio-demographic risk (e.g., poverty) and protective influences (e.g., living in a region with stringent tobacco laws) can modify risk for persistent cigarette smoking. Using data on 17,919 individuals with a lifetime history of smoking 100 or more cigarettes, from a nationally representative U.S. sample, the authors examine the constellation of risk and protective factors that correlate with smoking cessation (defined as remaining smoke-free in the past 12 months) across four cohorts: young (18-31 years), intermediate-aged (32-43 years), middle-aged (44-60 years) and older (61-99 years) adults. Using survival analyses, they demonstrate that in addition to a

history of DSM-IV nicotine dependence, which is negatively associated with smoking cessation, living below the poverty line is also associated with persistent smoking across all age cohorts. Residents over the age of 31 years living on the U.S. West Coast are less likely to be persistent smokers as well. Major depressive disorder is associated with persistent smoking, but interestingly, only in middle-aged and older adults. Alcoholism and a family history of substance use problems are both correlated with persistent smoking but only in older adults. The authors suggest that psychopathology may hinder successful quit attempts during the developmental period when a majority of quit attempts are made (early to mid- 40's). However, the analyses also highlight the important benefits of effective tobacco legislation on the U.S. West Coast and suggest policy makers actively consider addressing issues surrounding tobacco taxation and the impact of poverty on tobacco use, in addition to the risks posed by co-occurring psychiatric problems and other substance use disorders. Agrawal, A., Sartor, C., Pergadia, M., Huizink, A., and Lynskey, M. Correlates of Smoking Cessation in a Nationally Representative Sample of US. Adults. Addict. Behav., 33(9), pp. 1223-1226, 2008.

Trends in Prescription Drug Abuse and Dependence, Co-occurrence with Other Substance Use Disorders, and Treatment Utilization

This study examined trends in prescription drug abuse and dependence (sedatives, tranquilizers, opioids, and stimulants), co-occurrence with other substance use disorders and substance abuse treatment utilization among those with diagnoses of prescription drug abuse and dependence in two large, nationally representative, samples of adults aged 18 and over in the United States in 1991-1992 and 2001-2002. National prevalence estimates were derived from the 1991-1992 National Longitudinal Alcohol Epidemiologic Survey (n = 42,862) and the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (n = 43,093). Data were collected from structured diagnostic interviews using the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule: Diagnostic and Statistical Manual version IV (DSM-IV). The past-year prevalence of prescription sedative abuse, sedative dependence, opioid abuse, and opioid dependence increased from 1991-1992 to 2001-2002. The majority of individuals with past-year sedative (56.8%), tranquilizer (89.0%), stimulant (67.9%) and opioid (74.2%) use disorders also met DSM-IV criteria for an additional past-year substance use disorder. The co-occurrence of several forms of prescription drug use disorders and other substance use disorders increased from 1991-1992 to 2001-2002. A minority of individuals with past-year prescription drug abuse and approximately one-half of those with past-year prescription drug dependence utilized substance abuse treatment. These findings reinforce the importance of continued national monitoring based on the increases in prescription drug abuse and dependence, high co-occurrence with other substance use disorders, and underutilization of substance abuse treatment services. McCabe, S., Cranford, J., and West, B. Trends in Prescription Drug Abuse and Dependence, Co-occurrence with Other Substance Use Disorders, and Treatment Utilization: Results from Two National Surveys. Addict Behav, 33(10), pp. 1297-1305, 2008.

Stimulant Treatment and Later Risk for SUDs

This study sought to examine the effects of early stimulant treatment on subsequent risk for cigarette smoking and substance use disorders (SUDs) in female adolescents with attention-deficit/hyperactivity disorder (ADHD). The authors used data from a case-controlled, prospective, 5-year follow-up study. Subjects were 114 female adolescents with ADHD originally ascertained from psychiatric and pediatric sources; mean age at follow up was 16.2 years; 94 had been treated with psychostimulants. The authors modeled time to onset of

SUDs and smoking as a function of stimulant treatment. They found no differences in SUD risk factors between naturalistically treated and untreated groups other than family history of ADHD. Results indicated no increased risks for cigarette smoking or SUDs associated with stimulant therapy, and significant protective effects of stimulant treatment on the development of any SUD (hazard ratio [HR], 0.27; 95% confidence interval [CI], 0.13-0.60; P = .001) and cigarette smoking (HR, 0.28; 95% CI, 0.14-0.60; P = .001) that were maintained when controlling for conduct disorder. No effects of time to onset or duration of stimulant therapy on subsequent SUDs or cigarette smoking in subjects with ADHD were found. The authors conclude that stimulant therapy does not increase but rather reduces the risk for cigarette smoking and SUDs in female adolescents with ADHD, similar to their findings in boys. Other research by this group has shown that this reduction in SUDs is neutralized by adulthood, so it is possible that the stimulant therapy, if it has an effect, is delaying rather than preventing subsequent SUDs. Further research is awaited to address this important public health question. Wilens, T., Adamson, J., Monuteaux, M., Faraone, S., Schillinger, M., Westerberg, D., and Biederman, J. Effect of Prior Stimulant Treatment for Attention-Deficit/Hyperactivity Disorder on Subsequent Risk for Cigarette Smoking and Alcohol and Drug use Disorders in Adolescents. Arch. Pediatr. Adolesc. Med., 162(10), pp. 916-921, 2008.

Associations between Cigarette Smoking and ADHD

This study sought to evaluate the association between attention deficit hyperactivity disorder (ADHD) and severity of physical dependence on nicotine using a sample of adolescents and young adults with ADHD and controls. Data were drawn from two previous longitudinal case-control family studies of ADHD, and used self-reports on the modified Fagerstroem Tolerance Questionnaire (mFTQ) for degrees of physical dependence on nicotine. The final sample included 80 ADHD probands (43% male, mean age 19.3) and 86 control probands (38% female, mean age 19.2 years) on whom mFTQ data were available. The smokers with ADHD had significantly higher scores on the mFTQ, indicative of more severe physical dependence on nicotine. Similarly, in current smokers, a positive linear relationship was found between mFTQ score and both inattentive and hyperactive ADHD symptoms. Environmental factors, such as current parental smoking, peer smoking, and living with a smoker, all increased the risk for smoking in those with ADHD compared with controls. The authors conclude that male and female smokers with ADHD manifest more severe physical dependence on nicotine compared with controls, and that important environmental factors appear to add to the risk of smoking associated with ADHD. Wilens, T., Vitulano, M., Upadhyaya, H., Adamson, J., Sawtelle, R., Utzinger, L., and Biederman, J. Cigarette Smoking Associated with Attention Deficit Hyperactivity Disorder. J. Pediatr., 153(3), pp. 414-419, 2008.

Conduct Problems, Depressed Mood, and Adolescent Substance Use

Conduct problems are strong positive predictors of substance use and problem substance use among teens, whereas predictive associations of depressed mood with these outcomes are mixed. Conduct problems and depressed mood often co-occur, and such co-occurrence may heighten risk for negative outcomes. Thus, this study examined the interaction of conduct problems and depressed mood at age 11 in relation to substance use and problem use at age 18, and possible mediation through peer substance use at age 16. Analyses of multirater longitudinal data from a population-based sample of 429 rural youths (222 girls) and their families recruited and first interviewed in 1993 were conducted using a methodology for testing latent variable interactions. The link between the conduct problems x depressed mood interaction and adolescent substance use was negative and statistically significant.

Unexpectedly, positive associations of conduct problems with substance use were stronger at lower levels of depressed mood. A significant negative interaction in relation to peer substance use also was observed, and the estimated indirect effect of the interaction on adolescent use through peer use as a mediator was statistically significant. These complex findings, some consistent with prior findings and some in contrast, illustrate the complexity of multiproblem youth. Mason, W., Hitchings, J., and Spoth, R. The Interaction of Conduct Problems and Depressed Mood in Relation to Adolescent Substance Involvement and Peer Substance Use. Drug Alcohol Depend., 96(3), pp. 233-248, 2008.

An Autosomal Linkage Scan for Cannabis Use Disorders in the Nicotine Addiction Genetics Project

Despite accumulating evidence that there is a genetic basis for cannabis use disorders (i.e., abuse and dependence), few studies have identified genomic regions that may harbor biological risk and protective factors. The researchers sought to conduct autosomal linkage analyses that identify genomic regions that may harbor genes conferring a vulnerability to cannabis use disorders. In 289 Australian families who participated in the Nicotine Addiction Genetics Project, 423 autosomal markers were genotyped. Families were ascertained for heavy cigarette smoking. Linkage analyses were conducted for DSM-IV cannabis dependence and for a novel factor score representing problems with cannabis use, including occurrence of 3 of 4 abuse criteria (excluding legal problems) and 6 DSM-IV dependence criteria. A maximum logarithm of odds (LOD) of 3.36 was noted for the cannabis problems factor score on chromosome arm 1p. An LOD of 2.2 was noted on chromosome 4 in the region of the gamma-aminobutyric acid type A gene cluster, including GABRA2, which has been implicated in drug use disorders. For DSM-IV cannabis dependence, a modest LOD score on chromosome 6 (1.42) near cannabinoid receptor 1 (CNR1) was identified. In addition, support for an elevation on chromosome 3, identified in prior independent studies, was noted for the factor score and cannabis dependence (LOD, 1.4). In conclusion, genes such as ELTD1 on chromosome 1, in addition to genes on chromosomes 4 (eg, GABRA2) and 6 (eg, CNR1), may be associated with the genetic risk for cannabis use disorders. The authors also introduce a novel quantitative phenotype, a cannabis problems factor score composed of DSM-IV abuse and dependence criteria, that may be useful for future linkage and association studies. Agrawal, A., Pergadia, M., Saccone, S., Lynskey, M., Wang, J., Martin, N., Statham, D., Henders, A., Campbell, M., Garcia, R., Broms, U., Todd, R., Goate, A., Rice, J., Kaprio, J., Heath, A., Montgomery, G., and Madden, P. An Autosomal Linkage Scan for Cannabis Use Disorders in the Nicotine Addiction Genetics Project. Arch. Gen. Psychiatry, 65(6), pp. 713-721, 2008.

Comorbidity of Psychiatric Disorders and Nicotine Dependence among Adolescents: Findings from a Prospective, Longitudinal Study

The authors examine prospectively the comorbidity of DSM-IV psychiatric disorders and nicotine dependence in adolescence. A multiethnic sample (N = 1,039) of adolescents from grades 6 to 10 in the Chicago public schools (mean age 14.1 years) was interviewed at home five times, and mothers were interviewed three times over a 2-year period (2003-2005). Completion rates at each wave were 96% of the initial sample. Selected DSM-IV psychiatric disorders were ascertained from youths and mothers about youths at two annual waves with the NIMH Diagnostic Interview Schedule for Children, Version IV-Y and IV-P; DSM-IV symptoms of nicotine dependence were ascertained from youths at every wave using a measure developed for adolescents. Psychiatric disorders most often preceded the onset of the first criterion of nicotine dependence. Prospective associations between psychiatric

disorders and nicotine dependence were examined through logistic regressions. After controlling for comorbid disorders, it was found that lifetime disruptive disorder significantly predicted the onset of a nicotine dependence criterion (adjusted odds ratio 2.1). Early onset of any psychiatric disorder increased this risk. Other predictors included novelty seeking and extensiveness of smoking. By contrast, nicotine dependence did not predict the onset of a psychiatric disorder; significant predictors included the youths' prior other psychiatric disorders, novelty seeking, and parental depression and antisocial behavior. Nicotine dependence does not seem to contribute to the onset of psychiatric disorders, whereas disruptive disorder is an important etiologic factor for nicotine dependence in adolescence. Griesler, P., Hu, M., Schaffran, C., and Kandel, D. Comorbidity of Psychiatric Disorders and Nicotine Dependence among Adolescents: Findings from a Prospective, Longitudinal Study. J. Am. Acad. Child Adolesc. Psychiatry, 47(11), pp. 1340-1350, 2008.

Prevalence and Correlates of Jugular Injections among Injection Drug Users

Jugular injection of drugs has been reported although little is known about the prevalence of and risk factors associated with this behavior. Researchers used univariate statistics and logistic regression to examine factors associated with jugular injection among a cohort of injection drug users (IDU) in the Vancouver Injecting Drug Users Study (VIDUS), a large prospective cohort study of IDU recruited through snowball sampling methods in Vancouver, Canada. Between December 2004 and November 2005, 780 IDU were followed up as part of VIDUS and 198 (25%) reported jugular injection in the previous 6 months. In multivariate analyses, factors independently associated with jugular injection included being of the female gender [adjusted odds ratio (aOR) = 1.72, 95% confidence interval (CI): 1.14-2.59; p = 0.010], daily heroin use (aOR = 2.89, 95% CI: 1.93-4.34; p < 0.001), daily cocaine use (aOR = 1.76, 95% CI: 1.12-2.76; p = 0.014], requiring help injecting (aOR = 4.44, 95% CI: 2.64-7.46; p < 0.001), and involvement in the sex-trade (aOR = 2.71, 95% CI: 1.6-4.55; p < 0.001). These findings indicate that reporting a history of jugular injecting was alarmingly high in the cohort and significantly so among individuals with identifiable demographic and drug-using characteristics. Given previous reports demonstrating the risk of infection and vascular trauma due to this behavior, the findings underscore the need for interventions to reduce jugular injection and, for those who continue to inject, to provide information on safer injecting practices. Hoda, Z., Kerr, T., Li, K., Montaner, J., and Wood, E. Prevalence and Correlates of Jugular Injections among Injection Drug Users. Drug Alcohol Rev., 27(4), pp. 442-446, 2008.

A Twin Study of SES and Social Support following Illicit Drug Use

This study analyzed twin data to parse out the source of negative social attributes associated with drug use and abuse/dependence, asking if these associations may arise as a result of shared genetic or environmental factors rather than through causal pathways. The study used data from structured interviews conducted for 3969 male and female twins from the Mid-Atlantic Twin Registry and evaluations of their socioeconomic status (SES), social interactions, and use of drugs. Drug involvement was categorized as never used, tried, or met criteria for abuse or dependence. A co-twin control design was implemented using hierarchical linear modeling to assess whether twins who used drugs experienced lower SES and social support than non-using co-twins. Poorer social functioning in the drug-exposed twin would be consistent with a causal relationship, while similar functioning in the drug exposed versus naive twins would imply shared genetic or common environmental factors. Use of drugs was not significantly related to any SES measures. However, education and job status appear to share genetic influences with drug abuse/dependence. Lower income was not related to abuse/dependence of

drugs. Negative interactions with friends and relatives share genetic factors with use of drugs, but the escalation from trying drugs to abusing them appears to generate discord between the abuser and friends and relatives in a causal fashion. These results indicate that presumptive causal influences of drug abuse/dependence on low SES may actually be mediated by shared genes. Drug use and social discord also appear to have shared genetic factors, but increased levels of drug involvement seem to causally influence social interactions. The authors discuss possible preventive implications of some presumptive causal mechanisms actually being due to shared liability. Bergen, S.E., Gardner, C.O., Aggen, S.H., and Kendler, K.S. Socioeconomic Status and Social Support Following Illicit Drug Use: Causal Pathways or Common Liability? Twin Res. Hum. Genet., 11(3), pp. 266-274, 2008.

Psychiatric Disorders Among Detained Youth

This study examined the prevalence of psychiatric disorders among youths transferred to adult criminal court and youths processed in the juvenile court. Participants were a stratified random sample of 1,829 youths, ten to 18 years of age, who were arrested and detained in Chicago. Data from version 2.3 of the Diagnostic Interview Schedule for Children were presented for 1,715 youths, 13 to 18 years of age, including 1,440 youths processed in juvenile court and 275 youths processed in adult criminal court. Males, African Americans, Hispanics and older youths had greater odds of being processed in adult criminal court than females, non-Hispanic whites and younger youths, even after the analyses controlled for felony-level violent crime. Among youths processed in adult criminal court, 68% had at least one psychiatric disorder and 43% had two or more types of disorders. Prevalence rates and the number of comorbid types of disorders were not significantly different between youths processed in adult criminal court and those processed in juvenile court. Among youths processed in adult criminal court, those sentenced to prison had significantly greater odds than those receiving a less severe sentence of having a disruptive behavior disorder, a substance use disorder or comorbid affective and anxiety disorders. Community and correctional systems need to be prepared to provide psychiatric services to youths transferred to adult criminal court and especially to youths sentenced to prison. Washburn, J., Teplin, L., Voss, L., Simon, C., Abram, K., and McClelland, G. Psychiatric Disorders among Detained Youths: A Comparison of Youths Processed in Juvenile Court and Adult Criminal Court. Psychiatr. Serv., 59(9), pp. 965-973, 2008.

Child Abuse and Risk for Cannabis Abuse

This study used an offspring of twins design to control for genetic environmental risk factors while examining the association between childhood physical abuse (CPA) and sexual abuse (CSA) and the development of cannabis abuse and dependence among adolescents and young adults. To control for familial risk differences related to paternal drug dependence that might confound the relationship between CSA and CPA and cannabis abuse/dependence, the authors created four groups based on father 's', and uncle 's' substance use dependence (SUD) status reflecting different degrees of genetic and environmental risks to offspring: (i) high genetic, high environmental risk; (ii) high genetic, low environmental risk; (iii) medium genetic, low environmental risk; and (iv) low genetic, low environmental risk. Participants included adolescent and young adult offspring of monozygotic and dizygotic US military veteran twin fathers (n = 819; 425 males, 394 females, mean age 23, interviewed in 2002-3). Data on CPA and CSA, DSM-IV offspring cannabis abuse/dependence, other SUD and psychopathology and maternal and paternal SUD and psychopathology were collected via semi-structured telephone interview. Twenty-three percent of the offspring sample met life-time criteria for cannabis abuse/dependence and 8.55% and 12.82% reported CSA and CPA, respectively. Offspring exposed to CSA, but not CPA, were at

significantly greater risk of developing cannabis abuse/dependence compared to those who had not experienced CSA (hazard ratio = 2.16; 95% confidence interval = 1.48-3.16) after controlling for genetic and familial environmental risk and offspring gender, alcohol abuse and dependence and conduct disorder. The authors conclude that these results indicate that there are effects of CSA on development of cannabis abuse/dependence in addition to the genetic and familial environmental risk imparted by having a drug-dependent father. Duncan, A., Sartor, C., Scherrer, J., Grant, J., Heath, A., Nelson, E., Jacob, T., and Bucholz, K. The Association Between Cannabis Abuse and Dependence and Childhood Physical and Sexual Abuse: Evidence from an Offspring of Twins Design. Addiction, 103(6), pp. 990-997, 2008.

Prescription Pain Reliever Abuse and Dependence Among Adolescents: a Nationally Representative Study

This study examined the prevalence, patterns, and correlates of adolescents' abuse, subthreshold dependence ("diagnostic orphans"), and dependence on prescription pain relievers (PPRs) such as opioids in a representative national sample (N = 36,992). Data were from the 2005-2006 National Surveys of Drug Use and Health. DSM-IV criteria for abuse and dependence were examined. Of all adolescents ages 12 to 17, 7% (n = 2,675) reported nonprescribed PPR use in the past year, and 1% (n = 400) met criteria for past-year PPR abuse or dependence. Among the 2,675 adolescents who reported nonprescribed PPR use, more than one in three reported symptoms of abuse or dependence: 7% abuse, 20% subthreshold dependence, and 9% dependence. Regular PPR use, major depressive episodes, and alcohol use disorders were associated with each diagnostic category. Compared with asymptomatic nonprescribed PPR users, increased odds of abuse were noted among nonstudents (adjusted odds ratio [AOR] 2.6), users of mental health services (AOR 1.8), and those reporting poor or fair health (AOR 2.4); and increased odds of dependence were observed among females (AOR 1.6), those who were involved in selling illicit drugs (AOR 1.7), and users of multiple drugs (AOR 2.9). Subthreshold dependent users resembled dependent users in major depressive episodes (AOR 1.5), alcohol use disorders (AOR 1.8), and use of multiple drugs (AOR 1.7). The study findings indicate that dependence on prescription pain relievers can occur without abuse. The authors stress that subthreshold dependence should be investigated further for consideration in major diagnostic classification systems. Wu, L., Ringwalt, C., Mannelli, P., and Patkar, A. Prescription Pain Reliever Abuse and Dependence Among Adolescents: A Nationally Representative Study. J. Am. Acad. Child Adolesc. Psychiatry, 47(9), pp. 1020-1029, 2008.

HIV Risk Among Youth in the Justice System

This study examines the prevalence and persistence of 20 human immunodeficiency virus (HIV)/sexually transmitted infection (STI) sexual and drug use risk behaviors and to predict their occurrence in four mutually exclusive diagnostic groups of delinquent youths: major mental disorder (MMD), substance use disorder (SUD), comorbid MMD and SUD (MMD+SUD) and neither disorder. At the baseline interview, HIV/STI risk behaviors were assessed in 800 juvenile detainees, ages 10 to 18 years; youths were reinterviewed approximately 3 years later. The final sample (N = 689) includes 298 females and 391 males. The prevalence and persistence of HIV/STI risk behaviors were high in all of the diagnostic groups. Youths with an SUD at baseline were greater than 10 times more likely to be sexually active and to have vaginal sex at follow-up than youths with MMD+SUD and four times more likely to be sexually active and to have vaginal sex than youths with neither disorder. Youths with an MMD at baseline were less likely to have engaged in unprotected vaginal and oral sex at follow-up compared with youths with neither disorder, and with youths with an SUD. Youths with MMD+SUD were

less likely to engage in unprotected oral sex compared with those with neither disorder. Irrespective of diagnostic group, delinquent youths are at great risk for HIV/STIs as they enter into adulthood. SUD increases risk. Because detained youths are released after approximately 2 weeks, their risk behaviors become a community health problem. Pediatricians and child and adolescent psychiatrists must collaborate with corrections professionals to develop HIV/STI interventions and ensure that programs started in detention centers continue after youths are released. Elkington, K., Teplin, L., Mericle, A., Welty, L., Romero, E., and Abram, K. HIV/Sexually Transmitted Infection Risk Behaviors in Delinquent Youth with Psychiatric Disorders: A Longitudinal Study. J. Am. Acad. Child Adolesc. Psychiatry, 47(8), pp. 901-911, 2008.

Methamphetamine Color and its Relation to Adverse Health Outcomes

In a study of injection drug users (IDUs) in Tijuana, Mexico, logistic regression identified factors associated with injection of colored versus clear methamphetamine in the prior six months (N = 613). Colors injected most often were clear (50%), white (47%), yellow (2%), and pink (1%). IDUs injecting colored meth were more likely to experience recent abscesses (34%) compared to those injecting clear meth (24%; p = 0.008), an association that persisted after adjusting for confounders. Market characteristics, possibly relating to purity or adulterants, may be associated with abscesses among methamphetamine injectors. Further study is needed to confirm and determine the mechanism of this association to better inform prevention messages. Strathdee, S., Case, P., Lozada, R., Mantsios, A., Alvelais, J., Pu, M., Brouwer, K., Miller, C., and Patterson, T. The Color of Meth: Is It Related to Adverse Health Outcomes? An Exploratory Study in Tijuana, Mexico. Am. J. Addict., 17(2), pp. 111-115, 2008.

Inattention as a Key Predictor of Tobacco Use in Adolescence

Researchers examined inattention among children as a predictor of tobacco use in adolescence in a longitudinal cohort of 177 African American and White boys, originally assessed at ages 7 and 13 as part of the Pittsburgh Youth Study, a community sample, and followed yearly to young adulthood (age 20). The overall study retention rate was 93.8%. Changes in self-reported tobacco use were tested with marginal transitional regression models, using parent and teacher ratings of inattention, hyperactivity-impulsivity, and other psychopathology, along with other factors, as predictors. Inattention, but not hyperactivity-impulsivity, significantly predicted adolescent tobacco use and young adult daily tobacco use. Peer substance use, parental substance use, and conduct disorder also predicted increases in tobacco use. African American ethnicity was strongly protective against later tobacco use. These results support the hypothesis that problems of inattention in childhood have a key role in increased tobacco use in adolescence and young adulthood. Burke, J., Loeber, R., White, H., Stouthamer-Loeber, M., and Pardini, D. Inattention as a Key Predictor of Tobacco Use in Adolescence. J. Abnorm. Psychol., 116(2), pp. 249-259, 2007.

Adolescence Drug Use Associated with Increased Risk for SUD

The authors aimed to extend the literature on the association of early onset of drug use and estimated risk for developing a substance use disorder (SUD) by investigating the risk that recent onset of alcohol and cannabis use confers for developing a substance use disorder at each chronological age of adolescence and young adulthood (12-21-years-old). Using 2003 data on 27,708 subjects in this age range from the National Survey on Drug Use and Health, they computed separate risk indices for developing an alcohol and cannabis use

disorder for recent (prior 2 years) alcohol and cannabis users, respectively, at each age from 12 to 21 years of age, and compared estimated risk to recent onsets users among respondents aged 22-26. The results indicated that onset of use during the teenage years was strongly linked to an elevated risk status. The odds ratio (OR) of having a prior year alcohol use disorder (AUD) among recent onset alcohol users was significantly elevated for youth at ages 14, 16, 17 and 18 (range of ORs=2.0-2.1) compared to the estimated risk for AUD among recent onset users aged 22-26. For cannabis, significantly elevated ORs were found for a cannabis use disorder (CUD) at each of teenage years (ages 12-18; range of ORs=3.9-7.2), when compared to older recent onset users (aged 22-26). The authors conclude that the data provide further epidemiological support that adolescence is a particularly vulnerable period for developing a SUD. Winters, K., and Lee, C. Likelihood of Developing an Alcohol and Cannabis use Disorder during Youth: Association with Recent Use and Age. Drug Alcohol Depend., 92(1-3), pp. 239-247, 2008.

Factors Associated with Geographic Migration among a Cohort of Injection Drug Users

Researchers sought to determine factors associated with migration among 1587 injection drug users participating in the Vancouver Injection Drug Users Study in Vancouver, Canada. All participants were residents of Vancouver at the time of recruitment. Correlates of migration, defined as living outside of Greater Vancouver between June 1999 and May 2005, were identified using generalized estimating equations. Various factors were negatively associated with migration, including frequent crack cocaine smoking (AOR = 0.44, 95% CI: 0.37-0.52), current methadone use (AOR = 0.50, 95% CI: 0.40-0.63), frequent heroin injection (AOR = 0.51, 95% CI: 0.41-0.64), requiring help injecting (AOR = 0.60, 95% CI: 0.47-0.77), sex trade involvement (AOR = 0.64, 95% CI: 0.51-0.82), living in unstable housing (AOR = 0.69, 95% CI: 0.58-0.83), public injecting (AOR = 0.75, 95% CI: 0.60-0.94), and incarceration (AOR = 0.77, 95% CI: 0.61-0.96). Alcohol use was positively associated with migration in this analysis (AOR = 1.25, 95% CI: 1.05-1.48). These findings suggest that participants who migrated were less at risk for HIV infection, given their lower levels of reported risk-taking. Rachlis, B., Hogg, R., Wood, E., Li, K., and Kerr, T. Factors Associated with Geographic Migration Among a Cohort of Injection Drug Users. Health Place, 14(3), pp. 536-543, 2008.

Environmental Contributions to Cannabis Abuse in Twin Design

Genetic and environmental factors are known to contribute to cannabis abuse/dependence (CAD). The authors sought to determine the magnitude of the contribution from measured environmental variables to offspring cannabis dependence in a design that controls for familial vulnerability. Data come from a study of 725 twin members of the Vietnam Era Twin Registry, 720 of their biological offspring (age 18-32 years, almost half female) and 427 mothers interviewed beginning in 2002. Data were obtained on offspring perception of family and peer support and substance use behaviors and offspring CAD. After adjusting for familial risk, and environmental covariates, CAD was significantly more likely among male offspring (OR=2.73; 95% CI: 1.69-4.41). Offspring CAD was associated with reporting: siblings used illicit drugs (OR=3.40; 95% CI: 1.81-6.38), a few friends used drugs (OR=2.72; 95% CI: 1.04-7.09), a quarter or more friends used drugs (OR=8.30; 95% CI: 3.09-22.33) and one-half or more 12th grade peers used drugs (OR=3.17; 95% CI: 1.42-7.08). Perceived sibling, friend and school peer substance use are strongly associated with CAD in young adults even after accounting for latent familial risk and for multiple measured intra-family and extra-family environmental influences. However, the authors acknowledge that these data cannot distinguish between peer influence and peer selection, and thus gene-environment correlation

cannot be ruled out; future analyses are planned to investigate this question. Scherrer, J., Grant, J., Duncan, A., Pan, H., Waterman, B., Jacob, T., Haber, J., True, W., Heath, A., and Bucholz, K. Measured Environmental Contributions to Cannabis Abuse/Dependence in an Offspring of Twins Design. Addict. Behav., 33(10), pp. 1255-1266, 2008.

Comorbidity and Course of Substance Use from 12 to 22

The present study sought to understand concurrent links among diagnoses of substance use disorders, internalizing disorders, and behavior disorders at age 18 as well as developmental trajectories of illicit substance use prior to and after this point. Using data from 585 participants (52% male) in the Child Development Project, this study examined comorbidity among substance use, behavior, and internalizing disorders at age 18 and trajectories of growth in illicit substance use from age 12 to age 22. In this community sample, meeting diagnostic criteria for comorbid internalizing disorders, a behavioral disorder (conduct disorder or oppositional defiant disorder) alone, or both internalizing and behavioral disorders predicted higher concurrent substance use disorders (abuse, dependence, or withdrawal). Meeting diagnostic criteria for an anxiety disorder alone or depression alone did not predict higher concurrent substance use diagnoses. Over time, youths with behavioral disorders at age 18 showed a pattern of increasing substance use across early adolescence and higher levels of substance use than those with no diagnosis at age 18. Substance use declines from late adolescence to early adulthood were observed for all groups. Similar to previous literature, substance use disorders were more highly comorbid with behavior disorders than with internalizing disorders at age 18, and behavior disorder and comorbid behavior-internalizing disorders at age 18 were related to trajectories characterized by steep increases in illicit substance use during adolescence and high rates of illicit substance use over time. Lansford, J., Erath, S., Yu, T., Pettit, G., Dodge, K., and Bates, J. The Developmental Course of Illicit Substance Use from Age 12 to 22: Links with Depressive, Anxiety, and Behavior Disorders at Age 18. J. Child Psychol. Psychiatry, 49(8), pp. 877-885, 2008.

Sex Risk Behaviors of Drug Users: a Dual Site Study of Predictors Over Time

Reducing sex risk behaviors among high-risk injection drug users (IDUs) and crack smokers is a continuing challenge for controlling the spread of HIV. In a longitudinal study of sexually active Puerto Rican IDUs and crack smokers in New York (n = 573) and Puerto Rico (n = 264), researchers examined baseline predictors of changes in sex risk (number of unprotected sex acts) at 6 month and 36-month follow-up interviews. In New York, predictors of higher sex risk were younger age, having primary partners, having more other sex partners, never exchanging sex, having lower self-efficacy for reducing sex risk behaviors, and being HIV-negative. These predictors were significant at both postbaseline periods. In Puerto Rico, short-term predictors included being male, having primary partners, never exchanging sex, lower sex risk norms and lower self-efficacy. However, only having primary partners was significant in longer-term behaviors. These findings suggest the need for enhancing self-efficacy and for developing risk reduction strategies related to community differences. Deren, S., Strauss, S., Kang, S., Colon, H., and Robles, R. Sex Risk Behaviors of Drug Users: A Dual Site Study of Predictors Over Time. AIDS Educ. Prev., 20(4), pp. 325-337, 2008.

Characteristics of Injection Drug Users who Participate in Drug Dealing: Implications for Drug Policy

Researchers evaluated factors associated with drug dealing among injection

drug users (IDUs) in Vancouver, Canada, and examined self-reported drug-dealing roles and reasons for dealing. Among 412 IDUs seen from March through December 2005, 68 (17%) had dealt drugs during the previous six months. Variables independently associated with drug dealing included: recent incarceration (adjusted odds ratio [AOR] = 2.9; 95%CI: 1.4-6.0); frequent heroin injection (AOR = 2.5; 95% CI: 1.4-4.6); frequent cocaine injection (AOR = 2.0; 95%CI: 1.1-3.8); and recent overdose (AOR = 2.7; 95%CI: 1.0-7.3). The most common drug-dealing roles were direct selling (82%), middling (35%), and steering (19%), while the most common reasons for dealing included obtaining drugs (49%) and money (36%). Drug dealing among IDUs was predicted by several markers of higher intensity addiction, and drug-dealing IDUs tended to occupy the most dangerous positions in the drug-dealing hierarchy. These findings suggest that elements of "balanced" drug policies may undermine each other and indicate the need for alternative interventions. Kerr, T., Small, W., Johnston, C., Li, K., Montaner, J., and Wood, E. Characteristics of Injection Drug Users who Participate in Drug Dealing: Implications for Drug Policy. J. Psychoactive Drugs, 40(2), pp. 147-152, 2008.

Adolescent Cannabis Problems and Young Adult Depression: Male-female Stratified Propensity Score Analyses

Cannabis use and depression are two of the most prevalent conditions worldwide. Adolescent cannabis use is linked to depression in many studies, but the effects of adolescent cannabis involvement on young adult depression remain unclear and may differ for males versus females. In this cohort study of youth from a mid-Atlantic metropolitan area of the United States, repeated assessments from 1985 (at age 6 years) through 2002 (at age 21 years) were made for 1,494 individuals (55% female). Measured covariate differences between individuals with and without cannabis problems were controlled via propensity score techniques. The estimated risk of young adult depression for adolescents with cannabis problems was not significantly different from that for comparison adolescents for either females (odds ratio = 0.7, 95% confidence interval: 0.2, 2.3) or males (odds ratio = 1.7, 95% confidence interval: 0.8, 3.6). The evidence does not support a causal association linking adolescent-onset cannabis problems with young adult depression. Harder, V., Stuart, E., and Anthony, J. Adolescent Cannabis Problems and Young Adult Depression: Male-Female Stratified Propensity Score Analyses. Am. J. Epidemiol., 168(6), pp. 592-601, 2008.

Children Taking Risks: The Association with Cocaine and Other Drug Use by Young Adulthood

The authors evaluate the long-term predictive strength of a novel cartoon-based risk-taking trait assessment, which might prove to have utility in future research on mechanisms leading toward illegal drug involvement. The longitudinal study population originated as 2311 first-graders entering 19 elementary schools during two successive school years. The assessments started soon after the children entered primary school. The key response variable was participants' use of cocaine by the time of a young adult assessment. The authors found that for each standard deviation increase in the risk-taking scale there was a two-fold increase in the risk of becoming a cocaine user by young adulthood (estimated relative risk, RR=1.9; 95% confidence interval, CI=1.3, 2.7). Independently, onset of cannabis use by young adulthood was also predicted by risk-taking scale values, but use of legal drugs (alcohol and tobacco) was not. These long-span associations provide support for new research on very early risk-taking mechanisms that lead toward illegal drug involvement. Rios-Bedoya, C., Wilcox, H., Piazza, M., and Anthony, J. Children Taking Risks: The Association with Cocaine and Other Drug Use by Young Adulthood. Addict. Behav., 33(9), pp. 1154-1161, 2008.

Some Moms Quit Cigarettes, Marijuana, & Alcohol during Pregnancy, but Dads Don't

With the possible exception of cigarette smoking, little attention is paid to substance abuse among men whose partner is pregnant. An understanding of men's patterns of substance use during their partner's pregnancy is necessary to identify critical periods for intervention to reduce children's exposure to paternal substance use. This study examined the relationship between pregnancy or partner's pregnancy and patterns of binge drinking, cigarette use, and marijuana use, desistance, and return to use over a 3-year period from age 21 to 24 years. Data were drawn from the Seattle Social Development Project, a longitudinal study of prosocial and antisocial behavior. 808 (412 male, 396 female) students entering 5th grade in participating schools in the fall of 1985 that consented to participate constitute the sample. Interviews were conducted yearly from ages 10 to 16, at ages 18, 21, and 24. The data used in this study were obtained from age 24 data. Event history calendars were administered at age 24 and were retrospective to 21 years. To provide temporal context, a series of questions about live events, work, and school history were asked. Reports of events were probed to identify the month and year in which they occurred, and repeated events were probed to identify the month and year of each occurrence. Pregnancy was deduced based on the birth date of the child. Men were as likely to binge drink during their partner's pregnancy as they were when their partner was not pregnant. In contrast, women were significantly less likely to binge drink during pregnancy compared with before or after pregnancy. Men were less likely to smoke when their partner was pregnant than they were when their partner was not pregnant. Similarly, women were less likely to smoke during pregnancy than they were before or after pregnancy. Men were as likely to use marijuana during their partner's pregnancy as they were when their partner was not pregnant. Women were less likely to use marijuana when they were pregnant than when they were not pregnant. Because of a return to cigarette smoking among men and to all three forms of substance use among women occurs so soon after birth, the first few months postpartum may provide a critical opportunity for intervention. Men's binge drinking and marijuana use were unaffected by their partner's pregnancy or by the birth of their child suggesting the importance of reaching new fathers-to-be with messages about the importance of stopping substance use during their partner's pregnancy. Reductions in substance use among fathers both during pregnancy and after the birth of their child may increase the probability that mothers will desist from substance use during pregnancy, decrease the probability that mothers will relapse to use postpartum, and reduce children's exposure to harmful substance use in the home environment. Bailey, J.A., Hill, K.G., Hawkins, J.D., Catalano, R.F., and Abbott, R.D. Men's and Women's Patterns of Substance Use Around Pregnancy. Birth, 35(1), pp. 50-59, 2008.

Validity of Self-reported Substance Use in Men who Have Sex with Men: Comparisons with a General Population Sample

The authors examined the validity of self-reported recent drug use in men who have sex with men (MSM). They obtained a probability sample of Chicago men who have sex with men (MSM; n=216) and administered urine and saliva drug testing after a self-administered interview. Analyses examined participation in drug testing, the agreement between self-reported past month drug use and drug test results, correlates of underreporting, and the relative utility of drug testing versus self-reports in identifying recent marijuana and cocaine use. For marijuana and cocaine, findings were compared with those obtained from a general population sample of men (n=241). More than three quarters of the participants in both samples provided at least one specimen for drug testing. Self reports in both samples showed a high degree of correspondence with drug tests for marijuana but not for cocaine. Sensitivity for cocaine use

reporting was 60% for the MSM sample and 40% for the general-population men. Conditional kappa and sensitivity statistics for marijuana, cocaine, 3, 4 methylenedioxy methamphetamine (i.e., MDMA, "ecstacy"), and methamphetamine suggested that self reports among MSM are provided with a high degree of validity. Underreporting was a correlate of social class (education, income, and employment) in the general population but not in the MSM sample. The utility of drug testing was dependent on social class in the general population sample. The authors suggest that drug testing is feasible in epidemiological surveys of drug use. Self reports among MSM are at least as valid as those provided by a general population sample of men. In some instances (e.g., cocaine use), they may actually be of higher quality. Although the findings support the merit of epidemiological studies of MSM drug use that have relied completely on self-reporting, drug tests may be useful for clarifying club drug ingestion patterns. Fendrich, M., Mackesy-Amiti, M., and Johnson, T. Validity of Self-reported Substance Use in Men who Have Sex with Men: Comparisons with a General Population Sample. Ann. Epidemiol., 18(10), pp. 752-759, 2008.

Autosomal Linkage Analysis for Cannabis Use Behaviors in Australian Adults

Cannabis is the most commonly used illicit drug in developed and in developing nations. Twin studies have highlighted the role of genetic influences on early stages of cannabis use, such as a lifetime history of use, early-onset use and frequent use, however, there have been few genomic studies that have examined these phenotypes. Using data on 2,314 families consisting of 5,600 adult Australian offspring and their parents, all of whom were scanned using 1,399 unique autosomal markers, the authors conducted autosomal linkage analyses for lifetime history of cannabis initiation, early-onset cannabis use and frequency of use, using a variance components approach in the linkage package MERLIN. Suggestive evidence for linkage was found on chromosome 18 (logarithm of odds (LOD) 2.14 for frequency of use, LOD 1.97 for initiation, at 90-97cM) and also on chromosome 19 (LOD 1.92 for early-onset at 17cM). These LOD scores did not meet genome-wide significance. Further replication of these linkage regions in other samples will be required, although these initial results suggest further targeted efforts on chromosome 18 may yield interesting candidate genes for early stages of cannabis-related behaviors. Agrawal, A., Morley, K., Hansell, N., Pergadia, M., Montgomery, G., Statham, D., Todd, R., Madden, P., Heath, A., Whitfield, J., Martin, N., and Lynskey, M. Autosomal Linkage Analysis for Cannabis Use Behaviors in Australian Adults. Drug Alcohol Depend., 98(3), pp. 185-190, 2008.

Genetic and Environmental Contributions to Nicotine, Alcohol, and Cannabis Dependence in Male Twins

The authors sought to compute the common and specific genetic and environmental contributions to nicotine dependence (ND) alcohol dependence (AD) and cannabis dependence (CD), utilizing a twin model design for the study. Data from 1874 monozygotic and 1498 dizygotic twin pair members of the Vietnam Era Twin Registry were obtained via telephone administration of a structured psychiatric interview in 1992. Data to derive life-time diagnoses of DSM-III-R ND, AD and CD were obtained via telephone administration of the Diagnostic Interview Schedule. The best-fitting model allowed for additive genetic contributions and unique environmental influences that were common to all three phenotypes. Risks for ND and AD were also due to genetic and unique environmental influences specific to each drug. A specific shared environmental factor contributed to CD. These results suggest that the life-time co-occurrence of ND, AD and CD is due to common and specific genetic factors as well as unique environmental influences, and vulnerability for CD is also due to shared environmental factors that do not contribute to ND and AD. The

majority of genetic variance is shared across drugs and the majority of unique environmental influences are drug-specific in these middle-aged men. Because differences between models allowing for specific genetic versus shared environment were small, the authors suggest that there are specific familial contributions-either additive genetic or shared environment-to CD. Xian, H., Scherrer, J., Grant, J., Eisen, S., True, W., Jacob, T., and Bucholz, K. Genetic and Environmental Contributions to Nicotine, Alcohol and Cannabis Dependence in Male Twins. Addiction, 103(8), pp. 1391-1398, 2008.

The HCV Synthesis Project: Scope, Methodology, and Preliminary Results

Hepatitis C virus (HCV) is hyper-endemic among injecting drug users, and increasingly so among non-injection drug users who smoke, snort, or sniff heroin, cocaine, crack, or methamphetamine. To summarize the research literature on HCV in drug users and identify gaps in knowledge, researchers conducted a synthesis of the relevant research carried out between 1989 and 2006. They used rigorous search methods to identify and extract data from published and unpublished reports of HCV among drug users. They designed a quality assurance system for all phases of the project and created a set of items to assess study design quality of each report that they included. In all, they found 629 reports containing HCV prevalence rates, incidence rates and/or genotype distribution among injecting or non-injecting drug user populations published between January 1989 and December 2006. The majority of reports were from Western Europe (41%), North America (26%), Asia (11%) and Australia/New Zealand (10%). They also identified reports from Eastern Europe, South America, the Middle East, and the Caribbean. The number of publications reporting HCV rates in drug users increased dramatically between 1989 and 2006, to 27-52 reports per year after 1998. The data collection and quality assurance phases of the HCV Synthesis Project have now been completed and are providing a rich source of information on HCV in drug users worldwide. Specifically, analyses are underway to understand HCV etiology relative to type of drug used and route of administration. Further, the project is able to examine data across a larger set of studies, which is especially important for HCV seroconversion studies that suffer from small sample sizes and low power to examine risk factors. Stern, R., Hagan, H., Lelutiu-Weinberger, C., Des Jarlais, D., Scheinmann, R., Strauss, S., Pouget, E., and Flom, P. The HCV Synthesis Project: Scope, Methodology, and Preliminary Results. BMC Med. Res. Methodol., 8, pp. 62-74, 2008.

Are There Genetic Influences on Addiction: Evidence from Family, Adoption and Twin Studies

In this era of gene discovery, the authors review evidence from family, adoption and twin studies that examine the genetic basis for addiction. With a focus on the classical twin design that utilizes data on monozygotic and dizygotic twins, they examine support in favor of heritable influences on alcohol, nicotine, cannabis and other illicit drug dependence. They review whether these genetic factors also influence earlier stages (e.g. experimentation) of the addictive process and whether there are genetic influences specific to each psychoactive substance. Converging evidence from these studies supports the role of moderate to high genetic influences on addiction. The changing role of these heritable factors as a function of gender, age and cultural characteristics is also discussed. The authors highlight the importance of the interplay between genes and the environment as it relates to risk for addiction and the utility of the children-of-twins design for emerging studies of gene-environment interaction is presented. Despite the advances being made by low-cost high-throughput whole genome association assays, the authors suggest that information garnered from twin studies, especially

extended twin designs with power to examine gene-environment interactions, will continue to form the foundation for genomic research. Agrawal, A., and Lynskey, M. Are There Genetic Influences on Addiction?: Evidence from Family, Adoption and Twin Studies. Addiction, 103(7), pp. 1069-1081, 2008.

Director's Report to the National Advisory Council on Drug Abuse - February, 2009

Research Findings - Prevention Research

National Youth Anti-Drug Media Campaign: No Effect on Youths

This study examined the cognitive and behavioral effects of the National Youth Anti-Drug Media Campaign on youths aged 12.5 to 18 years and reports core evaluation results. From September 1999 to June 2004, 3 nationally representative cohorts of US youths aged 9 to 18 years were surveyed at home 4 times. Sample size ranged from 8,117 in the first to 5,126 in the fourth round (65% first-round response rate, with 86%-93% of still eligible youths interviewed subsequently). Main outcomes were self-reported lifetime, past-year, and past-30-day marijuana use and related cognitions. Most analyses showed no effects from the campaign. From interview round three to interview round four, however, more ad exposure predicted less intention to avoid marijuana use, and weaker antidrug social norms at the subsequent round. Indeed, campaign ad exposure at round 3 predicted marijuana initiation at round 4. Through June 2004, the campaign is unlikely to have had favorable effects on youths and may have had delayed unfavorable effects. This evaluation challenges the usefulness of the campaign. Hornik, R., Jacobsohn, L., Orwin, R., Piesse, A., and Kalton, G. Effects of the National Youth Anti-Drug Media Campaign on Youths. Am. J. Public Health, 98(12), pp. 2229-2236, 2008.

Intervention Effects Foster Parent Stress and Child Cortisol Levels

Foster children exhibit high rates of atypical neuroendocrine functioning compared to children in the general population. In particular, alterations in the daytime diurnal activity of the hypothalamic-pituitary-adrenal (HPA) axis have been observed in foster children, often characterized by blunted salivary cortisol levels (i.e., low morning levels that remain low throughout the day). There is emerging evidence that therapeutic interventions for foster children can affect this pattern of HPA axis activity, but the specific intervention components responsible for change have not been fully explicated. Within a randomized trial to evaluate a therapeutic intervention for foster preschoolers (n = 57 intervention condition; n = 60 comparison condition; n = 60 community comparison condition), the present study examined whether diurnal cortisol activity was associated with caregiver self-reported stress in response to child problem behavior. Results showed immediate reductions in caregiver stress that were sustained through 12 months postbaseline in the intervention condition. In contrast, caregivers in the regular foster care condition showed higher rates of stress across time and increased stress sensitivity to child problem behaviors. In addition, among caregivers in regular foster care, higher self-reported stress was associated with lower morning cortisol levels and more blunted diurnal cortisol activity. These results provide evidence that interventions can simultaneously impact caregiver stress and buffer children

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from the negative impacts of caregiver stress on HPA axis regulation. Fisher, P., and Stoolmiller, M. Intervention Effects on Foster Parent Stress: Associations with Child Cortisol Levels. Dev. Psychopathol., 20(3), pp. 1003-1021, 2008.

Long-Term Effects of Universal Preventive Interventions on Youth Prescription Drug Use

This article reports on the long-term effects of universal preventive interventions conducted during middle school on 17-21-year-olds' prescription drug misuse. Two randomized controlled prevention trials were conducted in public schools in the rural Midwest of the United States. Study 1 began in 1993, with 667 6th-graders and follow-ups with 12th-graders and 21-year-olds included 457, and 483 participants, respectively. Study 2 began in 1998 with 7th-graders (total sample across waves 2127) and follow-ups with 11th- and 12th-graders included 1,443 and 1,212 participants, respectively. In study 1, schools were assigned to the Iowa Strengthening Families Program (ISFP), Preparing for the Drug Free Years, or a control condition. In study 2, schools were assigned to the school-based Life Skills Training (LST) plus a revised ISFP, called SFP 10-14 (LST + SFP 10-14), LST-only, or a control condition. Measures for this study included self reports of lifetime and past-year prescription drug misuse, collected starting in 10th grade in study 1 and 9th grade in study 2. The findings for study 1 indicated that 12th-grade ISFP intervention condition participants' past year narcotic misuse was significantly less than controls, as was life-time narcotic and barbiturate misuse rates for 21 year-old ISFP intervention participants. In study 2, LST + SFP 10-14 showed significant effects on life-time prescription drug misuse at the 11th-grade follow-up, while effects at the 12th-grade follow-up were marginally significant. The results suggest that universal interventions have potential for public health impact by reducing some types of prescription drug misuse among adolescents and young adults. Spoth, R., Trudeau, L., Shin, C., and Redmond, C. Long-Term Effects of Universal Preventive Interventions on Prescription Drug Misuse. Addiction, 103(7), pp. 1160-1168, 2008.

5.5 Year Follow-up Substance Use Outcomes for Universal Family and School Adolescent Preventive Interventions

This study examines adolescent substance use outcomes of universal family and school preventive interventions 5.5 years past baseline. Seventh grade students from 36 schools were randomly assigned to one of three conditions: (1) the school-based Life Skills Training (LST) plus the Strengthening Families Program for Parents and Youth 10-14 (SFP 10-14), (2) LST-alone, or (3) a control condition. Self-reported measures, including substance initiation, frequency of substance use, and measures of problematic or serious substance use, were collected at baseline, 6 months after the interventions, and again yearly through the 12th grade. A composite substance initiation index measure (SII) was derived from the data. Both the LST + SFP 10-14 condition and the LST alone condition reduced the growth in substance initiation as measured by the SII index. Program effectiveness results for individual substance initiation measures varied by study condition and by analytic method used to assess effectiveness. While no program effects on the overall sample were detected for the more serious substance use outcomes, intervention conditions prevented escalation into more problematic behaviors among high-risk youth (those who reported use of at least two substances at pretest). Spoth, R., Randall, G., Trudeau, L., Shin, C., and Redmond, C. Substance Use Outcomes 5 1/2 Years Past Baseline for Partnership-Based, Family-School Preventive Interventions. Drug Alcohol Depend., 96(1-2), pp. 57-68, 2008.

Risk and Protective Factors During Adolescence that Predict

Future Smoking and Other Problem Behaviors

This study identifies risk and protective factors during early and later adolescence that predict future regular smoking and multiple problem behavior among at-risk youth, defined as those who tried smoking by grade 7. At grades 7, 10, and 12, data were collected from 2,000 early smokers drawn from California and Oregon. Multivariate regression analyses tested predictors of the two grade 12 outcomes in separate models using data from grades 7 and 10. Gender interactions and buffering of risk factors by protective factors were assessed. The results indicate that for at-risk youth, consistent protective factors against future smoking and problem behavior included living in an intact nuclear family, getting good grades, and parental disapproval of smoking/drug use. Consistent risk factors included exposure to substance-using peers and problems in school. Adult substance use was a predictor during early, but not later, adolescence. Pro-smoking/drug use beliefs were significant predictors during later adolescence. There were few differences across gender and no significant buffers against risk. The authors suggest that at-risk youth would benefit from peer resistance training, parental involvement in prevention efforts, and efforts to improve educational performance during both middle school and high school. Changing pro-drug beliefs may be more effective among older adolescents. Ellickson, P., Tucker, J., and Klein, D. Reducing Early Smokers ' Risk for Future Smoking and Other Problem Behavior: Insights from a Five-Year Longitudinal Study. J. Adolesc. Health, 43(4), pp. 394-400, 2008.

Temporal Associations of Cigarette Smoking with Social Influences, Academic Performance, and Delinquency

This study examined the temporal associations of cigarette smoking in youth with prosmoking social influences, academic performance, and delinquency in order to strengthen existing data that informs the development of anti-smoking prevention efforts. The investigators examined data from a cohort of 6,527 adolescents surveyed at ages 13, 16, 18, and 23 years as a part of trial to test the Project Alert prevention program. Results suggest that prosmoking peer and family influences were risk factors for future smoking throughout adolescence, with family influences perhaps also operating indirectly through the adolescents' exposure to prosmoking peers. There were reciprocal associations of youth smoking with parental approval, peer smoking, and poor grades (but not delinquency), with youth smoking emerging as a stronger antecedent than consequence of these psychosocial factors. Few gender differences in these associations were observed. These results suggest that adolescent smoking is associated with increased risk for future problems including delinquent behavior, academic difficulties, involvement with prosmoking peers, and perceiving greater parental approval of smoking. Tucker, J., Martinez, J., Ellickson, P., and Edelen, M. Temporal Associations of Cigarette Smoking with Social Influences, Academic Performance, and Delinquency: A Four-Wave Longitudinal Study from Ages 13-23. Psychol. Addict. Behav., 22(1), pp. 1-11, 2008.

Early Steps to Drug Abuse Prevention

This study presents the age 4 outcomes of children enrolled in the Early Steps Multi-site Project targeting the prevention of drug use risk. Seven hundred thirty-one families with a 2 year old child, in 3 geographical regions, who were enrolled in the Women Infants and Children (WIC) national food supplement program were screened for high risk behaviors related to a developmental trajectory leading to early-onset substance use and abuse were recruited and randomized to a brief family intervention or usual WIC services. At child ages 2 and 3, the intervention group caregivers were offered the Family Check-Up and linked parenting support services. Assessments were completed at baseline

when the children were age 2, and again when the children were age 3 and age 4. Latent growth models on caregiver reports at child ages 2, 3, and 4 revealed decreased behavior problems when compared with the control group. Intervention effects occurred predominantly among families reporting high levels of problem behavior at child age 2. Families in the intervention condition improved on direct observation measures of caregivers' positive behavior support at child ages 2 and 3. Improvements in positive behavior support mediated improvements in children's early problem behavior. These findings support the potential long-term benefits of brief, family-based interventions in early childhood. Dishion, T., Shaw, D., Connell, A., Gardner, F., Weaver, C., and Wilson, M. The Family Check-Up with High-Risk Indigent Families: Preventing Problem Behavior by Increasing Parents' Positive Behavior Support in Early Childhood. Child. Dev., 79(5), pp. 1395-1414, 2008.

Messages About Social Harms of Inhalants More Effective than Physical Harm Messages

This study investigates an approach for reducing inhalant initiation among younger adolescents. The approach seeks to alter Socio-Personal Expectations (SPEs), a term referring to perceived linkages between behavior and personally relevant social outcomes. The study focuses specifically on expectations regarding outcomes associated with increased social status and popularity. An anti-inhalant message was embedded within a short anti-bullying education video. Young adolescents (N = 893) were assigned randomly to receive a message focused on the physical or the social harms of inhalant use. The objectives of this study were to test: (1) the malleability of socio-personal expectations, (2) the predictive validity of socio-personal expectations for future inhalant use, and (3) whether being exposed to a socio-personal threat, rather than a physical threat, leads to different decision-making processes. Analysis of variance suggested the malleability of socio-personal expectations, and multiple regression analysis revealed that these expectations were predictive of future inhalant use. Socio-personal expectations accounted for a significant portion of variance in future intentions over and above demographic variables, prior use, psychosocial variables, and perceived physical harm. Moreover, being exposed to a social, rather than a physical threat, message resulted in different variables being predictive of future intentions to use inhalants. The findings of the current study lend support to broaden the focus of media intervention efforts to include expectations regarding social acceptance or popularity along with discussion of physical harms. Based on current knowledge, there appears little to be gained by focusing solely on physical harms. A more intensive focus on social expectations could prove effective in persuading adolescents to refrain from use of a class of drugs that represents a serious threat to the well-being of all who use them. Siegel, J., Alvaro, E., Crano, W., Skenderian, J., Lac, A., and Patel, N. Influencing Inhalant Intentions by Changing Socio-Personal Expectations. Prev. Sci., 9(3), pp. 153-165, 2008.

One Year Outcome Study of 4th Replication of Project Towards No Drug Abuse

This study examined the one-year outcomes of the fourth experimental trial of Project Towards No Drug Abuse. Two theoretical content components of the program (i.e., cognitive perception information and cognitive perception information plus behavioral skills) were examined to increase understanding of the relative contribution of each to the effectiveness of the program. High schools in Southern California (n=18) were randomly assigned to one of three conditions: the two comparative program conditions and a standard care condition. The curricula were delivered to high school students (n=2734) by project health educators and regular classroom teachers. Program effectiveness was assessed with both dichotomous and continuous measures of

30-day substance use at baseline and one-year follow-up. Across all program schools, the two different curricula failed to significantly reduce dichotomous measures of substance use (cigarette, alcohol, marijuana, and hard drugs) at one-year follow-up. Both curricula exerted an effect only on the continuous measure of hard drug use, indicating a 42% ($p=0.02$) reduction in the number of times hard drugs were used in the last 30 days in the program groups relative to the control. In summary, the one-year effects of Project TND on hard drug use that have been shown in previous trials were replicated in the present study. The lack of main effects on the use of cigarettes, alcohol, and marijuana is contrary to previous findings. Sun, P., Sussman, S., Dent, C., and Rohrbach, L. One-Year Follow-Up Evaluation of Project Towards No Drug Abuse (TND-4). Prev. Med., 47, pp. 438-442, 2008.

Early Findings from the Community Youth Development Study

This study reports findings from Communities That Care (CTC), a prevention system designed to reduce levels of adolescent delinquency and substance use through the selection and use of effective preventive interventions tailored to a community's specific profile of risk and protection. This article describes early findings from the first group-randomized trial of CTC. A panel of 4,407 fifth-grade students was surveyed annually through seventh grade. Analyses were conducted to assess the effects of CTC on reducing levels of targeted risk factors and reducing initiation of delinquent behavior and substance use in seventh grade, 1.67 years after implementing preventive interventions selected through the CTC process. Results indicate that mean levels of targeted risks for students in seventh grade were significantly lower in CTC communities compared with controls. Specifically, significantly fewer students in CTC communities than in control communities initiated delinquent behavior between grades 5 and 7. No significant intervention effect on substance use initiation by spring of seventh grade was observed. CTC's theory of change hypothesizes that it takes from 2 to 5 years to observe community-level effects on risk factors and 5 or more years to observe effects on adolescent delinquency or substance use. These early findings indicating hypothesized effects of CTC on targeted risk factors and initiation of delinquent behavior are promising. Hawkins, J., Brown, E., Oesterle, S., Arthur, M., Abbott, R., and Catalano, R. Early Effects of Communities That Care on Targeted Risks and Initiation of Delinquent Behavior and Substance Use. J. Adolesc. Health, 43(1), pp. 15-22, 2008.

Improving Implementation Through the Communities That Care Operating System

This paper describes the development, application, and results of an implementation monitoring component of the Communities That Care (CTC) prevention framework used in the Community Youth Development Study (CYDS) to ensure high-fidelity prevention program implementation. CYDS is a randomized controlled trial of 24 communities (12 CYDS, 12 usual services), designed to test the effects of the CTC operating system on community prevention services and on levels and trends in drug abuse risk and protective factors among youth aged 9 through 18. The implementation monitoring system was created based on research that community-based implementation of evidence-based prevention programs often includes adaptations in program design, content, or manner of delivery. A lack of fidelity to the implementation standards delineated by program designers is one indicator of a gap between prevention science and practice which can lessen the likelihood that communities will realize the positive participant effects demonstrated in research trials. By using the CTC model to select and monitor the quality of prevention activities, the 12 CYDS communities replicated 13 prevention programs with high rates of adherence to the programs' core components and in accordance with dosage requirements regarding the number, length, and

frequency of sessions. This success indicates the potential of the CTC program implementation monitoring system to enhance community Prevention Delivery Systems and to improve the likelihood of desired participant changes. Fagan, A., Hanson, K., Hawkins, J., and Arthur, M. Bridging Science to Practice: Achieving Prevention Program Implementation Fidelity in the Community Youth Development Study. Am. J. Community Psychol., 41(3-4), pp. 235-249, 2008.

Drug Treatment is Associated with Better HIV Treatment Adherence

Using longitudinal data from the Women's Interagency HIV Study, this paper evaluated the relationship between drug abuse treatment modality and adherence to antiretroviral therapies. In prospective analyses, individuals who reported accessing any drug abuse treatment program were significantly more likely to report adherence to antiretroviral regimens. Involvement in either a medication-based or medication-free program was similarly associated with improved adherence. Drug abuse treatment programs, irrespective of modality, were associated with improved adherence to antiretroviral therapies among drug users. Concerted efforts to enroll individuals with drug use histories in treatment programs are warranted to improve HIV disease outcomes. Kapadia, F., Vlahov, D., Wu, Y., Cohen, M., Greenblatt, R., Howard, A., Cook, J., Goparaju, L., Golub, E., Richardson, J., and Wilson, T. Impact of Drug Abuse Treatment Modalities on Adherence to ART/HAART Among a Cohort of HIV Seropositive Women. Am. J. Drug Alcohol Abuse, 34(2), pp. 161-170, 2008.

Early Intervention for Externalizing Behavior Problems Can Also Impact Comorbid Internalizing Problems

This study used latent transition analysis (LTA) to examine changes in early emotional and behavioral problems in children age 2 to 4 years resulting from participation in a family-centered intervention. A sample of 731 economically disadvantaged families was recruited from among participants in the Women Infants and Children (WIC) program, a national food supplement and nutrition program--from three geographic locations. Families with toddlers between age 2 and 3 were randomized to receive either the Family Check-Up (FCU) or a no intervention (control). The FCU's linked interventions were tailored to each family's needs. Assessments occurred at age 2, 3, and 4. The FCU followed age 2 and age 3 assessments. Latent class analyses were conducted on mother reports of behavior and emotional problems from age 2 to 4 to study transitions among the following four groups: (a) externalizing only, (b) internalizing only, (c) comorbid internalizing and externalizing, and (d) normative. Results revealed that participation in the FCU increased the likelihood of transitioning from either the comorbid or the internalizing class into the normative class by age 4. These results suggest the potential for family interventions in early childhood to disrupt the early emergence of both emotional and behavioral problems. Connell, A., Bullock, B., Dishion, T., Shaw, D., Wilson, M., and Gardner, F. Family Intervention Effects on Co-occurring Early Childhood Behavioral and Emotional Problems: A Latent Transition Analysis Approach. J. Abnorm. Child Psychol., 36(8), pp. 1211-1225, 2008.

Bidirectional Relations Between Child Behavior and Parental Well-Being

Although much has been written about transactional models in the study of parenting practices, relatively few researchers have used this approach to examine how child behavior might be related to parental well-being. This study used latent growth curve modeling to test transactional models of age 2 child noncompliance, parental depressive symptoms, and age 4 internalizing and externalizing behaviors using a subsample of families in the Early Steps

Multisite Study, a randomized controlled trial of the Family Check-up Intervention with 731 families with a toddler at high risk for early onset child behavior problems. In unconditional models, maternal depressive symptoms showed a linear decrease from child ages 2 to 4, whereas paternal depression did not show significant change. Observed child noncompliance at age 2 showed significant associations with concurrent reports of maternal depressive symptoms and trend-level associations with paternal depressive symptoms. For both parents, higher levels of initial depressive symptoms were related to increased age 4 child internalizing behaviors. The findings provide support for reciprocal process models of parental depression and child behavior, and this study is one of the first to present empirical evidence that fathers' depressive symptoms have bidirectional associations with their children's behavior in early childhood. Gross, H., Shaw, D., Moilanen, K., Dishion, T., and Wilson, M. Reciprocal Models of Child Behavior and Depressive Symptoms in Mothers and Fathers in a Sample of Children at Risk for Early Conduct Problems. J. Fam. Psychol., 22(5), pp. 742-751, 2008.

Increasing School Success through Partnership-Based Family Competency Training

This research tests a model examining the mediational pathways of effects of a universal partnership-based family competency training program on academic success in youth. Twenty-two rural schools were randomized to receive the Iowa Strengthening Families Program (ISFP) or a minimal contact control condition. Data on academic success, school engagement, substance related risk, and parent competency were collected from 445 families. Structural equation modeling was conducted to test the hypothesized relationships. The intervention increased parenting competencies and reduced students' substance-related risk in the sixth grade, thereby positively affecting school engagement and positively impacting upon twelfth grade academic performance. This research, conducted through a school-community-university partnership underscores the benefits of such collaborative efforts on academic outcomes and complements previous work on the impact of this intervention on substance use. Spoth, R., Randall, G.K., and Shin, C. Increasing School Success through Partnership-Based Family Competency Training: Experimental Study of Long-Term Outcomes. School Psychology Quarterly, 23(1), pp. 70-89, 2008.

Positive Effects of Media, Community, and School-Based Anti-Violence Intervention

In a community randomized controlled trial, intervention middle school students from small towns were exposed to a community and school-based anti-violence intervention ("Resolve It, Solve It"). The primary intervention was a media campaign in which local high school students served as models in print, radio, and television PSAs and spearheaded local school and community activities. The media campaign was supported with school and community events that reinforced campaign messages. Six middle schools across five different communities participated: two schools from one community in Kentucky and one school each from Louisiana, Illinois, Indiana, and California. All classrooms with seventh and eighth grade students were invited to participate. A total of 1,492 middle school students were surveyed with 404 male and 376 female students in the control condition, and 307 male and 405 female students in the intervention condition. Tests of recognition and recall indicated widespread exposure to the media intervention. Multiple group latent growth models indicated that relative to control students, intervention students reported significant differences in rates of growth for intent for violence, physical assault against people, verbal victimization, and perceived safety at school. No differences were found for verbal assault, physical assault against objects, physical victimization, or self-efficacy for avoiding violence. When

examined by sex, it was determined that results for physical assault against people were obtained only among female students, and changes in verbal victimization and perceived school safety were observed only among male students. These results suggest that a media and reinforcing community intervention led by older peers can alter rates of growth for some measures of violence and associated factors among small-town youth. Further research is indicated to determine how different campaign messages influence students by sex. Swaim, R., and Kelly, K. Efficacy of a Randomized Trial of a Community and School-based Anti-violence Media Intervention Among Small-Town Middle School Youth. Prev. Sci., 9(3), pp. 202-214, 2008.

Evaluating Retailer Behavior through Measurement of Youth Purchase Attempts

This study evaluated the potential of youth purchase attempts to detect actual changes in retail availability of harmful legal products to get high. These results were triangulated with self-reports from retailers about their own policies and practices. Before the intervention, less than half of retailers reported using any of six possible strategies identified as ways to reduce youth access to harmful products, and less than 8% of baseline youth attempts to purchase potentially harmful legal products were refused or questioned. After the low-dosage intervention, retailers reported increased use of three strategies and a statistically significant increase in the percentage of purchase attempts that were either questioned or refused by retail clerks. These findings demonstrate the potential feasibility of retailer-focused environmental strategies and support continued use of youth purchase attempts as a measure of actual retailer behavior. Courser, M., Holder, H., Collins, D., Johnson, K., and Ogilvie, K. Evaluating Retailer Behavior in Preventing Youth Access to Harmful Legal Products: A Feasibility Test. Eval. Rev., 31(4), pp. 343-363, 2008.

Effects of Mexican Origin Family Structure on Parental Monitoring and Pre-Adolescent Substance Use and Expectancies

This study examines the relationship between the structure of Mexican origin families (i.e., nuclear, single-parent, blended or extended), and the parental monitoring, substance use expectancies, and substance use reported by pre-adolescents. The findings indicate that family structure did not differentiate the substance use prevalence, expectancies or parental monitoring among the 1224 low-income, Mexican-origin fifth grade participants. Parents from all family types demonstrated similar levels of parental monitoring. Most importantly, family composition was not related to pre-adolescents' substance use. In addition, findings indicated that the relationship between substance use and certain demographic variables (e.g., gender, country of birth, language use) did not differ across family structures. Warren, J.R., Wagstaff, D.A., Hecht, M.L., and Elek, E. The Effects of Mexican Origin Family Structure on Parental Monitoring and Pre-Adolescent Substance Use Expectancies and Substance Use. Journal of Substance Use, 13(4), pp. 283-292, 2008.

Innovative Technologies for Monitoring Intervention Fidelity in Rural School Sites

The present study examined the feasibility of an innovative technology designed to assess implementation fidelity of the Early Risers conduct problems prevention program across 27 geographically dispersed school sites. Previous randomized trials of the Early Risers program established the efficacy and effectiveness of the intervention. The current study is assessing the associations between fidelity and participants' psychosocial outcomes. In this article on feasibility of the fidelity monitoring system, a multidimensional construct of fidelity was used to assess the quantity of services provided

(exposure), the degree to which program strategies conformed to the manual (adherence), and how well implementers delivered the program (quality of delivery). The measurement technology featured a fidelity monitoring system that required (a) weekly reporting on a web-based documentation system to assess program exposure and adherence, and (b) five annually administered telephone interviews with a technical assistant to assess quality of program implementation. The results showed that the fidelity monitoring system was feasible, with all sites achieving 100% compliance in completion of their required on-line reporting and on average over 80% of the required teleconference interviews. User feedback indicated satisfaction with the web-based program. The system was successful in measuring multiple indices of fidelity. The strengths and limitations of measuring fidelity at a distance with web-based and teleconferencing technologies are discussed. Lee, C., August, G., Realmuto, G., Horowitz, J., Bloomquist, M., and Klimes-Dougan, B. Fidelity at a Distance: Assessing Implementation Fidelity of the Early Risers Prevention Program in a Going-to-Scale Intervention Trial. Prev. Sci., 9(3), pp. 215-229, 2008.

Higher Behavioral Problems Associated with Reentry into Foster Care

A recognized goal of family reunification programs is preventing the reentry of children into foster care. Although rates of reentry vary widely, the available evidence has demonstrated that reentry to foster care after a failed reunification attempt is not a rare event. Using data from the National Survey of Child and Adolescent Well-Being, this study examined reentry for 273 children between the ages of 5 and 12 years. In multivariate models, reentry into foster care was associated with higher Child Behavior Checklist (CBCL) scores and higher numbers of children in the household when the child is living at home. Although these are not the only risk factors that should be considered in deciding whether to reunify a child, these characteristics appear to be high valence problems for families and their children who are reunified. Future research on reentry and on placement disruptions from foster care should routinely include information about the number of children in the family and behavior problems when endeavoring to explain caseload dynamics. Barth, R.P., Weigensberg, E.C., Fisher, P.A., Fetrow, B., and Green, R.L. Reentry of Elementary Aged Children Following Reunification from Foster Care. Children and Youth Services Review, 30 pp. 353-364, 2008.

Evidence-Based Kernels: Fundamental Units of Behavioral Influence

This paper describes evidence-based kernels, fundamental units of behavioral influence that appear to underlie effective prevention and treatment for children, adults, and families. A kernel is a behavior-influence procedure shown through experimental analysis to affect a specific behavior and that is indivisible in the sense that removing any of its components would render it inert. Existing evidence shows that a variety of kernels can influence behavior in context, and some evidence suggests that frequent use or sufficient use of some kernels may produce longer lasting behavioral shifts. The analysis of kernels could contribute to an empirically based theory of behavioral influence, augment existing prevention or treatment efforts, facilitate the dissemination of effective prevention and treatment practices, clarify the active ingredients in existing interventions, and contribute to efficiently developing interventions that are more effective. Kernels involve one or more of the following mechanisms of behavior influence: reinforcement, altering antecedents, changing verbal relational responding, or changing physiological states directly. The paper describes 52 of these kernels, and details practical, theoretical, and research implications, including calling for a national database of kernels that influence human behavior. Embry, D., and Biglan, A. Evidence-Based Kernels:

Fundamental Units of Behavioral Influence. Clin. Child Fam. Psychol. Rev., 11(3), pp. 75-113, 2008.

Diffusion of Evidence-Based Drug Abuse Prevention: The Communities That Care System

Recent advances in prevention science provide evidence that adolescent health and behavior problems can be prevented by high-quality prevention services. However, many communities continue to use prevention strategies that have not been shown to be effective. This paper describes the rationale, aims, intervention, and design of the Community Youth Development Study, a randomized controlled community trial of the Communities That Care (CTC) system, and investigates the baseline comparability of the 12 intervention and 12 control communities in the study. Studying processes for promoting the dissemination and high-quality implementation of prevention strategies found to be effective in controlled research trials has become an important focus for prevention science. The CTC prevention operating system provides manuals, tools, training, and technical assistance to activate communities to use advances in prevention science to plan and implement community prevention services to reduce adolescent substance use, delinquency, and related health and behavior problems. Results indicate baseline similarity of the intervention and control communities in levels of adolescent drug use and antisocial behavior prior to CTC intervention. Hawkins, J., Catalano, R., Arthur, M., Egan, E., Brown, E., Abbott, R., and Murray, D. Testing Communities That Care: The Rationale, Design and Behavioral Baseline Equivalence of The Community Youth Development Study. Prev. Sci., 9(3), pp. 178-190, 2008.

Differences in Substance Use Among Bisexual and Heterosexual Young Women

This study examined similarities, and differences between bisexual, and heterosexual women in their substance use at ages 14 and 18, compared these groups at ages 14 and 18 on key psychosocial factors known to predict young adult substance use, and determined whether these psychosocial factors at age 18 could account for sexual orientation differences in substance use at age 23. Longitudinal survey data from a West Coast cohort were used to compare heterosexual (n = 1,479) and bisexual (n = 141) women on their substance use and psychosocial characteristics. Results indicated that during adolescence, bisexual women were more likely to have been current and solitary substance users, to have reported stronger pro-drug beliefs and lower resistance self-efficacy, to have reported greater perceived parental approval of their substance use, to have had more exposure to substance-using peers, and to have reported poorer mental health. By age 23, bisexual women had higher rates of current substance use, greater quantity and frequency of use, and more problematic alcohol and drug use. Differences in problematic use at age 23 could be partially explained by risk factors assessed five years earlier at age 18, particularly pro-drug social influences and beliefs. Notwithstanding the lack of longitudinal data on sexual orientation, these results provide important insights regarding the drug prevention needs of bisexual women. Tucker, J., Ellickson, P., and Klein, D. Understanding Differences in Substance Use Among Bisexual and Heterosexual Young Women. Womens Health Issues, 18(5), pp. 387-398, 2008.

Gender Differences in Physical and Relational Aggression as Predictors of Drug Use in High School Students

The present study investigated the longitudinal relationships between physical and relational aggression and later drug use, as moderated by gender. Self-reported data were gathered from 2,064 high school students at pretest and 1-

year post-test to test the hypotheses that (1) males would engage in more physical aggression than females, whereas females would engage in more relational aggression than males; and (2) physical aggression would be a stronger drug use predictor for males and relational aggression a stronger predictor for females. Results indicated that males reported engaging in more physical aggression than females at baseline; however, females and males reported engaging in similar rates of relational aggression. After controlling for relational aggression, baseline drug use, and demographic variables, physical aggression at baseline was found to predict alcohol use 1-year later for males but not for females. After controlling for physical aggression, baseline drug use, and demographic variables, relational aggression was found to predict cigarette use and marijuana use for females but not for males. However, relational aggression was found to predict later alcohol and hard drug equally across gender. These findings suggest that both physical and relational aggression are predictive of subsequent drug use and have important implications for violence and drug use prevention intervention efforts. Skara, S., Pokhrel, P., Weiner, M., Sun, P., Dent, C., and Sussman, S. Physical and Relational Aggression as Predictors of Drug Use: Gender Differences Among High School Students. Addict. Behav., 33(12), pp. 1507-1515, 2008.

Cross-National Study of Substance Use Rates among Preadolescents in Spain and Arizona

This study aims to comparatively examine drug use in Arizona and Spain, in order to know if similarities and differences in drug use patterns justify the administration in Spain of U.S. prevention intervention programs. Data were obtained from independent samples of seventh-grade students recruited from urban public schools and surveyed in 1998. The samples included 4,035 ethnically diverse Arizona students (Latinos and non-Hispanic Whites), and 2,243 Spanish-White students. Odds ratios and Chi-square tests were used to assess and compare differences in drug use rates between preadolescents in Arizona and Spain taking into account gender. Ethnicity differences in preadolescent drug use and in psychosocial risk factors were examined using multivariate analysis. The results revealed similar trends in drug use between Arizona and Spain students, with gateway drugs already in use by early adolescents, and with higher rates of drug use among males than among females. However, cross-national differences in marijuana/cannabis use were noteworthy: Arizona preadolescents were over 25 times more likely to report marijuana/cannabis use than preadolescents from Spain. Moreover, when ethnic differences were considered, Latinos in Arizona reported higher marijuana/cannabis use compared with non-Latino students. Drug use patterns among Latino preadolescents, as well as the relevance of some risk factors among the diverse groups, were strongly influenced by their level of acculturation. Luengo, M., Kulis, S., Marsiglia, F., Romero, E., Gomez-Fraguela, J., Villar, P., and Nieri, T. A Cross-National Study of Preadolescent Substance Use: Exploring Differences Between Youth in Spain and Arizona. Subst. Use Misuse, 43(11), pp. 1571-1593, 2008.

Parents Influence Teen's Peer Relations and Drinking in College

This study examined the possible indirect influence that parents may have on their teen's alcohol use. Friends' alcohol use served as a mediator of the relationship between parenting characteristics and teen alcohol use in a longitudinal college sample. As part of a larger study of college student drinking, 392 incoming college freshmen were assessed for their perceptions of their parent's parenting practices, and their peer alcohol use. Results from SEM indicated that friend alcohol use (gathered in first semester freshman year) mediated the relationship between parental knowledge about what their teen was doing in his/her free time (gathered at baseline pre-matriculation to college) and individual use in college (gathered at second semester freshman

year). Findings suggest that during college parents continue to exhibit influence on the choices their teens make as far as friends, which in turn influences their teens' drinking in college. Abar, C., and Turrisi, R. How Important are Parents During The College Years? A Longitudinal Perspective of Indirect Influences Parents Yield on Their College Teens' Alcohol Use. Addict. Behav., 33(10), pp. 1360-1368, 2008.

Gambling Among African-American Adolescents

This study explores gender differences in lifetime and recent substance use/internalizing behavior, childhood externalizing behavior, and gambling preferences among African-American youth gamblers. Data are from a prospective study conducted within the context of a group randomized prevention trial targeting academic achievement and aggression in 27 first grade classrooms in nine urban primary schools primarily located in western Baltimore (N = 678). The study sample for this study focuses on the 452 African-American adolescents (54% male, mean age 17.1 years). The participants were enrolled in the study at entry into first grade and were followed for ten years. The overall estimated past-year gambling prevalence was 47.4%; 56.6% of males (n = 138), and 36.5% of females (n = 76) had gambled in the year preceding the interview. There were no differences in neighborhood disadvantage, parents' level of education, or first grade intervention status between gamblers and non-gamblers. Gambling was associated with high teacher ratings of childhood externalizing behaviors among males and with high parent ratings of childhood impulsivity and hyperactivity among both genders. Internalizing behavior was associated with female gambling. No male-female differences in substance use/lifetime or conduct disorder among gamblers were noted, however, overall, male gamblers had higher levels of externalizing behaviors as compared to female gamblers. Martins, S., Storr, C., Ialongo, N., and Chilcoat, H. Gender Differences in Mental Health Characteristics and Gambling Among African-American Adolescent Gamblers. Am. J. Addict., 17(2), pp. 126-134, 2008.

Adolescent Alcohol Involvement Predicts Major Depression in Young Adults

This study examined the extent to which four different adolescent alcohol dimensions (i.e., frequency of alcohol use, quantity of consumption, frequency of heavy episodic drinking, and frequency of problem use) were predictive of young-adult major depressive disorder (MDD). Participants in this prospective longitudinal study were 429 rural teens and their families. Self-reports of each dimension of adolescent alcohol involvement were obtained at ages 16 and 18. Depression diagnoses were obtained at age 22, using a structured interview. Analyses included adolescent depressed mood, measured via self-report at ages 16 and 18. Data were analyzed using confirmatory factor analysis and structural equation modeling. Results indicated that the multidimensional nature of adolescent alcohol involvement was best represented by a first-order problem-use factor and a second-order alcohol-intake factor comprised of quantity, frequency, and heavy drinking. After controlling for gender and depressed mood, adolescent problem use, but not alcohol intake, was a significant positive predictor of young-adult MDD. The findings help clarify the link between alcohol involvement and depression and suggest that harm-reduction strategies may help prevent later mood disorders. Mason, W., Kosterman, R., Haggerty, K., Hawkins, J., Redmond, C., Spoth, R., Shin, C., and Shin, C. Dimensions of Adolescent Alcohol Involvement as Predictors of Young-Adult Major Depression. J. Stud. Alcohol Drugs, 69(2), pp. 275-285, 2008.

Predictors of Heavy Drinking Among Youth Living in Permissive

Households

This study identified psychosocial factors that may deter adolescents living in permissive households from heavy drinking in Grades 9 and 11. Longitudinal data were obtained from 710 youth who participated in a study of the efficacy of the Alert Plus curriculum. Study participants completed surveys in grades 7 through 11. Permissive household was defined based on adolescent reports of whether the parents (1) would be upset if the adolescent drank or used marijuana, (2) knew their child's whereabouts when the adolescent was away from home, and (3) set curfews. The outcome of interest was frequency of heavy drinking in the last 30 days, defined as the number of days the adolescent had at least three alcoholic drinks. Three quarters of adolescents from permissive households reported heavy drinking at Grade 9, with less frequent heavy drinking among those who concurrently reported less exposure to peer and adult drinking, less peer approval of drinking, weaker positive beliefs about drinking, a stronger academic orientation, higher resistance self-efficacy, and less delinquency. Further, social influences and alcohol beliefs predicted the frequency of heavy drinking 2 years later among adolescents from permissive households. Although most of these factors were also predictive for adolescents from nonpermissive households, social influences, alcohol beliefs and resistance self-efficacy were stronger predictors of heavy drinking at Grade 9 among youth from permissive households. The authors conclude that alcohol prevention programs that target pro-drinking peer and adult influences, positive attitudes toward drinking, and resistance self-efficacy may be particularly important in deterring heavy drinking among adolescents living in permissive households. Tucker, J., Ellickson, P., and Klein, D. Growing Up in a Permissive Household: What Deters At-Risk Adolescents From Heavy Drinking? J. Stud. Alcohol Drugs, 69(4), pp. 528-534, 2008.

Developing Teacher Proficiency in Culturally-Grounded Drug Use Prevention

The authors describe the training model used to develop proficiency in teaching "keepin it REAL," a culturally-grounded prevention curriculum. Training effects were evaluated using three datasets. Analyses suggested that training should emphasize teaching adult learners, it should encompass culture from many perspectives, it should address the teaching of prevention curricula, and it should emphasize fidelity as imperative. Trainers found the embedded focus on culture in the program essential to success. Teachers learned that a prevention curriculum can be instructionally engaging while theory-driven and academically rigorous. Harthun, M., Dustman, P., Reeves, L., Hecht, M., and Marsiglia, F. Culture in the Classroom: Developing Teacher Proficiency in Delivering a Culturally-grounded Prevention Curriculum. J. Prim. Prev., 29, pp. 435-454, 2008.

Self-Efficacy as a Moderator of Self-Fulfilling Prophecy Effects: Mothers' Beliefs and Children's Alcohol Use

This study examined two issues relevant to self-fulfilling prophecies: 1) it examined whether children's risk for alcohol use, as indicated by their self-efficacy to refuse alcohol from peers, moderated their susceptibility to negative and positive self-fulfilling prophecy effects created by their mothers; and 2) it explored behavioral mediators that could be involved in the self-fulfilling process between mothers and children. Longitudinal data were collected from 540 mother-child dyads. Participants were families of seventh graders enrolled in 36 rural schools in 22 counties in Iowa. The results indicated that: 1) low self-efficacy children were more susceptible to their mothers' positive than negative self-fulfilling effects, whereas high self-efficacy children's susceptibility did not vary, 2) mothers' global parenting and children's perception of their

friends' alcohol use partially mediated mothers' self-fulfilling effects, and 3) these mediators contributed to low self-efficacy children's greater susceptibility to positive self-fulfilling prophecy effects. Willard, J., Madon, S., Guyll, M., Spoth, R., and Jussim, L. Self-Efficacy as a Moderator of Negative and Positive Self-Fulfilling Prophecy Effects: Mother's Beliefs and Children's Alcohol Use. European Journal of Social Psychology, 38, pp. 499-520, 2008.

Mediation of Mothers' Self-Fulfilling Effects on Children's Alcohol Use: Self-Verification, Informational Conformity, and Modeling Processes

This study examined whether self-fulfilling prophecy effects are mediated by self-verification, informational conformity, and modeling processes. These mediational processes were examined across multiple time frames using longitudinal data obtained from two samples of mother-child dyads (Sample 1 n=486; Sample 2 = n=287). Children's alcohol use was the outcome variable in these analyses. The results provided consistent support for self-verification as a mediator of mother's self-fulfilling effects. In both samples and across several years of adolescence, there was a significant indirect effect of mothers' beliefs on children's alcohol use through children's self-assessed likelihood of drinking alcohol in the future. Comparatively less support was found for informational conformity and modeling processes as mediators of mothers' self-fulfilling effects. Madon, S., Guyll, M., Buller, A., Scherr, K., Willard, J., and Spoth, R. The Mediation of Mothers' Self-Fulfilling Effects on Their Children's Alcohol Use: Self-Verification, Informational Conformity, and Modeling Processes. J. Pers. Soc. Psychol., 95(2), pp. 369-384, 2008.

Therapist Identification of Intimate Partner Violence

This study is a replication of research conducted more than a decade ago to examine mental health providers' ability to accurately perceive violence within couples presenting for therapy and to intervene in a manner that reduces risk. A decade ago, 40% of therapists sampled failed to identify the presence of intimate partner violence (IPV) and non predicted lethality. In the current study, a list of therapists, compiled from on-line websites maintained by 15 states within the United States consisting of independently licensed psychologists, clinical social workers, and marriage and family therapists was compiled. Twenty names and addresses from each of the states' licensing websites were randomly downloaded for the three different types of mental health providers, and a mail questionnaire was sent out for completion. The questionnaire included a case vignette and a series of open ended questions. One-hundred eleven of the 900 mailed surveys were returned. Two independent raters coded all of the vignette surveys. The expectation was that today's therapists are better prepared to identify IPV within a clinical vignette. Results show that therapists did have an improved ability to identify IPV. Thirteen percent of respondents from the present study failed to identify IPV within the relationship and about 80% suggested some sort of crisis intervention as a therapeutic approach. However, only one therapist accurately predicted lethality in the present study. Implications concerning IPV training for therapists are discussed. Dudley, D.R., McCloskey, K., and Kustron, D.A. Therapist Perceptions of Intimate Partner Violence: A Replication of Harway and Hansen's Study after More than a Decade. Journal of Aggression, Maltreatment and Trauma, 17(51), pp. 80-102, 2008.

Acceptance and Commitment: Implications for Prevention Science

Recent research in behavior analysis and clinical psychology points to the importance of language processes having to do with the control of negative cognition and emotion and the commitment to valued action. Efforts to control

unwanted thoughts and feelings, also referred to as experiential avoidance (EA), appear to be associated with a diverse array of psychological and behavioral difficulties. Recent research shows that interventions that reduce EA and help people to identify and commit to the pursuit of valued directions are beneficial for ameliorating diverse problems in living. These developments have the potential to improve the efficacy of many preventive interventions. This paper reviews the basic findings in these areas and points to some ways in which these developments could enhance the impact of preventive interventions. Biglan, A., Hayes, S., and Pistorello, J. Acceptance and Commitment: Implications for Prevention Science. Prev. Sci., 9(3), pp. 139-152, 2008.

Director's Report to the National Advisory Council on Drug Abuse - February, 2009

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

New Interview on Client Money Mismanagement Superior to Clinician Judgment

Dually diagnosed drug abusers often receive Social Security disability or public assistance. Money mismanagement is frequently reported as a difficulty by these clients and their treatment and service providers yet reliable measures of money mismanagement prior to this study have not existed. This is important because in the Veterans' Health Administration an assessment of money management ability may be used to make a determination of whether to assign a payee to the Veteran's money. This procedure reduces the Veteran's autonomy and should not be undertaken lightly. Moreover, assigning a representative payee to a capable client is a drain on taxpayer dollars. This study examined the reliability and validity of a new semi-structured interview measure of money mismanagement. The measure had excellent test-retest reliability but did not correlate well with clinician judgments of capability to manage funds. The structured interview correlated closely with the client's own assessment of money management skill and also with global assessment of functioning by clinicians. High reliability and construct validity suggest the new measure may have greater utility than clinician judgment for assessment of money management. Black, R.A., Rounsaville, B.J., Rosenheck, R.A., Conrad, K.J., Ball, S.A., and Rosen, M.I. Measuring Money Mismanagement among Dually Diagnosed Clients. Journal of Nervous and Mental Diseases, 196(7), pp. 576-579, 2008.

Gender Differences in Body Mass Index for Different Lifetime and Current Substance Use Diagnoses

Researchers have posited concerns about weight as both risk factors for initiation of substance use and for relapse to substance use but this relationship and its interaction with gender is poorly understood. This study analyzed data from the National Epidemiological Study on Alcohol and Related Conditions which included body mass index (BMI) and substance use disorder diagnoses for specific substances (both lifetime and past year) with the aim of understanding the relationship between these disorders, BMI and gender. Researchers did not find association between BMI and either past year or lifetime use of "any substance of abuse" (e.g., tallying across all substance categories). However, when alcohol and tobacco were dropped from the analysis, men but not women showed a negative association between past year substance abuse and obesity. When substances were analyzed separately there was no relationship between use of marijuana or cocaine by weight for either gender. There was a non-significant trend for increased lifetime risk of opioid use disorders in overweight women but not men. More research is needed to

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determine if this reflects post-cessation weight gain or higher vulnerability to opioids in overweight women. In overweight and obese men lifetime and past year nicotine addiction was significantly lower than for men with normal BMI. Overweight was significantly and positively associated with lifetime nicotine addiction in women possibly reflecting post-cessation weight gain in women than in men. Obesity was significantly and inversely associated with past-year nicotine dependence in women. In men, alcohol use disorders both past year and lifetime were correlated with higher BMIs. For women higher BMI did not relate to lifetime alcohol use disorder. Additionally obese women were statistically unlikely to have a past year diagnosis of alcohol dependence. This suggests that male alcoholics are at higher risk for weight gain and related consequences. It may indicate that women alcoholics may substitute calories from alcohol with calories from food. Overall this study is important because it suggests that a history of nicotine, alcohol, and possibly opioid use may have important long term consequences for body mass index that differs between men and women. Additionally it is possible that substance use histories are reflective of underlying differences in reward sensitivity or metabolism which predispose people both to certain drugs and to overeating and interact with gender because of physiological, hormonal or societal factors. More research is needed to determine how to address weight gain and obesity for male and female substance users. Barry, D. and Petry, N. Associations between Body Mass Index and Substance Use Disorders Differ by Gender: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Addictive Behavior, 34(1), pp. 51-90, 2009.

Computerized Behavior Therapy for Opioid-Dependent Outpatients: A Randomized Controlled Trial

The purpose of this study was to evaluate the efficacy of an interactive, computer-based behavioral therapy intervention. Specifically, Dr. Bickel and colleagues computerized the community reinforcement approach (CRA) plus voucher-based contingency management model of behavior therapy. Participants were 135 volunteer adult outpatients who met DSM-IV criteria for opioid dependence. All participants received maintenance treatment with buprenorphine and were randomly assigned to one of three treatments: (1) therapist-delivered CRA treatment with vouchers, (2) computer-assisted CRA treatment with vouchers, or (3) standard treatment. Results showed the therapist-delivered and computer-assisted CRA plus vouchers interventions produced comparable weeks of continuous opioid and cocaine abstinence ($M = 7.98$ and 7.78, respectively), and significantly greater weeks of abstinence than the standard intervention ($M = 4.69$; $p < .05$). However, participants in the computer-assisted CRA condition had over 80% of their intervention delivered by an interactive computer program. The comparable efficacy obtained with computer-assisted and therapist-delivered therapy may enable more widespread dissemination of the evidence-based CRA plus vouchers intervention in a manner that is cost-effective and ensures treatment fidelity. Bickel, W.K., Marsch, L.A., Buchhalter, A.R., and Badger, G.J. Computerized Behavior Therapy for Opioid-Dependent Outpatients: A Randomized Controlled Trial. Experimental and Clinical Psychopharmacology, 16(2), pp. 132-143, 2008.

Pretreatment Brain Activation during Stroop Task is Associated with Outcomes in Cocaine-Dependent Patients

Cognitive behavioral and related therapies for cocaine dependence may enhance cognitive control over drug use behavior. This study was designed to examine the neural correlates of cognitive control as related to treatment outcomes for cocaine dependence. Twenty treatment-seeking cocaine-dependent individuals performed a Stroop color-word interference task while

undergoing functional magnetic resonance imaging (fMRI) prior to initiating treatment. In this study, Dr. Brewer and colleagues from Yale found that during Stroop performance, cocaine-dependent patients activated brain regions similar to those reported in nonaddicted individuals, including the anterior cingulate cortex, dorsolateral prefrontal cortex, parietal lobule, insula, and striatum. Activations at treatment onset correlated differentially with specific outcomes: longer duration of self-reported abstinence correlated with activation of ventromedial prefrontal cortex, left posterior cingulate cortex, and right striatum; percent drug-free urine screens correlated with striatal activation; and treatment retention correlated with diminished activation of dorsolateral prefrontal cortex. A modest correlation between Stroop effect and treatment retention was found. These findings implicate neurocircuitry underlying cognitive control in behavioral treatment outcome and provide insight into the mechanisms of behavioral therapies for cocaine dependence. The authors suggest neural activation patterns during cognitive control tasks are more sensitive predictors of treatment response than behavioral measures. Brewer, J.A., Worhunsky, P.D., Carroll, K.M., Rounsaville, B.J., and Potenza, M.N. Pretreatment Brain Activation during Stroop Task Is Associated with Outcomes in Cocaine-Dependent Patients. Biological Psychiatry, 64(11), pp. 998-1004, 2008.

Computer-Assisted Delivery of Cognitive-Behavioral Therapy for Addiction: A Randomized Trial of CBT4CBT

There are a number of obstacles to delivering cognitive-behavioral therapy (CBT) and other empirically validated therapies in clinical practice, including limited training, supervision, and the relative complexity and cost of training clinicians in CBT. Drs. Carroll, Ball, and colleagues from Yale University evaluated the efficacy of a computer-based version of CBT for substance dependence. This was a randomized clinical trial in which 77 individuals seeking treatment for substance dependence at an outpatient community setting were randomly assigned to standard treatment or standard treatment with biweekly access to computer-based training in CBT (CBT4CBT) skills. Treatment retention and data availability were comparable across the treatment conditions. Participants assigned to the CBT4CBT condition submitted significantly more urine specimens that were negative for any type of drugs and tended to have longer continuous periods of abstinence during treatment. The CBT4CBT program was positively evaluated by participants. In the CBT4CBT condition, outcome was more strongly associated with treatment engagement than in treatment as usual; furthermore, completion of homework assignments in CBT4CBT was significantly correlated with outcome and a significant predictor of treatment involvement. These data suggest that CBT4CBT is an effective adjunct to standard outpatient treatment for substance dependence and may provide an important means of making CBT, an empirically validated treatment, more broadly available. Carroll, K.M., Ball, S.A., Martino, S., Nich, C., Babuscio, T.A., Nuro, K.F., Gordon, M.A., Portnoy, G.A., and Rounsaville, B.J. Computer-Assisted Delivery of Cognitive-Behavioral Therapy for Addiction: A Randomized Trial of CBT4CBT. American Journal of Psychiatry, 165 (7), pp. 881-888, 2008.

Enduring Effects of a Computer-Assisted Training Program for Cognitive Behavioral Therapy: A 6-Month Follow-Up of CBT4CBT

Following an initial randomized clinical trial to examine the efficacy of a six-module, multimedia computer-based version of CBT ("CBT4CBT") as an adjunct to standard outpatient treatment, Dr. Carroll and colleagues examined the durability of effects of CBT4CBT. Specifically, study participants were assessed 1, 3, and 6 months after the termination of study treatments in which they were assigned (treatment-as-usual [TAU] or TAU with bi-weekly access to CBT4CBT). Sixty of the 73 participants were reached for follow-up (82%);

follow-up rates and availability of data were comparable across treatment conditions. Random effects regression analyses of use across time indicated significant differences between groups, such that those assigned to TAU increased their drug use across time while those assigned to CBT4CBT tended to improve slightly. The durability of the CBT4CBTeffect remained significant even after controlling for treatment retention, treatment substance use outcomes, and exposure to other treatment during the follow-up period. These data show strong support for the durability of effects from computer-assisted CBT, in that they were obtained even after controlling for important prognostic indicators. Additionally, this is the first study to demonstrate enduring effects of computer-assisted CBT on a behavioral indicator of outcome (urine specimens). CBT4CBT may be used in drug abuse treatment settings as an adjunct to standard treatment. Carroll, K.M., Ball, S.A., Martino, S., Nich, C., Babuscio, T.A., and Rounsaville, B.J. Enduring Effects of a Computer-Assisted Training Program for Cognitive Behavioral Therapy: A 6-Month Follow-Up of CBT4CBT. Drug and Alcohol Dependence, 2008 November 26. [Epub ahead of print].

Drug Abuse and Responsible Fathering: A Comparative Study of Men Enrolled in Methadone Maintenance Treatment

The purpose of this study was to examine ways that drug abuse contributes to the compromise of responsible fathering. Drs. McMahon, Winkel, and Rounsaville from Yale University identified dimensions of responsible fathering used to clarify ways that the fathering of 106 men receiving methadone maintenance treatment differed from that of 118 men living in the same community with no history of alcohol or drug abuse. Men who enrolled in the study completed two structured interviews and a battery of five self-report measures selected to document current and historical dimensions of responsible fathering. When the opioid-dependent fathers were compared to the other fathers, there were significant differences in economic resources to support family formation, patterns of pair-bonding, patterns of procreation, and parenting behavior. When fathering of the youngest biological child was examined, the opioid-dependent fathers confirmed few differences in historical dimensions of fathering, but they reported significant differences in current dimensions reflecting constricted personal definitions of the fathering role, poorer relationships with biological mothers, less frequent residence with the child, less frequent provision of financial support, less involvement in positive parenting, poorer appraisal of self as a father, and less satisfaction as a father. The findings highlight ways that drug abuse contributes to compromise of responsible fathering, and ways in which the drug abuse treatment system might better address parenting as a treatment issue for men. McMahon, T.J., Winkel, J.D., and Rounsaville, B. Drug Abuse and Responsible Fathering: A Comparative Study of Men Enrolled in Methadone Maintenance Treatment. Addiction, 103(2), pp. 269-283, 2008.

Greater Participation in Religious Activities During Treatment Linked to Better Outcomes

Although religious activity participation is often encouraged during treatment, little research exists on whether or how such participation might impact treatment outcomes. This study examined whether better outcomes were obtained by people who completed religious activity goals as part of two contingency management studies in which people received opportunities to draw for prizes in exchange for completing treatment goals they selected. Attending a religious service was by far the most frequently chosen type of religious activity. Overall those completing 3 or more religious activities had better treatment attendance, longer durations of continuous abstinence during treatment and a greater proportion of drug negative urine samples even when controlling for total goals completed. These findings are important because

they suggest one class of activities (religious event participation) that may have an important impact on treatment outcome. Results should be interpreted with caution because religious activities are often the only socially inclusive activities available to drug abusers to participate in and thus it is not clear whether religious activities or general social activities might convey similar benefits. Additionally, it is possible that these findings reveal that it is an ability to participate in religious activities rather than the spiritual or social nature of the activities themselves which are important. Religious activity participation like treatment requires coordination of transportation and timely meeting attendance, attention to a lecture format, and a willingness to follow rules, etc. More research is needed to determine whether religious activities themselves confer benefits to abstinent lifestyles or whether people who have the skills to abstain from drugs are simply also likely to become engaged in non-drug related social activities. Petry, N., Lewis, M., and Ostvik-White, E. Participation in Religious Activities during Contingency Management Interventions is Associated with Substance Use Treatment Outcomes. American Journal of Addiction, 17(5), pp. 408-413, 2008.

Voucher Reinforcement Does Not Improve Abstinence Outcomes In Drug Court

Drug courts provide judicial oversight and treatment to non-violent offenders but it is not known whether application of an efficacious behavioral treatment approach such as voucher reinforcement of abstinence, or voucher reinforcement of prosocial activities might improve on treatment outcomes obtained for community drug court participants. This study examined whether community drug court participants engaged in outpatient "drug free" treatment (not methadone maintenance) primarily with methamphetamine use disorders would receive benefits over and above the benefits of methadone from either $10.00 voucher payments for successive drug free urine submissions or for completion of prosocial behaviors thought to influence recovery. Participants in a California drug court (N=163) who were sent to the Matrix treatment program, a comprehensive outpatient treatment program, were randomly assigned to drug court plus treatment, drug court plus treatment plus vouchers for urine submission without any contingency, drug court plus treatment with vouchers for abstinent urines and prosocial behavior and drug court plus treatment with vouchers for prosocial behaviors only. The prosocial behavior contingencies involved client determined counselor approved weekly treatment goals. No differences emerged between groups on during treatment measures of retention in treatment, drug use, or psychosocial functioning relative to the standard drug court treatment condition. This is important because virtually all other tests of voucher reinforcement have shown the treatment to impact outcomes. There are several possible reasons for this surprising finding including a ceiling effect from the Matrix standard treatment, which is evidence based and the judicial rewards and sanctions already used in drug court as well as the fact that the value of the vouchers used in the program remained a consistent relatively low flat rate in contrast with other models that increased in values with increasing abstinence duration. Prendergast, M.L., Hall, E.A., Roll, J., and Warda, U. Use of Vouchers to Reinforce Abstinence and Positive Behaviors among Clients in a Drug Court Treatment program. Journal of Substance Abuse Treatment, 35(2), pp. 125-136, 2008.

Treating Adolescent Drug Abuse: A Randomized Trial Comparing Multidimensional Family Therapy and Cognitive Behavior Therapy

This study examined the efficacy of individual cognitive behavioral therapy (CBT) and multidimensional family therapy (MDFT) for adolescents in a community-based drug abuse clinic. A total of 224 youth, primarily male (81%), African American (72%), from low-income single-parent homes (58%) with an average age of 15 years were recruited into the study. All youth were

drug users, with 75% meeting DSM-IV criteria for cannabis dependence and 13% meeting criteria for abuse. A 2 (treatment condition) x 4 (time) repeated-measures intent to-treat randomized design was applied, and data were gathered at baseline, termination, and at 6 and 12 months post-termination. Both treatments produced significant decreases in cannabis consumption and slightly significant reductions in alcohol use, but there were no treatment differences in reducing frequency of cannabis and alcohol use. Significant treatment effects were found favoring MDFT on substance use problem severity, other drug use and minimal use (zero or one occasion of use) of all substances, and these effects continued to 12 months following treatment termination. Consistent with previous controlled trials, MDFT is distinguished by the sustainability of treatment effects. Liddle, H.A., Dakof, G.A., Turner, R.M., Henderson, C.E., and Greenbaum, P.E. Treating Adolescent Drug Abuse: A Randomized Trial Comparing Multidimensional Family Therapy and Cognitive Behavior Therapy. Addiction, 103(10), pp. 1660-1670, 2008.

Treatment Adherence, Competence, and Outcome in Individual and Family Therapy for Adolescent Behavior Problems

This study examined the impact of treatment adherence and therapist competence on treatment outcome in a controlled trial of individual cognitive behavioral therapy (CBT) and multidimensional family therapy (MDFT) for adolescent substance use and related behavior problems. Participants included 136 adolescents (62 CBT, 74 MDFT) assessed at intake, discharge, and 6-month follow-up. Observational ratings of adherence and competence were collected on early and later phases of treatment (192 CBT sessions, 245 MDFT sessions) by using a contextual measure of treatment fidelity. Adherence and competence effects were tested after controlling for therapeutic alliance. In CBT only, stronger adherence predicted greater declines in drug use (linear effect). In CBT and MDFT, (a) stronger adherence predicted greater reductions in externalizing behaviors (linear effect) and (b) intermediate levels of adherence predicted the largest declines in internalizing behaviors, with high and low adherence predicting smaller improvements (curvilinear effect). Therapist competence did not predict outcome and did not moderate adherence-outcome relations; however, competence findings are tentative due to relatively low inter-rater reliability for the competence ratings. Hogue, A., Henderson, C.E., Dauber, S., Barajas, P.C., Fried, A., and Liddle, H.A. Treatment Adherence, Competence, and Outcome in Individual and Family Therapy for Adolescent Behavior Problems. Journal of Consulting and Clinical Psychology, 76(4), pp. 544-555, 2008.

Predictors of Homelessness Among Street Living Youth

While few studies have identified predictors of exiting homelessness among adults, even fewer studies have attempted to identify these predictors among homeless youth. The current study explored predictors of change in homelessness among 180 homeless youth between the ages of 14 and 22, recruited through an urban drop-in center. All youth were assessed at baseline, 3 and 6 months. The sample included 118 males and the reported ethnicity included Latino (n = 54), Anglo (n = 73), Native American (n = 24), African American (n = 6) and mixed ethnicity or "other" (n = 23). Four distinct patterns of change in homelessness were identified among youth which included those who (1) had fairly low rates of homelessness at each follow-up point, (2) started in the mid-range of homelessness, increased at 3 months and sharply declined at 6-months (MHL), (3) reported high rates of homelessness at baseline and low rates at each follow-up point (HLL), and finally, (4) remained consistently homeless across time (HMH). These patterns of change were most strongly predicted by social connections and engagement in HIV risk behaviors. The author concludes that findings from this study suggest that developing trust and linkages between homeless youth and service providers

may be a more powerful immediate target of intervention than targeting child abuse issues, substance use and mental health problems. Slesnick, N., Bartle-Haring, S., Dashora, P., Kang, M.J., and Aukward, E. Predictors of Homelessness Among Street Living Youth. J. Youth Adolesc., 37(4), pp. 465-474, 2008.

Consequences of Misspecifying the Number of Latent Treatment Attendance Classes in Modeling Group Membership Turnover within Ecologically Valid Behavioral Treatment Trials

Historically, difficulties in analyzing treatment outcome data from open-enrollment groups have led to their avoidance in use in federally funded treatment trials despite the fact that 79% of treatment programs use open-enrollment groups. Recently, latent class pattern mixture models (LCPMM) have shown promise as a defensible approach for making overall (and attendance-class-specific) inferences from open enrollment groups with membership turnover. Morgan-Lopez and Fals-Stewart present a statistical simulation study comparing LCPMMs to longitudinal growth models (LGM) to understand when both frameworks are likely to produce conflicting inferences concerning overall treatment efficacy. LCPMMs performed well under all conditions examined; meanwhile, LGMs produced problematic levels of bias and Type I errors under certain conditions. This study highlights key concerns about using LGM for open-enrollment data: treatment effect overestimation and advocacy for treatments that may be ineffective in reality. Morgan-Lopez, A.A. and Fals-Stewart, W. Consequences of Misspecifying the Number of Latent Treatment Attendance Classes in Modeling Group Membership Turnover within Ecologically Valid Behavioral Treatment Trials. Journal of Substance Abuse Treatment, 35, pp. 396-409, 2008.

Physical Activity as a Strategy for Maintaining Tobacco Abstinence

Dr. Prochaska and colleagues from UCSF conducted this randomized controlled trial to examine (1) the impact of an extended relapse prevention program on increasing moderate to vigorous physical activity in adults enrolled in a tobacco cessation treatment trial; (2) whether changes in activity were associated with sustained abstinence from smoking; and (3) mechanisms by which activity may support sustained abstinence from smoking. Participants were 407 adult smokers receiving a 12-week group-based smoking cessation treatment with bupropion and nicotine patch. At week 12, participants were randomized to no further treatment or to 40 weeks of bupropion or placebo with or without an 11-session relapse prevention intervention of which 2 sessions focused on physical activity. Participants receiving the physical activity intervention (n=163) received a pedometer, counseling to increase steps 10% biweekly towards a 10,000 steps/day goal, and personalized reports graphing progress with individualized goals. The results showed that participants receiving the physical activity intervention significantly increased their activity relative to control participants. Pedometer step counts also increased significantly although pedometer monitoring dropped off. Controlling for treatment condition, increased physical activity predicted sustained smoking abstinence at week 24. Among participants with sustained abstinence, increased activity was associated with increased vigor and decreased perceived difficulty with staying smoke-free. The authors conclude that the addition of a low cost, two session physical activity program to a smoking cessation intervention served to increase participants' physical activity with changes predictive of sustained abstinence at 24 weeks. The timing of the physical activity sessions, promotion of lifestyle activity of moderate intensity, and tailoring of step goals to participants' baseline activity levels are factors that likely contributed to the significant changes observed. Prochaska, J.J., Hall, S.M., Humfleet, G., Munoz, R.F., Reus, V., Gorectki, J., and Hu, D. Physical Activity as a Strategy for Maintaining Tobacco Abstinence: A Randomized Trial. Preventive Medicine, 27,

pp. 215-220, 2008.

Women's Interest in Treatment to Stay Abstinent from Cigarettes Postpartum

Dr. Michelle Levine at the Western Psychiatric Institute and Clinic in Pittsburgh conducted this study to determine the acceptability of a postpartum smoking relapse prevention intervention and the appeal of strategies to address concerns about mood, stress and weight to prevent postpartum relapse. A survey about relapse prevention program modalities, topics and barriers to treatment was administered to 36 women who had quit smoking during pregnancy and either remained abstinent or relapsed within the first year postpartum. Survey results of women who had and had not relapsed to smoking were compared. The findings showed that both groups endorsed the opportunity to talk with a counselor about relapse prevention and did not differ in their endorsement of treatment modalities. Discussing mood, stress, and weight concerns were endorsed by both groups of women, but those who had relapsed were more likely to endorse stress management as an intervention topic. Those who had relapsed were more likely to endorse the use of pharmacologic aids than were those who had remained abstinent. According to Dr. Levine, the data suggest that postpartum women would find a smoking relapse prevention program that includes group and individual counseling and the use of strategies to address mood, stress, and weight concerns acceptable. Levine, M.D. Women's Interest in Treatment to Stay Abstinent from Cigarettes Postpartum. Women's Health Issues, 18(5), pp. 381-6, 2008. Epub 2008 November 5.

Dual-Focus Mutual Aid for Co-Occurring Disorders

Double Trouble in Recovery (DTR) is a dual focus mutual aid group adapted from the 12-steps of AA, which aims to assist individuals with co-occurring substance use and psychiatric disorders. Dr. Magura conducted this quasi-experimental study to determine whether adding DTR mutual aid to a day treatment psychiatric program that primarily serves patients with co-occurring disorders improves patient outcomes. Patient outcomes in the same psychiatric day treatment program were compared for two consecutive admission cohorts. The first cohort did not have DTR available while the second cohort was exposed to DTR after it was established at the program. Both cohorts were assessed at program admission and at six-month follow-up. The post-DTR cohort as compared with the pre-DTR cohort had significantly fewer days of alcohol and drug use, more frequent traditional 12-step groups outside of the program and higher psychiatric medication adherence. There were no differences in psychiatric symptoms or program retention, however. This study demonstrates the benefits of introducing 12-step, dual-focus mutual aid into psychiatric treatment programs that serve patients with co-occurring disorders. Magura, S., Rosenblum, A., Villano, C.L., Vogel, H.S., Fong, C. and Betzler, T. Dual-Focus Mutual Aid for Co-Occurring Disorders: A Quasi-Experimental Outcome Evaluation Study. The American Journal of Drug and Alcohol Abuse, 34, pp. 61-74, 2008.

Extended Cognitive Behavior Therapy for Cigarette Smoking Cessation

Dr. Killen and colleagues at Stanford University School of Medicine conducted this randomized clinical trial to determine the efficacy of extended cognitive behavior therapy (CBT) for smoking cessation. During an open label trial 304 participants were randomized and received bupropion SR, nicotine patch and individual CBT. During extended treatment, half received additional CBT and half received telephone-based general supportive therapy. Findings show that

at week 20, CBT produced a higher point prevalence abstinence rate: 45% vs. 29%, p=.006; at 52 weeks the difference in abstinence rates (31% vs. 27%) was not significant. History of depression was a moderator of treatment. Those with a positive history had a better treatment response at 20 weeks when assigned to the less intensive telephone support therapy (p<.05). The superiority of CBT at 20 weeks in this trial suggests that continued emphasis on the development of cognitive and behavioral strategies for maintaining non-smoking during an extended treatment phase may help smokers to maintain abstinence in the longer term. Killen, J.D., Fortmann, S.P., Arredondo, C., Murphy Jr., G.M., Hayward, C., Cromp, D., Celio, M., Fong, D., Pandurangi, M., and Schatzberg, A.F. Extended Cognitive Behavior Therapy for Cigarette Smoking Cessation. Addiction, 103, pp. 1381-1390, 2008.

Adverse Events in an Integrated Trauma-focused Intervention for Women in Community Substance Abuse Treatment

A substantial number of women who enter substance abuse treatment have a history of trauma and meet criteria for posttraumatic stress disorder (PTSD). Fear regarding the extent to which PTSD treatment can evoke negative consequences remains a research question. This study explored adverse events related to the implementation of an integrated treatment for women with trauma and substance use disorder (Seeking Safety) compared with a nontrauma-focused intervention (Women's Health Education). Three hundred fifty-three women enrolled in community substance abuse treatment were randomized to one of the two study groups and monitored weekly for adverse events. There were no differences between the two intervention groups in the number of women reporting study-related adverse events. Implementing PTSD treatment in substance abuse treatment programs appears to be safe, with minimal impact on intervention-related adverse psychiatric and substance abuse symptoms. The authors do note, however, that more research is needed on the efficacy of such interventions to improve outcomes of PTSD and substance use. Killeen T., Hien, D., Campbell, A., Brown, C., Hansen, C., Jiang, H., Kristman-Valente, A., Neuenfeldt, C., Rocz-de la Luz, N., Sampson, R., Suarez-Morales, L., Wells, E., Brigham, G., and Nunes, E. Adverse Events in an Integrated Trauma-focused Intervention for Women in Community Substance Abuse Treatment. Journal of Substance Abuse Treatment, 35(3), pp. 304-311, 2008.

Addressing Heavy Drinking in Smoking Cessation Treatment: A Randomized Clinical Trial

Heavy alcohol use frequently co-occurs with cigarette smoking and may impede smoking cessation. In this clinical trial, Dr. Kahler and colleagues examined whether smoking cessation treatment that incorporates brief alcohol intervention can improve smoking cessation outcomes as well as reduce drinks consumed per week. All participants received 8 weeks of nicotine replacement therapy. Half were also randomized to a 4-session standard smoking cessation treatment (ST, n = 119), while the other half received a standard treatment of equal intensity that incorporated brief alcohol intervention (ST-BI, n = 117). Although initially (2 weeks post-treatment) individuals in the ST-BI group reported fewer drinks and greater smoking abstinence than those in the ST group, there were virtually no differences between the groups in the long-term (4 months and onward). The thrust of the findings suggest that integrating brief alcohol intervention into smoking cessation treatment appears feasible, but further development is needed to yield longer lasting effects on smoking. Kahler, C.W., Metrik, J., LaChance, H.R., Ramsey, S.E., Abrams, D.B., Monti, P.M., and Brown, R.A. Addressing Heavy Drinking in Smoking Cessation Treatment: A Randomized Clinical Trial. Journal of Consulting and Clinical Psychology, 76(5), pp. 852-862, 2008.

The Influence of Monetary Compensation on Relapse among Addicted Participants: Empirical vs. Anecdotal Evidence

Although it is quite common, the use of cash incentives to compensate drug-addicted participants is controversial. This is particularly true given concerns that cash incentives might precipitate or cause relapse, as is commonly believed. Dr. Brady and colleagues examined whether cash as compared to money order compensation influenced drug use among 34 non-treatment-seeking, cocaine-dependent individuals. Consistent with past evidence, results did not suggest that form of compensation was associated with either the likelihood of continued cocaine use or the dollar amount of cocaine consumed after participation. In sum, the data did not support commonly held concerns that cash incentives increase the risk of relapse following research participation. Dempsey, J.P., Back, S.E., Waldrop, A.E., Jenkins, L., and Brady, K.T. The Influence of Monetary Compensation on Relapse among Addicted Participants: Empirical vs. Anecdotal Evidence. American Journal of Addiction, 17(6), pp. 488-490, 2008.

Early Life Trauma and Sensitivity to Current Life Stressors in Individuals with and without Cocaine Dependence

This study investigated the link between exposure to early life trauma, sensitivity to current daily stressors, and cocaine dependence. Individuals (with or without cocaine dependence) completed assessments of early life trauma as well as current daily stressors. In comparison to controls, cocaine-dependent individuals reported almost twice as many daily hassles and perceived those hassles more negatively. In addition, among participants with cocaine dependence, there existed a significant relationship between exposure to early life trauma and negative perception of current daily hassles, while no such relationship was observed for participants without cocaine dependence. These data suggest that adverse childhood events may lead to an altered view of the environment that contributes to increased irritability with daily life events among cocaine-dependent individuals. Back, S.E., Brady, K.T., Waldrop, A.E., Yeatts, S.D., McRae, A.L., and Spratt, E. Early Life Trauma and Sensitivity to Current Life Stressors in Individuals with and without Cocaine Dependence. American Journal of Drug and Alcohol Abuse, 34(4), pp. 389-396, 2008.

Impact of Posttraumatic Stress Disorder on Early Smoking Relapse and Relapse During a Self-Guided Quit Attempt Among Community-Recruited Daily Smokers

The present investigation examined whether daily smokers with posttraumatic stress disorder (PTSD), as compared to daily smokers with either anxiety symptoms or no psychiatric diagnoses, exhibited less success in the early phases of a self-guided smoking quit attempt. Participants were 140 adult daily smokers; approximately one-third of the sample met criteria for current PTSD (n = 47), one-third met criteria for other current anxiety disorders (without PTSD; n = 33), and one-third did not meet criteria for any current Axis I disorder (n = 60). Consistent with the authors' predictions, participants with PTSD (as compared to membership in the other anxiety disorders group and the group with no current Axis I psychopathology) was associated with increased risk of lapse (smoking any amount following quit day) during the first week after treatment ended. In addition, daily smokers with PTSD and other anxiety disorders were at significantly increased risk of relapse (smoking at least 5 cigarettes per day on at least three consecutive days following quit day) during the first week after treatment ended. These data provide novel and provocative evidence that PTSD, and perhaps anxiety disorders more generally, may be important factors in reducing the odds of successful unaided quit attempts in the early phases of cessation. Zvolensky, M.J., Gibson, L.E.,

Vujanovic, A.A., Gregor, K., Bernstein, A., Kahler, C., Lejuez, C.W., Brown, R.A., and Feldner, M.T. Impact of Posttraumatic Stress Disorder on Early Smoking Relapse and Relapse during a Self-Guided Quit Attempt among Community-Recruited Daily Smokers. Nicotine & Tobacco Research, 10(8), pp. 1415-1427, 2008.

Changes in Psychiatric Patients' Thoughts about Quitting Smoking during a Smoke-Free Hospitalization

Investigators from UCSF conducted this study to examine whether smoking abstinence, as a consequence of psychiatric hospitalization in a smoke-free facility, was associated with changes in participants' thought about quitting smoking. Participants (N=100) on an inpatient psychiatry unit, were asked about their reported desire to quit smoking, their expectancy of success, their anticipated difficulty with quitting and their smoking abstinence goal. Assessments were conducted at hospital intake and shortly before hospital discharge. Follow-up assessments were conducted by phone at 1 week, 1 month, and 3 months post-hospitalization to measure smoking behavior. Participants were offered NRT to manage withdrawal, but were offered no other cessation treatment. From admission to discharge, participants reported an increased expectancy of success with quitting and a decreased expectancy of difficulty with staying quit. They also were more likely to endorse a smoking-related goal. The results suggest that by the time of their hospital discharge, patients may have increased their readiness for treatment, as evident by significantly greater confidence in and commitment to abstinence. Patients demonstrated a positive transformation in their thoughts about abstinence, which had beneficial effects on their subsequent smoking behavior in terms of reduction in the number of cigarettes smoked and later attempts at quitting. Shmueli, D., Fletcher, L., Hall, S.E., Hall, S.M., Prochaska, J.J. Changes in Psychiatric Patients' Thoughts about Quitting Smoking during a Smoke-Free Hospitalization. Nicotine & Tobacco Research, 10(5), pp. 875-881, 2008.

Influence of Premenstrual Symptomatology, Mood, Smoking Withdrawal and Smoking Behavior on Smoking Cessation Outcome

Dr. Sharon Allen and colleagues at the University of Minnesota conducted this study to characterize premenstrual symptomatology, mood and smoking withdrawal during the follicular and luteal phases under conditions of ad libitum smoking; as well as actual smoking behavior, and to determine whether phase-related variability in these measures influences likelihood of completing the protocol and smoking cessation outcome. During ad libitum smoking, all measures of premenstrual symptomatology, as well as some measures of mood and smoking withdrawal, were significantly higher during the luteal phase. Moreover, phase-related variability in premenstrual symptoms and urge to smoke were associated with relapse. These findings support the inference that sex hormones influence smoking cessation outcome. This knowledge may contribute to the development of more rational and effective smoking cessation interventions for women. Allen, S., Allen, A., and Pomerleau, C.S. Influence of Phase-Related Variability in Premenstrual Symptomatology, Mood, Smoking Withdrawal, and Smoking Behavior During Ad Libitum Smoking, on Smoking Cessation Outcome. Addictive Behaviors, 34, pp. 107-111, 2009.

Director's Report to the National Advisory Council on Drug Abuse - February, 2009

Research Findings - Research on Pharmacotherapies for Drug Abuse

Racemic Gamma Vinyl-GABA (R,S-GVG) Blocks Methamphetamine-triggered Reinstatement of Conditioned Place Preference

This article reports that conditioned place preference to methamphetamine can be blocked in rats using a 2.5 hour pretreatment dose of 300 mg/kg i.p. racemic GVG. Reinstatement is blocked regardless of training dose of priming dose of methamphetamine ranging from 1.0 to 10 mg/kg. These findings suggest that GVG may be an effective treatment to block methamphetamine reinstatement in human methamphetamine users. Demarco, A., Dalal, R.M., Pai, J., Aquilina, S.D., Mullapudi, U., Hammel, C., Kothari, S.K., Leibling, C.N., Patel, V., Schiffer, W.K., Brodie, J.K., and Dewey, S.L. Racemic Gamma Vinyl-GABA (R,S-GVG) Blocks Methamphetamine-triggered Reinstatement of Conditioned Place Preference Synapse 63(2), pp. 87-94, 2008.

Subchronic Racemic Gamma Vinyl-GABA Produces Weight Loss in Sprague Dawley and Zucker Fatty Rats

This paper reports that GVG was tested for its effects on body weight in adolescent Sprague-Dawley rats and in adolescent and adult genetically obese Zucker rats. GVG in doses ranging from 75-300 mg/kg ip dose dependently reduced body weight in all groups following a treatment period of 14 days, suggesting that GVG may be effective as a weight loss tool or obesity treatment. DeMarco, A., Dalal, R.M., Kahanda, M., Mullapudi, U., Pai, J., Hammel, C.., Liebling, C.N., Patel, V., Brodie, J.D., Schiffer, W.K., Dewey, S.L,, and Aquilina, S.D. Subchronic Racemic Gamma Vinyl-GABA Produces Weight Loss in Sprague Dawley and Zucker Fatty Rats. Synapse 63(11), pp. 870-872, 2008.

Opioid and Cocaine Combined Effect on Cocaine-induced Changes in HPA and HPG Axes Hormones in Men

This paper reports on effects of cocaine or the combination of cocaine and nalbuphine (a kappa/mu agonist) in human subjects. Cocaine stimulated ACTH, cortisol, and LH, whereas the combination of nalbuphine and cocaine produced smaller increases in ACTH, and decreased cortisol and LH. These data are consistent with previous studies suggesting that nalbuphine modestly attenuated subjective effects of cocaine, and that subjective and cardiovascular effects of cocaine and nalbuphine were not additive. Goletiani, N., Mendelson, J.H., Sholar, M.B., Sigel, A.J., and Mello, N.K. Opioid and Cocaine Combined Effect on Cocaine-induced Changes in HPA and HPG Axes Hormones in Men.

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Pharmacology, Biochemistry and Behavior, 2008 (online).

Data Mining in a Behavioral Test Detects Early Symptoms in a Model of Amyotrophic Lateral Sclerosis

This paper described a methodology called pattern array which involved analysis of genetically modified mice that exemplify an animal model of ALS. The technique was able to identify a unique motor pattern that differentiated the mutants from the wild-type mice two months before disease onset, at a stage whey there were no other measures that differentiated these animals. The early discovered symptom may enable the testing of potential therapeutics using these subtle behavioral effects. Kafkafi, N., Yekutieli, D., Yarowsky, P., and Elmer, G. Data Mining in a Behavioral Test Detects Early Symptoms in a Model of Amyotrophic Lateral Sclerosis. Behavioral Neuroscience 122(4), pp. 777-787, 2008.

A Data Mining Approach to In Vivo Classification of Psychopharmacological Drugs

Data mining is a powerful informatics strategy that has been applied to in vitro data. Pattern array is a data mining algorithm used to analyze mouse open field behavior and characterize the psychophamacological effects of three drug classes including stimulants, opioids, and psychomimetics. Pattern array has discovered behavioral predictors in all three drug classes and unknowns. Although still in its early stages, Pattern Array may develop into a tool for psychotherapeutic drug discovery. Kafkafi, N., Yekutieli, D., and Elmer, G. A Data Mining Approach to in vivo Classification of Psychopharmacological Drugs, Neuropsychopharmaco-logy.1-17, 2008 (online).

Disulfiram Enhances Subjective Effects of Dextroamphetamine in Humans

Disulfiram has shown promise in several clinical trials for cocaine addiction, but its potential utility in the treatment of amphetamine addiction has not been examined. The goal of this study was to determine the effects of disulfiram on acute physiological and subjective responses to dextroamphetamine in healthy volunteers. Five male and 5 female subjects participated in an outpatient double-blind, placebo-controlled, crossover study. Subjects were randomly assigned to a sequence of disulfiram (250 mg/day) or placebo treatments each lasting for 4 days. Day four of each treatment period was the experimental session, in which subjects orally ingested a single dose of dextroamphetamine (20 mg/70 kg). Outcome measures included heart rate, blood pressure, plasma cortisol and prolactin, subjective and performance on the Sustained Attention to Response Test (SART). Disulfiram did not affect dextroamphetamine-induced increases in heart rate, blood pressure, cortisol, or prolactin. Disulfiram did enhance some of the subjective effects of dextroamphetamine including ratings of "high," "anxious," "bad drug effects," "want more drug" and "drug liking" and was also associated with decreased performance in the SART test. How these enhanced subjective amphetamine responses affect cocaine use behavior remains to be determined in future clinical trials. Sofuoglu, M., Poling, J., Waters, A., Sewell, A., Hill, K., Kosten, T. Pharmacol. Biochem. Behav., 90(3), pp. 394-398, 2008.

Cocaine Effects During D-amphetamine Maintenance: A Human Laboratory Analysis of Safety, Tolerability and Efficacy

Results of preclinical laboratory studies and clinical trials indicate that agonist replacements like D-amphetamine may be a viable option for managing cocaine dependence. This study determined the physiological and behavioral effects of

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cocaine during D-amphetamine maintenance in seven cocaine-dependent participants, with the prediction that cocaine would be well tolerated during D-amphetamine maintenance, and that D-amphetamine would attenuate the behavioral effects of cocaine. After 3-5 days of D-amphetamine maintenance (0, 15, and 30 mg/day), volunteers were administered ascending doses of cocaine (4, 30, 60 mg IN) within a single session. Cocaine doses were separated by 90 min. Cocaine produced prototypical physiological (e.g., increased heart rate, blood pressure, and body temperature) and subject-rated (e.g., increased ratings of Good Effects) effects. During maintenance on the highest D-amphetamine dose, the heart rate increasing effects of cocaine were larger than observed during placebo maintenance. These effects were not clinically significant and no unexpected or serious adverse events were observed. D-amphetamine attenuated some of the subject-rated effects of cocaine. These results are concordant with those of previous preclinical studies, human laboratory experiments and clinical trials, further suggesting that agonist replacement therapy may be a viable strategy for managing cocaine abuse. Rush, C.R., Stoops, W.W., and Hays, L.R. Drug and Alcohol Dependence, 2008. (E-publication ahead of print).

The Safety, Tolerability, and Subject-Rated Effects of Acute Intranasal Cocaine Administration During Aripiprazole Maintenance II: Increased Aripiprazole Dose and Maintenance Period

The experiment reported here examined the safety and tolerability of intranasal cocaine during aripiprazole maintenance. Six cocaine-dependent human subjects were maintained on aripiprazole (15 mg) and placebo for 10 days in counterbalanced order prior to assessing the physiological and subject-rated effects of intranasal cocaine. The results showed that intranasal cocaine produced prototypical stimulant-like effects (e.g., increased blood pressure and heart rate, increased subject ratings of Like Drug and Stimulated), and aripiprazole enhanced these effects on several measures. The study conclusions are that aripiprazole (15 mg/day) is safe and tolerable when combined with cocaine; however, the usefulness of aripiprazole as a treatment for cocaine-use disorders remains to be determined. Lile, J.A., Stoops, W.W., Hays, L.R., and Rush, C.R. Am. J. Drug and Alcohol Abuse, 34, pp. 721-729, 2008.

Evaluation of the Cardiovascular and Subjective Effects of Rivastigmine in Combination With Methamphetamine in Methamphetamine-Dependent Human Volunteers

Acetylcholine (ACh) has been implicated in the reinforcing and locomotor activating effects produced by methamphetamine. Recent data suggest that acetylcholinesterase (AChE) inhibitors attenuate methamphetamine-seeking behavior in rates. This double-blind, between-subjects, placebo-controlled inpatient study was conducted in 23 non-treatment seeking methamphetamine-dependent subjects to determine the safety (adverse events, mood changes, cardiovascular effects) and preliminary efficacy (subjective effects) of the AChE inhibitor rivastigmine when tested in combination with methamphetamine. Prior to randomization to study drug, infusions of saline (day 4; 0 mg) and methamphetamine (day 5; 30 mg iv) were given to all participants in single-blinded fashion. On day 7 and continuing through day 11, participants were randomized to receive oral placebo (0 mg, N=7) or rivastigmine (1.5 mg, N=7; 3 mg, N=9). On day 11, subjects received saline and methamphetamine infusions again under double-blind conditions. Data analysis revealed that rivastigmine was not associated with increased adverse events or alterations in mood. As expected, acute methamphetamine exposure (30 mg, iv) increased heart rate and blood pressure as well as

several positive subjective effects, ARCI ratings, and reported monetary value ($p<0.05$). The date indicated that rivastigmine, at 3 mg, significantly attenuated methamphetamine-induced increases in diastolic blood pressure, and self-reports of "anxious" and "desire" ($p,0.05$). These findings suggest that pharmacological manipulations that enhance brain ACh warrant continued investigation as potential treatments for methamphetamine addiction. De La Garza, R., Shoptaw, S., and Newton, T.F. Int. J. Neuropsychopharmacol., 11(6), pp. 729-741, 2008.

Effects of Early and Recent Adverse Experiences on Adrenal Response to Psychosocial Stress in Depressed Adolescents

As observed in depressed adults, there is considerable variability in the degree and direction of hypothalamic pituitary adrenal (HPA) dysfunction in depressed adolescents. The variability in HPA findings may be attributed to experiential factors. In this study, a modified version of a standard psychosocial stressor used in adults, the Trier Social Stress Test (TSST) was administered to 30 adolescents with major depressive disorder and 25 healthy adolescent volunteers. Cortisol concentrations were measured in saliva samples collected before and after the stressor. Information was also gathered on early and recent adverse experiences with standard interviews. The results of this study showed that participants from both groups had increased cortisol secretion in response to TSST. The combination of early-life adversity and high levels of chronic stress during adolescence was the most powerful predictor of enhanced adrenal response to the TSST. These results support previous findings on the role of experiential factors on HPA response to stress and in the development of mood disorders. Dissection of the heterogeneous pathophysiology of adolescent depression will assist in developing more specific interventions for different subgroups of adults. Rao, U., Hammen, C., Ortiz, L.R., Chen, L., and Poland, R.E. Biol. Psychiatry, 64, pp. 521-526, 2008.

Stress-related Factors in Cannabis Use and Misuse: Implications for Prevention and Treatment

A systematic review of published studies on the role of stress as a risk factor and motivation for cannabis use/misuse suggest that cannabis is commonly used as a stress-coping strategy. Negative life events, trauma, and maladaptive coping were all related to consumption. Cannabis use for stress-coping purposes was most evident when examining chronic as compared with experimental use. Although many individuals may be able to use cannabis without consequences, there appears to be a subset of individuals who experience greater life stress and who may be more likely to use for stress-coping purposes and may be at greater risk for addiction. Chronic use may potentiate stress-related motivation to use/abuse cannabis and is associated with decision-making deficits and alterations in brain-stress pathways that may exacerbate compulsive drug seeking and sensitize individuals to stress-related drug use. Overall, stress-coping interventions and harm reduction focused on reducing the amount ingested may facilitate prevention and recovery efforts. Hyman, S.M., and Sinha, R. J. Substance Abuse Treatment, 2008 (E-publication ahead of print).

Chronic Stress, Drug Use, and Vulnerability to Addiction

This review article evaluates the role of stress as a risk factor in the development of addiction and in addiction relapse vulnerability and discusses research gaps in the connection between stress and addiction, with the aim of presenting questions the answers to which could significantly influence new prevention and treatment strategies. Preclinical research of stress exposure and reinstatement models, the underlying pathophysiology associated with

stress-related risk of addiction, and a discussion of population-based and epidemiological studies, are all presented. Sinha, R. Ann. N.Y. Acad. Sci. 1141, pp. 105-130, 2008.

Self-administration of Cocaine, Cannabis and Heroin in the Human Laboratory: Benefits and Pitfalls

This review describes self-administration procedures for modeling addiction to cocaine, cannabis and heroin in the human laboratory, the benefits and pitfalls of the approach, and the methodological issues unique to each drug. It also addresses the predictive validity of the model for testing treatment medications. The results show that all three drugs of abuse are reliably and robustly self-administered by non-treatment seeking research volunteers. In terms of pharmacotherapies, cocaine use is extraordinarily difficult to disrupt either in the laboratory or in the clinic. A range of medications has been shown to significantly decrease cocaine's subjective effects and craving without decreasing either cocaine self-administration or cocaine abuse by patients. These negative data combined with recent positive findings with Modafinil suggest that self-administration procedures are an important intermediary step between pre-clinical and clinical studies. In terms of cannabis, a recent study suggests that medications that improve sleep and mood during cannabis withdrawal decrease the resumption of marijuana self-administration in abstinent volunteers. Clinical data on patients seeking treatment for their marijuana use are needed to validate these laboratory findings. Finally, in contrast to cannabis or cocaine dependence, three are three efficacious FDA-approved medications to treat opioid dependence, all of which decrease both heroin self-administration and subjective effects in the human laboratory. In summary, self-administration procedures provide meaningful behavioral data in a small number of individuals. These studies contribute to our understanding of the variables maintaining cocaine, marijuana and heroin intake, and are important in guiding the development of more effective drug treatment programs. Haney, M. Addiction Biology, 14, pp. 9-21, 2008.

Controversies in Translational Research: Drug Self-administration

Laboratory animal and human models of drug self-administration are used to evaluate potential pharmacotherapies for drug abuse, yet the utility of these models in predicting clinically useful medications is variable. The purpose of this study was to track how antagonist, agonist, and partial agonist medication approaches influence heroin and cocaine self-administration by rodents, non-human primates, and humans and to compare these results to clinical outcomes. Self-administration across species was tested with various medications for heroin and cocaine. The conclusions were that the self-administration model has reliably identified medications to treat opioid dependence, and the recent data with Modafinil suggest that the human laboratory model also identifies medications to treat cocaine dependence. The study reports that there have been numerous false positives when subjective effects are the primary outcome measures, but not when self-administration is the outcome. Factors relevant to the predictive validity of self-administration procedures include medication maintenance and the concurrent assessment of a range of behaviors to determine abuse liability and the specificity of effect. Haney, M., and Spealman, R. Psychopharm. 199, pp. 403-419, 2008.

Substance Abuse Vaccines

Conventional substance-abuse treatments have only had limited success for drugs such as cocaine, nicotine, methamphetamine, and phencyclidine (PCP). This review article reports on the utility of vaccination to block the effects of these drugs on the brain and what factors influence the effects of antibodies on

drug pharmacodynamics. The review also presents the current status of vaccine development for nicotine, cocaine, methamphetamine, phencyclidine and morphine. There are currently three nicotine conjugate vaccines (NicVAX, NicQb, and TA-NIC) which were well tolerated in Phase I trials and have advanced to Phase IIb or Phase III. Both Phase I and Phase II trials have been completed using a cholera toxin B conjugated cocaine preparation (TA-CD) for cocaine dependence. Animal studies with conjugate vaccines have shown that substantial quantities of antibodies can reduce the accumulation of PCP in the brain; similar results have been found with passive immunization using anti-PCP monoclonal antibodies. Animal studies of methamphetamine vaccines are in the early stages, although passive administration of monoclonal antibodies has been shown to reduce methamphetamine self-administration in rats and to reduce locomotor activity in rats given high-dose methamphetamine. Although there are FDA-approved medications for opioid dependence, the spread of HIV/AIDS has sparked renewed interest in vaccines against heroin and morphine, as the economics of pharmacological and behavioral treatments make current substance-abuse programs less feasible in third-world countries. Early preclinical experiments with morphine conjugate vaccines showed some positive results which would justify continued research in this area. Orson, F.M., Kinsey, B.M., Singh, R.A.K., Wu, Y., Gardner, T., and Kosten, T.R. Ann. N.Y. Acad. Sci. 1142, pp. 257-269, 2008.

Sex and Opioid Maintenance Dose Influence Response to Naloxone in Opioid-dependent Humans: a Retrospective Analysis

Pooled self-report and physiological data from 32 male and 15 female methadone or levo-alpha-acetyl methadol (LAAM) maintained volunteers were retrospectively analyzed for individual differences in response to naloxone (0.15 mg/70 kg, IM) and placebo at 20 and 40 min post-injection. Males and females were each divided by the median split methadone maintenance dose (MMD, in mg/kg body weight) into high and low MMD groups and MMD was used as a factor in the analyses, along with sex, drug, and time post-drug. Females in the low but not high, MMD group showed naloxone-induced increases in ratings on the Antagonist and Mixed-Action sub-scales of the Adjective Rating Scale, and the Lysergic acid diethyl amine (LSD) sub-scale of the Addiction Research Center Inventory at 20 min post-injection. Males in the high MMD group showed significant naloxone-induced increases in scores of these measures at both post-injection time-points. In addition, low MMD subjects showed more short-lived naloxone-induced increases on Visual Analogue Scale (VAS) Bad and Any drug effects ratings than high MMD subjects. These results suggest that those on a lower MMD, especially women, experience a more intense, but short-lived, response to naloxone, whereas those on a higher MMD experience a more modest, but longer-lasting effect. Chopra, M.P., Feldman, Z., Mancino, M.J., and Oliveto, A. Sex and Opioid Maintenance Dose Influence Response to Naloxone in Opioid-dependent Humans: A Retrospective Analysis. Pharmacol. Biochem. Behav., 90(4), pp. 787-796, 2008.

A Phase 3 Placebo-controlled, Double-blind, Multi-site

Trial of the Alpha-2-Adrenergic Agonist, Lofexidine, for Opioid Withdrawal Lofexidine is an alpha-2-adrenergic receptor agonist that is approved in the United Kingdom for the treatment of opioid withdrawal symptoms. Lofexidine has been reported to have more significant effects on decreasing opioid withdrawal symptoms with less hypotension than clonidine. The objective of this study was to demonstrate that lofexidine is well tolerated and effective in the alleviation of observationally defined opioid withdrawal symptoms in opioid dependent individuals undergoing medically supervised opioid detoxification as compared to placebo. The study design was an inpatient, Phase 3, placebo-controlled, double-blind, randomized multi-site trial with three phases: (1)

opioid agonist stabilization phase (days 1-3), (2) detoxification/medication or placebo phase (days 4-8), and (3) post detoxification/medication phase (days 9-11). Sixty-eight opioid dependent subjects were enrolled at three sites with 35 randomized to lofexidine and 33 to placebo. The main outcome measure was a Modified Himmelsbach Opiate Withdrawal Scale (MHOWS) on study day 5 (second opioid detoxification treatment day). Due to significant findings, the study was terminated early. On the study day 5 MHOWS, subjects treated with lofexidine had significantly lower scores (equating to fewer/less severe withdrawal symptoms) than placebo subjects (least squares means 19.5+/-2.1 versus 30.9+/-2.7; p=0.0019). Lofexidine subjects had significantly better retention in treatment than placebo subjects (38.2% versus 15.2%; Log rank test p=0.01). The authors concluded that lofexidine is well tolerated and more efficacious than placebo for reducing opioid withdrawal symptoms in inpatients undergoing medically supervised opioid detoxification. Yu, E., Miotto, K., Akerele, E., Montgomery, A., Elkashef, A., Walsh, R., Montoya, I., Fischman, M.W., Collins, J., McSherry, F., Boardman, K., Davies, D.K., O'Brien, C.P., Ling, W., Kleber, H., and Herman, B.H. Drug Alcohol Depend., 97(1-2), pp. 158-168, 2008.

Safety and Feasibility of Sublingual Buprenorphine for the Treatment of Neonatal Abstinence Syndrome

In utero exposure to drugs of abuse can lead to neonatal abstinence syndrome, a condition that is associated with prolonged hospitalization. Buprenorphine is a partial mu-opioid agonist used for treatment of adult detoxification and maintenance. The primary objective of this study was to demonstrate the feasibility and the safety of sublingual buprenorphine in the treatment of neonatal abstinence syndrome. Secondary goals were to evaluate efficacy relative to standard therapy and to characterize buprenorphine pharmacokinetics when sublingually administered. The methodology was to conduct a randomized, open-label, active-control study of sublingual buprenorphine for the treatment of opiate withdrawal. Thirteen term infants were allocated to receive sublingual buprenorphine 13.2 to 39.0 g/kg per day administered in 3 divided doses and 13 to receive standard-of-care oral neonatal opium solution. Dose decisions were made by using a modified Finnegan scoring system. Results indicated that sublingual buprenorphine was largely effective in controlling neonatal abstinence syndrome. Greater than 98% of plasma concentrations ranged from undetectable to approximately 0.60 ng/mL, which is less than needed to control abstinence symptoms in adults. Three infants who received buprenorphine and 1 infant who received standard of care reached protocol-specified maximum doses and required adjuvant therapy with phenobarbital. The mean length of treatment for those in the neonatal-opium-solution group was 32 compared with 22 days for the buprenorphine group. The mean length of stay for the neonatal-opium-solution group was 38 days compared with 27 days for those in the buprenorphine group. Treatment with buprenorphine was well tolerated. In conclusion, buprenorphine administered via the sublingual route is feasible and apparently safe (small N) and may represent a novel treatment for neonatal abstinence syndrome. Kraft, W.K., Gibson, E., Dysart, K., Damle, V.S., Larusso, J.L., Greenspan, J.S., Moody, D.E., Kaltenbach, K., and Ehrlich, M.E. Sublingual Buprenorphine for Treatment of Neonatal Abstinence Syndrome: a Randomized Trial. Pediatrics 122(3), pp. 601-607, September 2008.

Treating Pregnant Women Dependent on Opioids Is Not the Same as Treating Pregnancy and Opioid Dependence

The aim of this review is to articulate a set of evidence-based recommendations for consideration as guidance in the management of opioid-dependent pregnant women and infants. Methods included PubMed literature searches carried out to identify recent key publications in the areas of

pregnancy and opioid dependence, neonatal abstinence syndrome (NAS) prevention and treatment, multiple substance abuse and psychiatric comorbidity. Results indicated that pregnant women dependent on opioids, require careful treatment to minimize harm to the fetus and neonate and to improve maternal health. Applying multi-disciplinary treatment as early as possible, while allowing medication maintenance and regular monitoring, benefits mother and child both in the short and the long term. However, there is a need for randomized clinical trials with sufficient sample sizes. Opioid maintenance therapy is the recommended treatment approach during pregnancy. Treatment decisions must encompass the full clinical picture, with respect to frequent complications arising from psychiatric comorbidities and the concomitant consumption of other drugs. In addition to standardized approaches to pregnancy, equivalent attention must be given to the treatment of NAS, which occurs frequently following opioid prescriptions. Unfortunately, methodological flaws and inconsistencies confound interpretation of today's literature. Winklbaur, B., Kopf, N., Ebner, N., Jung, E., Thau, K., and Fischer, G., Treating Pregnant Women Dependent on Opioids Is Not the Same as Treating Pregnancy and Opioid Dependence: A Knowledge Synthesis For Better Treatment For Women and Neonates. Addiction 103(9) pp. 1429-1440, Sepember 2008.

Clinical and Research Issues in the Treatment of Opioid-dependent Pregnant Women

This is an important methodological publication which addresses common questions that clinicians face when treating pregnant women with opioid dependence. Guidance, based on both research evidence and the collective clinical experience of the authors, is provided to aid clinical decision making. The authors are from the Maternal Opioid Treatment, Human Experimental Research (MOTHER) project. The MOTHER project is a double-blind, double-dummy, flexible-dosing, parallel-group clinical trial examining the comparative safety and efficacy of methadone and buprenorphine for the treatment of opioid dependence in pregnant women and their neonates. The article discusses appropriate assessment during pregnancy and addresses clinical management stages including maintenance medication selection, induction, and stabilization; as well as opioid agonist medication management before, during, and after delivery. In addition, methods of pain management; breast-feeding; and transfer to aftercare are reviewed. Lastly, other important clinical issues including managing co-occurring psychiatric disorders and medication interactions are explained. Jones, H.E., Martin, P.R., Heil, S.H., Kaltenbach, K., Selby, P., Coyle, M.G., Stine, S.M., O'Grady, K.E., Arria, A.M., and Fischer, G. Treatment of Opioid-dependent Pregnant Women: Clinical and Research Issues. J. Subst. Abuse Treat. 35(3) pp. 245-259, October 2008.

Neonatal Outcomes Correlated With Maternal Buprenorphine Dose and Metabolite Concentrations in Meconium

Relationships among maternal buprenorphine dose, meconium buprenorphine and metabolite concentrations, and neonatal outcomes are reported. Free and total buprenorphine and norbuprenorphine, nicotine, opiates, cocaine, benzodiazepines, and metabolites were quantified in meconium from 10 infants born to women who had received buprenorphine during pregnancy. Neither cumulative nor total third-trimester maternal buprenorphine dose predicted meconium concentrations or neonatal outcomes. Total buprenorphine meconium concentrations and buprenorphine/norbuprenorphine ratios were significantly related to neonatal abstinence syndrome (NAS) scores >4. As free buprenorphine concentration and percentage free buprenorphine increased, head circumference decreased. Thrice-weekly urine tests for opiates, cocaine, and benzodiazepines and self-reported smoking data from the mother were compared with data from analysis of the meconium to estimate in utero

exposure. Time of last drug use and frequency of use during the third trimester were important factors associated with drug-positive meconium specimens. The results suggest that buprenorphine and metabolite concentrations in the meconium may predict the onset and frequency of NAS. Kacinko, S.L., Jones, H.E., Johnson, R.E., Choo, R.E., and Huestis, M.A. Correlations of Maternal Buprenorphine Dose, Buprenorphine, and Metabolite Concentrations in Meconium With Neonatal Outcomes. Clin. Pharmacol. Ther. 84(5), pp. 604-612, November 2008.

Buprenorphine is Useful in the Treatment of Prescription Opioid Addiction

Dependence on and abuse of prescription opioid drugs is now a major health problem, with initiation of prescription opioid abuse exceeding cocaine in young people. Coincident with the emergence of abuse and dependence on prescription opioids, there has been an increased emphasis on the treatment of pain. Pain is now seen as the "5th vital sign" and physicians face disciplinary action for failure to adequately relieve pain. Thus, physicians are caught between the imperative to treat pain with opioids and the fear of producing addiction in some patients. The emerging epidemic of prescription opioid abuse is discussed in conjunction with the utility of buprenorphine in the treatment of this addiction. Case histories of successful treatment with buprenorphine are used to illustrate it's effectiveness. Mendelson, J., Flower, K., Pletcher, M.J., and Galloway, G.P. Addiction to Prescription Opioids; Characteristics of the Emerging Epidemic and Treatment With Buprenorphine. Exp. Clin. Psychopharmacol, 16(5), pp. 435-441, October 2008.

Nicotine Gum for Pregnant Smokers: a Randomized Controlled Trial

The purpose of this study was to estimate the safety and efficacy of treatment with 2-mg nicotine gum for smoking cessation during pregnancy. Pregnant women who smoked daily received individualized behavioral counseling and random assignment to a 6-week treatment with 2-mg nicotine gum or placebo followed by a 6-week taper period. Women who did not quit smoking were instructed to reduce the number of cigarettes smoked by substituting with gum. Measures of tobacco exposure were obtained throughout the study. Participants in the nicotine (n = 100) and placebo (n = 94) groups were comparable in age, race/ethnicity, and smoking history. Biochemically validated smoking-cessation rates were not significantly higher with nicotine gum compared with placebo (after 6 weeks of treatment: 13% compared with 9.6%, P=.45; at 32-34 weeks of gestation: 18% compared with 14.9%, P=.56). Using a completer analysis, nicotine gum significantly reduced the number of cigarettes smoked per day (nicotine gum: -5.7 [standard deviation (SD)=6.0]; placebo: -3.5 [SD=5.7], P=.035), and cotinine concentration (nicotine gum: -249 ng/mL [SD=397]; placebo: -112 ng/mL [SD=333]; P=.04). Birth weights were significantly greater with nicotine gum compared with placebo (3,287 g [SD=566] and 2,950 g [SD=653], respectively, P<.001). Gestational age was also greater with nicotine-replacement therapy than with placebo (38.9 weeks [SD=1.7] and 38.0 weeks [SD=3.3], respectively; P=.014). Although nicotine gum did not increase quit rates, use of nicotine gum increased birth weight and gestational age, two key parameters in predicting neonatal wellbeing. Oncken, C., Dornelas, E., Greene, J., Sankey, H., Glasmann, A., Feinn, R., and Kranzler, H.R. Obstet. Gynecol. 112(4), pp. 859-867, 2008.

Director's Report to the National Advisory Council on Drug Abuse - February, 2009

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

HIV-1 Expression Induces Tubular Cell G2/M Arrest and Apoptosis

Human renal biopsy studies suggest the presence of HIV-1 and associated signs of injury in renal tubular epithelial cells. Because renal epithelial cells lack conventional HIV-1 receptors, the modus operandi of HIV-1 in the induction of tubular cell injury remains a mystery. In the present study, the authors evaluated the role of HIV-1 gene expression in human proximal tubular cell apoptosis and cell cycle progression. HIV-1- or vector-transduced cells were assayed for cellular injury and cell cycle defect. HIV-1-transduced cells showed the progressive loss of viability in a time-dependent manner. Similarly, HIV-1-transduced cells showed greater apoptosis when compared with vector-transduced cells. A higher number of HIV-1 expressing cells showed cell cycle arrest at G2/M phase and enhanced tubular cell expression of phospho-p53 (ser15), phospho- cdc-2(Tyr 15), and phospho-chk-2 (Thr 68). These findings suggest that in addition to the activation of apoptotic pathway, HIV-1- induced G2/M arrest may also contribute to tubular cell injury. Vashistha, H., Husain, H., Kumar, D., Yadav, A., Arora, S., Singhal. P.C., and Failure, R. Renal Failure 30(6) pp. 655-664, 2008.

Drug Use and Weight Loss in HIV-infected Hispanic Men

Weight loss is an independent risk factor for mortality in HIV but the role of drug use in HIV-related weight loss is not well described. The authors conducted this study to determine the role of drug use in HIV-related weight loss. Men (n=304), all of whom were Hispanic, were recruited into one of three groups: HIV-infected drug users; HIV-non-infected drug users; and HIV-infected non-drug users. Body mass index (BMI) was measured at successive visits. The groups were re-categorized based on self-reported drug use at the current visit into: (1) users of cocaine alone; (2) users of cocaine and opiates; (3) users of opiates alone; (4) former drug users; and (5) those who denied ever using drugs (all HIV-infected). The effect on BMI of the duration of use of the specific drug types was evaluated using repeated-measures analyses. Longer duration of exclusive opiate use or mixed cocaine and opiate use did not affect BMI in the men, regardless of HIV status. Exclusive cocaine use was associated with a decline in BMI among HIV-infected men (-0.070 kg/m(2) per month duration of use; SE=0.033; p=0.037) but not among HIV-uninfected men (0.024 kg/m(2) per month; SE=0.023; p=0.29). Adjustment for marijuana, cigarette and alcohol use in all men, or for CD4 count, viral load or HIV medication use in the HIV-infected men, did not alter the conclusions. The authors conclude that the use of opiates or combined opiates and cocaine does not increase the risk of weight loss in the presence or absence of HIV infection. Exclusive Cocaine Use May Exacerbate Weight Loss in HIV-infection. Forrester,

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J.E., Tucker, K.L., Skinner, S., and Terrin, N. AIDS Care 20(7), pp. 868-875, August 2008.

Risk Factors for Proteinuria in HIV-infected and -uninfected Hispanic drug Users

Proteinuria may be an early marker of chronic kidney disease in human immunodeficiency virus (HIV)-infected patients with coexisting chronic hepatitis and/or drug use. Minorities are at greater risk of chronic kidney disease. Data are limited about risk factors for proteinuria in Hispanic drug users with and without HIV infection. In this cross-sectional study a community-recruited Hispanic cohort was employed to study the role of drug use in HIV-associated malnutrition composed of 4 groups (106 HIV-infected drug users, 96 HIV-uninfected drug users, 38 HIV-infected non-drug users, and 47 healthy controls). Patients on renal replacement therapy were excluded. Predictors were: HIV infection, chronic hepatitis, history of hypertension or diabetes, and intravenous drug use (never, prior, or current). The presence of proteinuria was defined as urine dipstick result of 1+ or greater. Multivariable logistic regression was used to identify independent risk factors for proteinuria. Of 287 patients with available data, 24 (8.4%) had proteinuria. In univariate analyses, those with HIV infection; prior, but not current, intravenous drug use; and a history of hypertension or diabetes were more likely to have proteinuria. In multivariate analyses, significant risk factors for proteinuria were HIV infection (odds ratio, 9.2; 95% confidence interval, 1.9 to 45.8; P = 0.007); prior, but not current, intravenous drug use (odds ratio, 4.7; 95% confidence interval, 1.4 to 15.3; P = 0.01); and history of hypertension or diabetes (odds ratio, 8.2; 95% confidence interval, 3.1 to 21.7; P < 0.001). The cross-sectional study design used here makes it difficult to establish the temporal relationship. The number of outcomes in relation to the number of predictors is small. The authors concluded that HIV and prior intravenous drug use, but not chronic hepatitis or current intravenous drug use, were independently associated with proteinuria in this Hispanic population. Longitudinal studies to assess the development of proteinuria and chronic kidney disease in this high-risk population are warranted. Rhee, M.S., Schmid, C.H., Stevens L.A., and Forrester, J.E. Am. J. Kidney Dis. 52(4), pp. 683-690, 2008. Epub June 24, 2008.

Methamphetamine Enhances HIV-1 Infectivity in Monocyte Derived Dendritic Cells

The US is currently experiencing an epidemic of methamphetamine (Meth) use as a recreational drug. Recent studies also show a high prevalence of HIV-1 infection among Meth users. The authors report that Meth enhances HIV-1 infectivity of dendritic cells as measured by multinuclear activation of a galactosidase indicator (MAGI) cell assay, p24 assay, and LTR-RU5 amplification. Meth induces increased HIV-1 infection in association with an increase in the HIV-1 coreceptors, CXCR4 and CCR5, and infection is mediated by downregulation of extracellular-regulated kinase (ERK2) and the upregulation of p38 mitogen-activated protein kinase (MAPK). A p38 inhibitor (SB203580) specifically reversed the Meth-induced upregulation of the CCR5 HIV-1 coreceptor. The dopamine D2 receptor antagonist RS +/- sulpiride significantly reversed the Meth-induced upregulation of CCR5, demonstrating that the Meth-induced effect is mediated via the D2 receptor. These studies report for the first time that Meth fosters HIV-1 infection, potentially via upregulating coreceptor gene expression. Further, Meth mediates its regulatory effects via dopamine receptors and via downregulating ERK2 with a reciprocal upregulation of p38 MAPK. Elucidation of the role of Meth in HIV-1 disease susceptibility and the mechanism through which Meth mediates its effects on HIV-1 infection may help to devise novel therapeutic strategies against HIV-1

infection in high-risk Meth-using HIV-1-infected subjects. Nair, M.P., Saiyed, Z.M., Nair, N., Gandhi, N.H., Rodriguez, J.W., Boukli, N., Provencio-Vasquez, E., Malow, R.M., and Miguez-Burbano, M.J. J. Neuroimmune Pharmacol. October 29, 2008.

Routine HIV Testing in Jails is Critical for the Early Diagnosis of HIV Infection in Men

The authors emphasize the need for development of new HIV testing and referral strategies for use in jails that will increase the number of diagnoses of HIV and facilitate earlier referral and entry of HIV positive patients to care, when CD4 cell counts are higher and treatment is more effective. Late presentation for care has been associated with black race and male sex, as well as increased likelihood of being poor and uninsured, less educated, disproportionately incarcerated and high levels of HIV infection, addiction and mental health disorders. It is recommended that interventions with maximum potential public health impact, such as routine rapid HIV testing performed as part of medical intake for processing persons in jails, be prioritized. Flanigan, T. P., and Beckwith, C.G. Clin. Infect. Dis. 47(10), pp. 1366, Novmber 2008.

HIV/HCV: Role of Molecular Mimickry of Hepatitis C-virus (HCV) Protein with Platelet GPIIIa in Hepatitis C-related Immunologic Thrombocytopenia

HIV-1-ITP patients have a unique Ab against platelet GPIIIa49-66 capable of inducing oxidative platelet fragmentation in the absence of complement. HIV-1-seropositive drug abusers are more prone to develop immune thrombocytopenia (HIV-1-ITP) than non-drug abusers and have a higher coinfection with Hepatitis C virus than non-drug abusers (90% vs 30%). Molecular mimickry with a Hepatitis C protein was sought by screening a phage peptide library with anti-GPIIIa49-66 antibody as bait for peptides sharing homology sequences with HCV protein. Several phage peptide clones had 70% homology with HCV protein. Sera from dually infected thrombocytopenic patients with HCV and HIV-ITP reacted strongly with 4 nonconserved peptides from HCV core envelope 1. Reactivity correlated inversely with platelet count, $r2=0.7$, $p<0.01$. Ab raised against peptide PHC09 in GPIIIa-/- mice induced severe thrombocytopenia in wild-type mice. Affinity-purified IgG against PHC09 induced oxidative platelet fragmentation in vitro. Drug abusers dually infected with HCV and HIV-1 had a greater incidence and severity of thrombocytopenia as well as greater incidence and titer of anti- GPIIIa49-66/PHC09 Ab. NZB/W F1 mice injected with recombinant core envelope 1 developed Ab vs PHC09 and significantly decreased their platelet count, $p<0.001$. Thus, HCV core envelope 1 can induce thrombocytopenia by molecular mimicry with GPIIIa49-66. Note: ITP (idiopathic immune thrombocytopenic purpura) A condition in which the body produces antibodies against the platelets in the blood, the cells responsible for blood clotting. ITP is very common in persons infected with HIV. If left untreated, ITP can lead to uncontrolled bleeding. Zhang, W., Nardi, A.M., Li, Z., Borkowsky, W., and Karpatkin, S. Blood. Prepublished online, November 20, 2008.

Platelet Fragmentation Requires a Specific Structural Conformation of Human Monoclonal Antibody against 3 Integrin

The authors have described an autoantibody against 3 (GPIIIa49-66), a region of platelet integrin IIb3 that is unique. It induces platelet fragmentation in the absence of complement via antibody activation of platelet NADPH oxidase and 12-lipoxygenase to release reactive oxygen species, which destroy platelets. To study the mechanism of anti-GPIIIa antibody-induced platelet fragmentation, the authors screened a human single chain Fv antibody library with the

GPIIIa49-66 peptide. Nine monoclonal antibodies were identified that were capable of binding to GPIIIa49-66. Surprisingly, binding avidity for GPIIIa49-66 did not correlate with activity of induction of platelet fragmentation. They therefore investigated the requirements for platelet fragmentation. Mutations were introduced into the heavy chain complementary-determining region-3 of clones 11, 43, and 54 by site-directed mutagenesis. The capability of these clones to induce platelet fragmentation or bind to GPIIIa49-66 subsequently changed. Molecular modeling of these clones with their mutants revealed that the ability to induce platelet fragmentation is affected by the side chain orientation of positively charged amino acids in the heavy chain of residues 99-102. Thus, a structural change in the conformation of anti- GPIIIa49-66 antibody contributes to its binding to the 3 integrin and subsequent antibody-induced platelet fragmentation and aggregate dissolution. Li, Z., Nardi, A.M., Wu, J., Pan, R., Zhang, W., and Karpatkin, S. J. Biol. Chem., 283(6), pp. 3224-3230, February 8, 2008.

Liver Fibrosis During an Outbreak of Acute Hepatitis C Virus Infection in HIV-Infected Men: A Prospective Cohort Study

Outbreaks of acute hepatitis C virus (HCV) infection are occurring in HIV-infected men who have sex with men. The authors evaluated risk factors and liver histopathology in 11 consecutively enrolled men with newly acquired HCV infection that was diagnosed on the basis of antibody seroconversion, new elevations in alanine aminotransferase level, and wide fluctuations in HCV RNA level. Ten patients reported unprotected anal intercourse, and 7 reported "club-drug" use, including methamphetamine. Liver biopsy showed moderately advanced fibrosis (Scheuer stage 2) in 9 patients (82%). No cause of liver damage other than acute HCV infection was identified. The specific pathways leading to periportal fibrosis in HIV-infected men with newly acquired HCV infection require investigation. Note: On the cover: Image showing a liver biopsy specimen from an HIV-infected man with acute hepatitis C virus infection obtained 8 weeks after presentation with clinical hepatitis. Fierer, S.D., Uriel, J.A., Carriero, C.D., Klepper, A., Dieterich, T.D., Mullen, P.M., Thung, N.S., Fiel, M.I., and Branch, D.A. The Journal of Infectious Diseases, 198(5), pp. 683, 1 September 2008.

Clinicopathologic Correlates of Hepatitis C Virus in Brain: A Pilot Study

Hepatitis C virus (HCV) has been detected in the brain tissues of 10 individuals reported to date; it is unclear what clinical factors are associated with this, and with what frequency it occurs. Accordingly, a pilot analysis utilizing reverse transcriptase-polymerase chain reaction (RT- PCR) to detect and sequence HCV in premortem plasma and postmortem brain and liver from 20 human immunodeficiency virus (HIV)-infected and 10 HIV-naive individuals was undertaken. RNA encoding the first 126 amino acids of the HCV E1 envelope protein and the majority of the E1 signal sequence was analyzed in parallel with an 80-base-long segment of the 5' untranslated region (UTR). Liver HCV was detected only in subjects with premortem HCV viremia (10 HIV-infected and 3 HIV-naive). Brain HCV was detected in 6/10 HCV/HIV-coinfected and 1/3 HCV-monoinfected subjects. In the setting of HIV, the magnitude of plasma HCV load did not correlate with the presence of brain HCV. However, coinfected patients with brain HCV were more often off antiretroviral therapy and tended to have higher plasma HIV loads than those with HCV restricted to liver. Furthermore, premortem cerebrospinal fluid (CSF) analysis revealed that HCV/HIV-coinfected patients with brain HCV had detectable CSF HIV, whereas those without brain HCV had undetectable CSF HIV loads ($P = .0205$). Neuropsychologic tests showed a trend for hierarchical impairment of abstraction/executive functioning in HIV/HCV coinfection, with mean T scores for HIV monoinfected patients 43.2 (7.3), for liver-only HCV 39.5 (9.0), and for

those with HCV in brain and liver 33.2 (5.1) (P = .0927). Predominant brain HCV sequences did not match those of the plasma or liver in 4 of the 6 coinfected patients analyzed. The authors conclude that in the setting of HIV/HCV coinfection, brain HCV is a common phenomenon unrelated to the magnitude of HCV viremia, but related to active HIV disease and detectable CSF HIV. Furthermore, there is sequence evidence of brain compartmentalization. Differences in abstraction/executive function of HCV/HIV coinfected patients compared to HIV monoinfected warrant further studies to determine if neuropsychiatric effects are predicated upon brain infection. Murray. J., Fishman, S.L., Ryan, E., Eng, F.J., Walewski, J.L., Branch, A.D., and Morgello, S. Journal of Neurovirology, 14(1), pp. 17 - 27, January 2008.

HCV/ HIV Co-infection: Time to Re-evaluate the Role of HIV in the Liver?

Because of major advances in the treatment of HIV /AIDS, HIV-positive persons now live longer, healthier lives; however, hepatitis C virus (HCV) is increasingly recognized as a major cause of morbidity and mortality in this population. Among HCV-infected persons, HIV co-infection is associated with increased HCV RNA levels, increased hepatic inflammation and fibrosis, and more rapid progression to cirrhosis and end-stage liver disease. Compounding this problem are reduced HCV treatment response rates among HCV /HIV co-infected persons. Moreover, antiretroviral therapy used to suppress HIV replication is often associated with a paradoxical increase in HCV RNA levels, as well as hepatotoxicity. Despite the adverse clinical consequences of HCV/ HIV co-infection, the mechanisms by which these two viruses interact at the cellular level remain largely unexplored. This review focuses on the evidence demonstrating direct infection of hepatocytes by HIV, as well as the indirect mechanisms by which HIV may regulate HCV replication at the cellular level. A comprehensive understanding of virus-virus and virus-cell interactions is critical to the development of novel treatment strategies to combat HCV/ HIV co-infection. Blackard, L.T., and Sherman, K.E. Journal of Viral Hepatitis, 15, pp. 323-330, 2008.

Quality of Life, Symptomatology and Healthcare Utilization in HIV/HCV Co-infected Drug Users in Miami

HIV/HCV co-infection is becoming one of the main causes of death in HIV+ persons. The authors determined quality of life, clinical symptoms and health care utilization in HIV mono-infected and HIV/HCV co-infected chronic drug users. After consenting 218 HIV+ drug users, a physical examination and questionnaires on demographics, quality of life, drugs of abuse, and healthcare utilization were completed. Blood was drawn for HCV status, CD4 cell count, HIV viral load, CBC and chemistry. HIV/HCV co-infected participants had significantly higher risk of having poorer perceived outlook and health, presented significantly more frequent depression and physical symptoms, and used significantly more healthcare services than those infected with HIV only, after adjusting for age, gender, ethnicity, CD4 cell count, and viral load. Diminished quality of life in the HIV/HCV co-infected group was explained by increased frequency of depression, physical symptoms, healthcare utilization, and poor access to HCV treatment in this population. Baum, M.K., Jayaweera, D.T., Duan, R., Sales, S., Lai, S., Rafie, C., Regev, A., Page, J.B., Berkman, R., and Campa, A. J. Addict. Dis. 27(2), pp. 37-48, 2008.

Low Frequency of GB Virus C Viremia in a Cohort of HIV-1-infected Elite Suppressors

The persistence of GB virus C viremia in patients with chronic HIV-1 infection has been associated with increased survival. Elite suppressors are untreated

HIV-1-infected patients who maintain viral loads of below 50 copies/ml. This study found that the frequency of GB virus C viremia in elite suppressors and chronically infected patients with progressive disease was not significantly different. Thus, GB virus C does not appear to explain the nonprogressive course seen in this cohort of elite suppressors. Blankson, J.N., Klinzman, D., Astemborski, J., Thomas, D.L., Kirk, G.D., and Stapleton, J.T. AIDS, 22(17), pp. 2398-2400, 2008.

HCV/ HBV, Liver Disease: Molecular and Bioinformatic Evidence of Hepatitis C Virus Evolution in Brain

HCV was present in the brains of 7 (54%) of 13 patients with viremia, as determined by 5' UTR and E1 (envelope 1) gene analysis. Brain HCV RNA consensus sequences differed from those in plasma and liver in 4 (57%) of 7 patients. The quality of HCVRNA from postmortem brain and liver was assessed and demonstrated to be suitable for sequence analysis. Quasispecies analysis revealed that several mutations present in clones from >1 brain region were absent in clones from liver and plasma. Brain-specific mutations defined several families of related sequences. The patterns of brain-specific mutations in these families were consistent with the evolution of HCV RNA from a common ancestor. Single-nucleotide-polymorphism analysis confirmed that a prominent brain-specific mutation constituted ~10% of HCV RNA in cerebellum and medulla but that this mutation was undetectable in the liver and plasma of the same patient. In conclusions, This study introduces novel methods for assessing RNA from postmortem samples. It increases the reported cases of HCV in the brain, provides the first E1 sequences from the brain, and contributes to the growing evidence that HCV replicates and evolves within the brain. Fishman, L.S., Murray, M.J., Eng, J.F., Walewski, L.J., Morgello, S., and Branch, D.A. The Journal of Infectious Diseases, 197, pp. 597-607, 2008.

Clinical Outcomes of Hepatitis C Treatment in a Prison Setting: Feasibility and Effectiveness for Challenging Treatment Populations

More than one-third of people in the United States with hepatic C virus (HCV) infection pass through the correctional system annually. Data are lacking on outcomes of treatment with pegylated interferon plus ribavirin (PEG-RBV) in correctional settings. During 2002-2006, the authors analyzed patients in the Connecticut Department of Correction who received PEG-RBV. They assessed the rates of sustained virological response, hospitalization, and use of medications to treat psychiatric disorders and anemia. Of 138 treatment-naive patients referred for treatment, 68 (49%) were approved. Overall, sustained virological response occurred in 47.1% of patients (for HCV genotype 1, 43.1%; for HCV genotypes 2 and 3, 58.8%). Only 9 patients (13%) discontinued treatment because of adverse effects. Multiple regression analysis revealed that not achieving a sustained virological response was correlated with HCV genotype 1 infection plus cirrhosis (adjusted odds ratio, 12.9; 95% confidence interval, 1.1-148) and baseline major depression (adjusted odds ratio, 3.4; 95% confidence interval, 1.01-11.6), but not with HIV infection, a baseline HCV RNA level >or=400,000 IU/mL, or black race. Compared with baseline, the rate of prescription of a new mood stabilizer (2.2 vs. 0.8 prescriptions per person-year) or an opioid (1.8 vs. 0.5 prescriptions per person-year) was higher during treatment, whereas there was no change in the rate of prescription of benzodiazepines and antipsychotic medications. These results support the feasibility and clinical effectiveness of PEG-RBV for the treatment of chronic HCV infection in correctional facilities. Maru, D.S., Bruce, R.D., Basu, S., and Altice, F.L. Clin. Infect. Dis. 47(7), pp. 952-961, October 2008.

Hepatitis C Virus-specific T-cell Immune Responses in Seronegative Injection Drug Users

T-cell responses to hepatits C virus (HCV) antigens have been reported in high-risk HCV seronegative persons, suggesting that an effective cellular immune response might be able to clear infection without the development of antibodies. Such findings, however, could be explained by waning antibody or cross-reactivity to other antigens. To address these issues, the authors evaluated HCV-specific T-cell responses in 26 young (age 18-33 years) aviremic, seronegative injection drug users (IDUs) (median duration of injection, 6 years) by interferon-gamma enzyme-linked immunospot (ELISpot) assay using 429 overlapping HCV peptides pooled in 21 mixes. Seventeen aviremic, seropositive IDUs (spontaneous resolvers) and 15 healthy people were used as positive and negative controls, respectively. The percentage of patients with HCV-specific cellular immune responses was similar in seronegative and seropositive aviremic IDUs (46%vs 59%, P = 0.4), while these responses were not detected in any of the negative controls. Among the seronegative IDUs, six (23%) had intermediate to very strong responses to 10-20 peptide mixes and another six (23%) had moderately strong responses for two to six mixes. The 12 seronegative IDUs with HCV-specific T-cell responses had higher demographical and behavioural risk profiles than the 14 IDUs without T-cell responses (estimated risk of HCV infection, 0.47 vs 0.26, P < 0.01). In conclusion, HCV-specific T-cell responses are common among high-risk, seronegative IDUs. The responses are broad and are associated with risk factors for HCV exposure, suggesting that they reflect true exposure to HCV in seronegative persons. Zeremski, M., Shu, M.A., Brown, Q., Wu, Y., DesJarlais, D.C., Busch, M.P., Talal, A.H., and Edlin, B.R. J. Viral Hepat. [Epub ahead of print] July 17, 2008.

The Inverse Relationship Between Chronic HBV and HCV Infections Among Injection Drug Users is Associated with Decades of Age and Drug Use

Infection with hepatitis C virus (HCV) may suppress co-infection with hepatitis B virus (HBV) during acute or chronic HBV infection. The authors examined relationships between HBV infection, HCV infection and other factors among injection drug users (IDUs) with antibodies to both viruses. Participants enrolled in a cross-sectional study during 1998-2000 were considered to have been infected with HBV if they had core antibody, to be chronically infected if they had hepatitis B surface antigen (HBsAg), to have been infected with HCV if they had HCV antibody and to be chronically infected if they had HCV RNA. Among 1,694 participants with antibody to both viruses, HBsAg prevalence decreased with increasing age among those positive for HCV RNA [from 4.55% in those 18-29 years to 1.03% in those >or=50 years old (P(trend) = 0.02)], but not among those who were negative for HCV RNA. Chronic HBV infection was less common overall among those with chronic HCV infection (odds ratio [OR], 0.25; P < 0.0001), but this inverse relationship was much stronger in the oldest (>50 years; OR = 0.15) than the youngest (18-29 years; OR = 0.81) participants (P(trend) = 0.03). Similar results were obtained when duration of injection drug use was substituted for age (P(trend) = 0.05). Among IDUs who have acquired both HBV and HCV, chronic HBV infection is much less common among those with chronic HCV infection, but this inverse relationship increases markedly with increasing years of age and injection drug use. Co-infection with HCV may enhance the resolution of HBsAg during the chronic phases of these infections. Tseng, F.C., Edlin, B.R., Zhang, M., Kral, A., Busch, M.P., Ortiz-Conde, B.A., Welzel, T.M., and O'Brien, T.R., J. Viral Hepat. 15(9), pp. 690-698, September 2008.

Hepatitis C Virus (HCV)-specific Immune Responses of Long-term

Injection Drug Users Frequently Exposed to HCV

Injection drug users (IDUs) who successfully clear hepatitis C virus (HCV) have a reduced risk of developing chronic reinfection, despite their continuing exposure to the virus. To identify immunological correlates for this apparent protection, the authors studied HCV-specific immune responses in long-term IDUs (duration, >10 years). HCV-specific T cell responses were assessed in proliferation, enzyme-linked immunospot (ELISPOT), interferon (IFN)-gamma secretion, and cytotoxicity assays, whereas HCV-specific antibodies were assessed in enzyme immunoassays (EIAs), chemiluminescent assays, and in vitro neutralization assays. HCV-specific T cell proliferation and IFN-gamma production were more common in nonviremic EIA-positive IDUs (16 [94%] of 17 IDUs) than in viremic EIA-positive IDUs (9 [45%] of 20 IDUs) (P= .003). They were also noted in 16 (62%) of 26 nonviremic EIA-negative IDUs. In contrast, 19 (90%) of 21 viremic IDUs displayed neutralizing antibodies (nAbs), compared with 9 (56%) of 16 nonviremic EIA-positive IDUs (P= .04) and 0 of 24 nonviremic EIA-negative IDUs. Nonviremic IDUs with nAbs were older (P= .0115) than those without nAbs, but these groups did not differ in terms of either injection drug use duration or HCV-specific T cell responses. The authors concluded that the reduced risk of HCV persistence in IDUs previously recovered from HCV infection correlated with T cell responses, and prolonged antigenic stimulation appears to be required to maintain humoral responses. Mizuk, L.H., Busch, M.P., Carrington, M., McKeating, J.A., O'Brien, T.R., and Rehermann, B. J. Infect. Dis. 198(2), pp. 203-212, 2008.

MBL2 and Hepatitis C Virus Infection Among Injection Drug Users

Genetic variations in MBL2 that reduce circulating levels and alter functional properties of the mannose binding lectin (MBL) have been associated with many autoimmune and infectious diseases. The authors examined whether MBL2 variants influence the outcome of hepatitis C virus (HCV) infection. Participants were enrolled in the Urban Health Study of San Francisco Bay area injection drug users (IDU) during 1998 through 2000. Study subjects who had a positive test for HCV antibody were eligible for the current study. Participants who were positive for HCV RNA were frequency matched to those who were negative for HCV RNA on the basis of ethnicity and duration of IDU. Genotyping was performed for 15 single nucleotide polymorphisms in MBL2. Statistical analyses of European American and African American participants were conducted separately. The analysis included 198 study subjects who were positive for HCV antibody, but negative for HCV RNA, and 654 IDUs who were positive for both antibody and virus. There was no significant association between any of the genetic variants that cause MBL deficiency and the presence of HCV RNA. Unexpectedly, the MBL2 -289X promoter genotype, which causes MBL deficiency, was over-represented among European Americans who were HCV RNA negative (OR = 1.65, 95% CI 1.05-2.58), although not among the African Americans. This study found no association between genetic variants that cause MBL deficiency and the presence of HCV RNA. The observation that MBL2 -289X was associated with the absence of HCV RNA in European Americans requires validation. Brown, E.E., Zhang, M., Zarin-Pass, R., Bernig, T., Tseng, F.C., Xiao, N., Yeager, M., Edlin, B.R., Chanock, S.J., and O'Brien, T.R. BMC Infect. Dis. 8(57), pp. 1-8, 2008.

Hepatitis C Patients' Self-reported Adherence to Pegylated Interferon and Ribavirin

Prior research on adherence to Hepatitis C treatment has documented rates of dose reductions and early treatment discontinuation, but little is known about patients' dose-taking adherence. The aims of this study were to assess the prevalence of missed doses of pegylated interferon and ribavirin and examine

the correlates of dose-taking adherence in clinic settings. 180 patients on treatment for Hepatitis C (23% co-infected with HIV) completed a cross-sectional survey at the site of their Hepatitis C care. Seven percent of patients reported missing at least one injection of pegylated interferon in the last four weeks and 21% reported missing at least one dose of ribavirin in the last 7 days. Dose-taking adherence was not associated with HCV viral load. The authors concluded that self-reported dose nonadherence to Hepatitis C treatment occurs frequently. Further studies of dose nonadherence (assessed by method other than self-report) and its relationship to HCV virologic outcome are warranted. Weiss, J.J., Bhatti, L., Dieterich, D.T., Edlin, B.R., Fishbein, D.A., Goetz, M.B., Yu, K., and Wagner, G.J. Aliment. Pharmacol. Ther. 28, pp. 289-293, 2008.

Interaction Between RANTES Promoter Variant and CCR5Delta32 Favors Recovery from Hepatitis B

Recovery from acute hepatitis B virus (HBV) infection occurs in 95% of adult-acquired infections. A 32-bp deletion in CCR5 (CCR5Delta32), which encodes for a nonfunctional receptor, increases the likelihood of recovery. Using 181 subjects with persistent HBV infection and 316 who had recovered, the authors tested the hypothesis that an epistatic interaction between functional polymorphisms in RANTES (a CCR5 ligand) and CCR5 impacts recovery. Specific models designed to assess individual contributions of compound genotypes demonstrated that the only combination associated with recovery from an HBV infection was RANTES -403A with CCR5Delta32 (odds ratio 0.36, $p = 0.02$). Because the phenotypic consequence of -403A is reported to be higher levels of RANTES, the authors propose a model in which excess RANTES in combination with low CCR5 favors recovery from an HBV infection, which will require validation through functional testing. Thio, C.L., Astemborski, J., Thomas, R., Mosbruger, T., Witt, M.D., Goedert, J.J., Hoots, K., Winkler, C., Thomas, D.L., and Carrington, M. J. Immunol. 181(11), pp. 7944-7947, 2008.

Exceeding the Limits of Liver Histology Markers

Alternatives to liver biopsy for staging liver disease caused by hepatitis C virus (HCV) have not appeared accurate enough for widespread clinical use. The authors characterized the magnitude of the impact of error in the "gold standard" on the observed diagnostic accuracy of surrogate markers. They calculated the area under the receiver operating characteristic curve (AUROC) for a surrogate marker against the gold standard (biopsy) for a range of possible performances of each test (biopsy and marker) against truth and a gradient of clinically significant disease prevalence. In the 'best' scenario where liver biopsy accuracy is highest (sensitivity and specificity of biopsy are 90%) and the prevalence of significant disease 40%, the calculated AUROC would be 0.90 for a perfect marker (99% actual accuracy) which is within the range of what has already been observed. With lower biopsy sensitivity and specificity, AUROC determinations >0.90 could not be achieved even for a marker that perfectly measured disease. The authors demonstrate that error in the liver biopsy result itself makes it impossible to distinguish a perfect surrogate from ones that are now judged by some as clinically unacceptable. An alternative gold standard is needed to assess the accuracy of tests used to stage HCV-related liver disease. Mehta, S.H., Lau, B., Afdhal, N.H., Thomas, D.L. J. Hepatol. 51, pp. 36-41, 2008.

Genetic Markers of IgG Influence the Outcome of Infection with Hepatitis C Virus

The authors examined the role that immunoglobulin GM and KM allotypes-genetic markers of gamma and kappa chains, respectively-play in the outcome

of hepatitis C virus (HCV) infection in white Americans. A total of 119 persons who had cleared HCV and 111 with persistent HCV infection were genotyped for the presence of several GM and KM determinants. Persistent HCV infection was more than three times as likely (odds ratio, 3.50; P= .01) in subjects who were carriers of the GM3 allele than in those who were noncarriers. These results show that particular GM alleles may be important determinants of the outcome of HCV infection. Pandey, J.P., Namboodiri, A.M., Luo, Y., Wu, Y., Elston, R.C., Thomas, D.L., Rosen, H.R., and Goedert, J.J. J. Infect. Dis. 198(9), pp. 1334-1336, 2008.

Detection of Liver Disease in Injection Drug Users

Detection of liver disease among injection drug users is an important challenge because liver disease is common, usually unrecognized, and treatable in early stages. Many forms of liver disease occur in injection drug users (IDUs). However, commensurate with its exceedingly high prevalence among IDUs, much of the published literature (and accordingly the focus of this review) regards liver disease caused by chronic hepatitis C. Existing guidelines for detection of liver disease are presented in the context of the current standard of care. Since recent research shows these guidelines rarely contribute to the medical management of IDUs, special emphasis is given to novel approaches that, when coupled with advances in treatment, the authors believe could substantially reduce the medical and psychological consequences of injection drug use. Thomas, D.L., and Sulkowski, M.S. J. Addict. Dis. 27(2), pp. 19-24, 2008.

HCV E2 Protein Binds Directly to Thyroid Cells and Induces IL-8 Production: A New Mechanism for HCV Induced Thyroid Autoimmunity

HCV infection is well-known to be associated with autoimmune thyroiditis. However, the mechanisms by which HCV triggers thyroiditis are unknown. The authors hypothesized that HCV envelope proteins could induce thyroidal inflammation directly, thereby triggering thyroiditis by a bystander activation mechanism. To test this hypothesis they examined whether the HCV receptor CD81 was expressed and functional on thyroid cells. The authors found significant levels of CD81 mRNA by QPCR analysis, as well as CD81 protein by flow cytometric (FACS) analysis. Incubation of thyroid cells with HCV envelope glycoprotein E2 resulted in E2 binding to thyroid cells and activation of IL-8, an important pro-inflammatory cytokine. Intriguingly, thyroid cells incubated with E2 continued to proliferate normally and did not undergo apoptosis, as was reported in hepatocytes. The authors conclude that: (1) HCV envelope glycoprotein E2 can bind to CD81 receptors which are expressed on thyroid cells and induce a cascade of signaling pathway leading to IL-8 release; and (2) HCV may trigger thyroiditis in genetically susceptible individuals by bystander activation mechanisms. Akeno, N., Blackard, J.T., and Tomer, Y. Journal of Autoimmunity, 31(4), pp. 339-344, 2008.

Efficacy and Safety of Peginterferon alfa-2a/ribavirin in Methadone Maintenance Patients: Randomized Comparison of Direct Observed Therapy and Self-administration

The investigators assessed the safety, tolerability, and efficacy of peginterferon alfa-2a/ribavirin treatment in methadone maintenance patients previously untreated for Chronic Hepatitis C (CHC). Based on defined efficacy stopping rules, 77% (37/48) completed their targeted length of treatment, and 44% (21/48) achieved sustained virologic response (SVR). Over 60% and 50% of each group were > 80% compliant with the planned cumulative doses of peginterferon alfa-2a and ribavirin, respectively, and over 60% with overall

treatment duration. SVR rates were 54% for Directly Observed Therapy (DOT) and 33% for Self Administration (SA); 23% and 38%, respectively, for genotype 1 and 91% and 25%, respectively, for genotypes 2 and 3. DOT and Caucasian race were found to be predictors of SVR. Peginterferon alfa-2a/ribavirin was found safe and successful for use in CHC patients receiving methadone maintenance. Bonkovsky, H.L., Tice, A.D., Yapp, R.G., Bodenheimer, H.C. Jr., Monto, A., Rossi, S.J., and Sulkowski. M. S. Am. J.Gastroenterol., 103(11), pp. 2757-2765, November 2008. Epub August 5, 2008.

Safety and Antiviral Activity of Albinterferon Alfa-2b in Prior Interferon Nonresponders With Chronic Hepatitis C

The safety/efficacy of albinterferon alfa-2b, a recombinant protein consisting of interferon alfa-2b fused to human albumin to increase drug exposure in Chronic Hepatitis C patients unresponsive to interferon-based regimens was evaluated for safety and efficacy. Among non-responders, higher doses of albinterferon showed significant early antiviral activity and low incidence of adverse events, with types of adverse events similar to those observed with interferon treatment. Nelson, D.R., Rustgi, V., Balan, V., Sulkowski, M.S., Davis, G.L., Muir, A.J., Lambiase, L.R., Dickson, R.C., Weisner, R.H., Fiscella, M., Cronin, P. W., Pulkstenis, E., McHutchison, J.G., and Subramanian, G.M. Clin. Gastroenterol. Hepatol. [Epub ahead of print], November 7, 2008.

Successful Treatment of Chronic Hepatitis C with Pegylated Interferon in Combination with Ribavirin in a Methadone Maintenance Treatment Program

Injection drug users (IDUs) constitute the majority of individuals with hepatitis C virus (HCV), however there are limited clinical outcome data regarding HCV treatment provided on-site in methadone maintenance settings. On-site HCV treatment with pegylated interferon and ribavirin was shown effective in methadone-maintained patients, with HCV treatment response rates nearly equivalent to previously published response rates for non-IDUs. Of 73 patients; 55% achieved end-of-treatment response and 45% achieved sustained viral response, despite high prevalences of ongoing drug use (49%), psychiatric comorbidity (67%), and HIV co-infection (32%). Methadone maintenance programs were shown as safe settings for the treatment of chronic hepatitis C. Litwin, A.H., Harris, K. A. Jr., Nahvi, S., Zamor, P.J., Soloway, I.J., Tenore, P.L., Kaswan, D., Gourevitch, M.N., and Arnsten, J.H., J. Subst. Abuse Treat. [Epub ahead of print]. November 25, 2008.

Naturally Occurring Dominant Resistance Mutations to Hepatitis C Virus Protease and Polymerase Inhibitors in Treatment-naive Patients

Resistance mutations to hepatitis C virus (HCV) nonstructural protein protease inhibitors in <1% of the viral quasispecies may still allow >1000-fold viral load reductions upon treatment, consistent with their reported reduced replicative fitness in vitro. Recently, however, an R155K protease mutation was reported as the dominant quasispecies in a treatment-naive individual, raising concerns about possible full drug resistance. The authors analyzed HCV genome sequences from 507 treatment-naive patients infected with HCV genotype 1 from the United States, Germany, and Switzerland, to investigate the prevalence of dominant resistance mutations against specifically targeted antiviral therapy for HCV (STAT-C) in the population. Phylogenetic sequence analysis and viral load data were used to identify the possible spread of replication-competent, drug-resistant viral strains in the population and to infer the consequences of these mutations upon viral replication in vivo. Naturally

occurring dominant STAT-C resistance mutations were found to be common in treatment-naive patients infected with HCV genotype 1. The authors suggest further development of drug resistance testing for individual tailoring of drug combinations when treatment options are limited, or unresponsivity to previous treatment. Kuntzen, T., Timm, J., Berical, A., Lennon, N., Berlin, A.M., et al., Hepatology, 48(6), pp. 1769-1778, December 2008.

Aldosterone Induces Mesangial Cell Apoptosis both In Vivo and In Vitro

Both clinical and experimental reports indicate that aldosterone contributes to the progression of renal failure independent of its hemodynamic effects. In the present study, the authors evaluated the effects of aldosterone on human mesangial cell (MC) growth. Aldosterone induced apoptotic and mitogenic effects on MCs. Aldosterone promoted MC Apoptosis in a dose- and time-dependent manner. Spironolactone, a mineralocorticoid receptor antagonist, inhibited aldosterone-induced MC Apoptosis. Similarly, antioxidants and free radical scavengers partially attenuated proapoaptotic effects of aldosterone. Aldosterone also enhanced dephosphorylation of phospho- Bad and accumulation of cytosolic cytochrome c in MCs. In in vivo studies, rats were randomly assigned to receive normal saline, aldosterone, or eplerenone + aldosterone for 28 days. Systolic blood pressure, urinary albumin excretion rate, serum creatinine, and aldosterone were measured. Aldosterone-infused rats developed elevated systolic blood pressure and albuminuria when compared with control rats. Aldosterone-treated rats also showed greater numbers of apoptosed MCs. This proapoptotic effect of aldosterone was inhibited by eplerenone, a selective aldosterone antagonist. These findings suggest that aldosterone, besides its hemodynamic effects, may also directly contribute to the occurrence of MC apoptosis. Mathew, T.J., Patni, H., Chaudhary, N.A., Liang, W., Gupta, A., Chander, N.P., Ding, G., and Singhal, C.P. Am. J. Physiol. Renal Physiol., 295, pp. F73-F81, 2008.

Angiotensin II Infusion Induces Nephrin Expression Changes and Podocyte Apoptosis

In in vitro studies, angiotensin (Ang) II has been demonstrated to promote podocyte apoptosis. The present study evaluates the effects of Ang II infusion in rats on podocyte nephrin expression and apoptosis and the molecular mechanisms involved in Ang II-induced proteinuria and mesangial expansion. Sprague-Dawley rats were randomly assigned to receive either normal saline or Ang II (400 ng.kg-1.min-1) by means of a mini-osmotic pump for variable time periods. Systolic blood pressure and urinary protein and albumin excretion rate measurements were carried out on days 7, 14, 21, and 28. The animals were sacrificed on days 14 and 28 and evaluated for serum creatinine, renal pathological changes, podocyte apoptosis, renal nephrin mRNA, and protein expression. The Ang II-infused rats developed hypertension and proteinuria. On day 14, the Ang II-infused rats showed narrowing of the slit diaphragm, an increase in podocyte nephrin mRNA and protein expression, and alterations in its distribution along the foot processes. On day 28, the Ang II-infused rats demonstrated the presence of apoptotic podocytes and decreased nephrin mRNA and protein expression. There was a negative correlation between nephrin expression and the numbers of apoptotic podocytes ($r = -0.63$, $p < 0.05$). These results suggest that changes in nephrin expression may play a role in the pathogenesis of Ang II-induced podocyte apoptosis. Jia, J., Ding, G., Zhu, J., Chen, C., Liang, W., Franki, N., and Singhal, C.P. Am. J. Nephrol. 28, pp. 500-507, 2008.

Ethical and Human Rights Imperatives to Ensure Medication-assisted Treatment for Opioid Dependence in Prisons and Pre-trial

Detention

Opioid dependence is a complex medical condition affecting neurocognitive and physical functioning. Forced or abrupt opioid withdrawal may cause profound physical and psychological suffering, including nausea, vomiting, diarrhea, extreme agitation and/or anxiety. Opioid-dependent individuals are especially vulnerable at the time of arrest or initial detention, when they may, as a result of their chemical dependency, be coerced into providing incriminating testimony, or be driven to engage in risky behaviour (such as sharing needles in detention) in order to avoid painful withdrawal symptoms. Upon incarceration, many opioid-dependent prisoners are forced to undergo abrupt opioid withdrawal (both from legally prescribed agonist therapy such as methadone as well as illicit opioids). Physical and psychological symptoms attendant to withdrawal may impair capacity to make informed legal decisions, and cause prisoners to risk HIV and other blood-borne diseases by sharing injection equipment. Although prisons must provide at least the standard of care to prisoners that is available in the general population, medication-assisted treatment, endorsed by international health and drug agencies as an integral part of HIV prevention and care strategies for opioid-dependent drug users, is unavailable to most prisoners. Medication-assisted treatment is a well-studied and validated pharmacological therapy for the medical condition known as opioid dependence. The failure to ensure prisoner access to this medical therapy threatens fundamental human rights protections against cruel, inhuman or degrading treatment and rights to health and to life. It also poses serious ethical problems for health care providers, violating basic principles of beneficence and non-maleficence (i.e., do good/do no harm). Governments must take immediate action to ensure access to opioid substitution to prisoners to ensure fulfillment of ethical and human rights obligations. Bruce, R. D., and Schleifer, R.A. Int. J. Drug Policy., 1, pp. 17-23, 2008.

Historical Analysis: Heroin in Brown, Black and White: Structural Factors and Medical Consequences in the US Heroin Market

Heroin coming into the United States historically comes from three widely dispersed geographical regions: Southwest Asia, Southeast Asia and Mexico. A fourth source of US-bound heroin, from Colombia, originated in the early 1990s. The fact that the four heroin sources produce differing morphologies and qualities of heroin has not been critically examined. In addition, it is not well established how the contemporary competing dynamics of interdiction, or restriction of heroin flows across international boundaries, and neoliberal, e.g., global expansion of free trade, policies are affecting heroin markets. This paper highlights changes in the US heroin market, including source trends, the political economy of the now dominant source and the resultant effects on the heroin risk environment by US region. Using a structural and historical framework this paper examines two decades of secondary data sources, including government and drug control agency documents, on heroin flows together with published work on the political and economic dynamics in Latin America. Co-occurring neoliberal economic reforms may have contributed to paradoxical effects of US/Colombian interdiction efforts. Since entering the US market, heroin from Colombia has been distributed at a much higher quality and lower retail price. An increasingly exclusive market has developed with Mexican and Colombian heroin gaining market share and displacing Asian heroin. These trends have had dramatic effects on the risk environment for heroin consumers. An intriguing factor is that different global sources of heroin produce substantially different products. Plausible associations exist between heroin source/form and drug use behaviors and harms. For example, coldwater-soluble powdered heroin (sources: Asia, Colombia) may be associated with higher HIV prevalence in the US, while low-solubility "black tar" heroin (BTH; source: Mexico) is historically used in areas with reduced HIV prevalence. BTH is associated with soft tissue infections caused by Clostridium

bacteria. The authors conclude that source and type of heroin are structural factors in the risk environment of heroin users: source dictates distribution and type predicts practice. How specific types of heroin are used and with what risk is therefore distributed geographically. Continued flux in the heroin market and its effects on the risk environment for drug users deserves further attention. Ciccarone, D. Int. J. Drug Policy, Available online 21 October, 2008.

Case Series of Buprenorphine Injectors in Kuala Lumpur, Malaysia

Diversion of buprenorphine has been described in settings where it is legally prescribed and has become an increasing concern in Malaysia; it resulted in banning of buprenorphine in Singapore where unsubstantiated case reports suggested that buprenorphine injection was associated with particularly poor outcomes. The authors therefore conducted a case series of qualitative interviews with buprenorphine injectors in Kuala Lumpur, Malaysia to examine further the issues surrounding buprenorphine injection as well as the abuse of midazolam in combination with buprenorphine. Interviews with 19 men do not suggest significant adverse health consequences from buprenorphine injection alone and injectors have adapted diverted buprenorphine as a treatment modality. A subset of these injectors, however, combined buprenorphine and midazolam for euphoric effects with resultant symptoms of a possible pharmacological interaction. Prospective cohort studies, rather than hospital-derived samples, are needed to better understand the safety of buprenorphine injection. Bruce, R.D., Govindasamy S.S.L., Haddad, M.S., Kamarulzaman, A., and Altice, F.L. Am. J. Drug Alcohol Abuse, 34(4), pp. 511-517, 2008.

Mechanism of Ritonavir Changes in Methadone Pharmacokinetics and Pharmacodynamics: II. Ritonavir Effects on CYP3A and P-Glycoprotein Activities

Ritonavir diminishes methadone plasma concentrations, an effect attributed to CYP3A induction, but the actual mechanisms are unknown. The authors determined short-term (2-day) and steady-state (2-week) ritonavir effects on intestinal and hepatic CYP3A4/5 (probed with intravenous (IV) and oral alfentanil (ALF) and with miosis) and P-glycoprotein (P-gp) (fexofenadine), and on methadone pharmacokinetics and pharmacodynamics in healthy volunteers. Acute ritonavir increased the area under the concentration-time curve (AUC) (0-infinity)/dose ratio (ritonavir/control) for oral ALF 25-fold. Steady-state ritonavir increased the AUC (0-infinity)/dose ratio for IV and oral ALF 4- and 10-fold, respectively; reduced hepatic extraction (from 0.26 to 0.07) and intestinal extraction (from 0.51 to 0); and increased bioavailability (from 37 to 95%). Acute ritonavir inhibits first-pass CYP3A >96%. Chronic ritonavir inhibits hepatic CYP3A (>70%) and first-pass CYP3A (>90%). Acute and steady-state ritonavir increased the fexofenadine AUC (0-infinity) 2.8- and 1.4-fold, respectively, suggesting P-gp inhibition. Steady-state compared with acute ritonavir caused mild apparent induction of P-gp and hepatic CYP3A, but net inhibition still predominated. Ritonavir inhibited both intestinal and hepatic CYP3A and drug transport. ALF miosis noninvasively determined CYP3A inhibition by ritonavir. Kharasch, E., Bedynek, P., Walker, A., Whittington, D., Hoffer, C. Clin. Pharmacol. Ther. Advance online publications July 9, 2008.

Molecular Characterization of CYP2B6 Substrates

CYP2B6 has not been as fully characterized at the molecular level as other members of the human cytochrome P450 family. As more widely used in vitro probes for characterizing the involvement of this enzyme in the metabolism of xenobiotics have become available, the number of molecules identified as CYP2B6 substrates has increased. In this study the authors have analyzed the available kinetic data generated by multiple laboratories with human

recombinant expressed CYP2B6 and along with calculated molecular properties derived from the ChemSpider database, they have determined the molecular features that appear to be important for CYP2B6 substrates. In addition they have applied 2D and 3D QSAR methods to generate predictive pharmacophore and 2D models. For 28 molecules with K(m) data, the molecular weight (mean +/- SD) is 253.78+/-74.03, ACD/logP is 2.68+/-1.51, LogD(pH 5.5) is 1.51+/-1.43, LogD(pH 7.4) is 2.02+/-1.25, hydrogen bond donor (HBD) count is 0.57 +/-0.57, hydrogen bond acceptor (HBA) count is 2.57+/-1.37, rotatable bonds is 3.50+/-2.71 and total polar surface area (TPSA) is 27.63+/-19.42. A second set of 15 molecules without K(m) data possessed similar mean molecular property values. These properties are comparable to those of a set of 21 molecules used in a previous pharmacophore modeling study (Ekins et al., J. Pharmacol. Exp. Ther. 288(1), pp. 21-29, 1999). Only the LogD and HBD values were statistically significantly different between these different datasets. The authors have shown that CYP2B6 substrates are generally small hydrophobic molecules that are frequently central nervous system active, which may be important for drug discovery research. Ekins, S., Iyer, M., Krasowski, M.D., and Kharasch, E.D. Curr. Drug Metab., 9(5), pp. 363-373, June 2008.

Role of CYP2B6 in Stereoselective Human Methadone Metabolism

Metabolism and clearance of racemic methadone are stereoselective and highly variable, yet the mechanism remains largely unknown. Initial in vitro studies attributed methadone metabolism to cytochrome P4503A4 (CYP3A4). CYP3A4 was also assumed responsible for methadone clearance in vivo. Nevertheless, recent clinical data do not support a primary role for CYP3A4 and suggest that CYP2B6 may mediate methadone clearance. Expressed CYP2B6 and also CYP2C19 N-demethylate methadone in vitro. This investigation tested the hypothesis that CYPs 2B6, 3A4, and/or 2C19 are responsible for stereoselective methadone metabolism in human liver microsomes and in vivo. N-demethylation of racemic methadone and individual enantiomers by expressed CYPs 2B6, 2C19, and 3A4 was evaluated. Stereoselective microsomal methadone metabolism was quantified, compared with CYP 2B6 and 3A4 content, and probed using CYP isoform-selective inhibitors. A crossover clinical investigation (control, CYP2B6 and CYP3A4 induction by rifampin, CYP3A inhibition by troleandomycin and grapefruit juice) evaluated stereoselective methadone disposition. At clinical concentrations, methadone enantiomer N-demethylation by recombinant CYPs 2B6, 3A4, and 2C19 was S > R, S = R, and S << R. Greater stereoselective metabolism (S > R) occurred in livers expressing high levels of CYP2B6 compared with CYP3A4. Clopidogrel, troleandomycin, and (+)-N-3-benzyl-nirvanol, selective inhibitors of CYPs 2B6, 3A4, and 2C19, respectively, inhibited microsomal methadone metabolism by 50-60%, 20-30%, and less than 10%. Only inhibition by clopidogrel was stereoselective. Clinically, rifampin diminished both R- and S-methadone plasma concentrations, but troleandomycin and grapefruit juice altered neither R- nor S-methadone concentrations. Plasma R/S-methadone ratios were increased by rifampin but unchanged by CYP3A inhibition. These results suggest a significant role for CYP2B6, but not CYP3A, in stereoselective human methadone metabolism and disposition. Totah, R.A., Sheffels, P., Roberts, T., Whittington, D., Thummel, K., and Kharasch, E.D. Comment in: Anesthesiology 108(3), pp. 351-352; March 2008.

Self-Reported Substance Use and Sexual Behaviors among Adolescents in a Rural State

Research finds a strong association between substance use and risky sexual behavior but more needs to be known about this relationship. Few studies have examined this relationship among rural sixth- to eighth-grade students. As such, the purposes of this study were to provide a descriptive profile of rural

sixth- to eighth-grade students' substance use behavior and sexual activity and to examine the relationship between substance use behaviors and sexual activity. Participants consisted of a convenience sample of 10,273 middle school students (sixth to eighth grade) attending 10 public schools in rural Tennessee. The middle school Youth Risk Behavior Survey was administered to these students during April and May 2004. Analysis found that a large percentage of students had tried cigarettes, alcohol, and inhalants. Additionally, it was found that sexual intercourse had been initiated by 18.8% of females and 25.4% of males. Of those students who reported ever having had sexual intercourse, 75% had reported the use of cigarettes and alcohol. In addition, approximately 50% of those students reported marijuana and inhalant use. The results suggest that substance use behavior has a relationship with the likelihood of initiating sexual activity. Additional longitudinal research with this population will be needed for explaining whether these select substance use behaviors are probable risk factors predisposing young rural adolescents to report engaging in sexual behaviors or a result of other factors. Dunn, M.S., Ilapogu, V., Taylor, L., Naney, C., Blackwell, R., Wilder, R., and Givens, C. J. Sch. Health. 78(11), pp. 587-593, November 2008.

Gender-related Differences in Muscle Injury, Oxidative Stress, and Apoptosis

Due to its alleged antioxidant properties, 17beta-estradiol (E2) may protect against muscle injury, oxidative stress, and apoptosis. This study sought to determine whether such mechanisms existed between genders for muscle injury, oxidative stress, and apoptosis after eccentric exercise. Eight men and eight women (no oral contraceptive use; midluteal phase of menstrual cycle) performed 7 x 10 eccentric repetitions of the knee extensors at 150% 1RM. Strength, soreness, and blood samples were taken before exercise and 6, 24, 48, and 72 h after exercise while muscle samples were collected before and 6 and 24 h after exercise. Blood samples were assayed for free E2, lactate dehydrogenase (LDH), superoxide dismutase (SOD), and 8-isoprostane (8-iso). Muscle samples were assayed for mitochondrial apoptosis (e.g., bax, bcl-2, cytochrome c, and cell death), total DNA content, and myofibrillar protein content. Men reported greater soreness levels at 24, 48, and 72 h after exercise, whereas strength changes were similar among genders. At baseline and independent of exercise, females had higher E2 ($P < 0.001$) and SOD in conjunction with lower 8-iso levels when compared with men. Bax increased in both genders, whereas bcl-2 increased only in women with no cytochrome c changes for either gender after exercise. The bax/bcl-2 ratio in women significantly decreased after 6 h ($P = 0.03$) and returned to baseline levels after 24 h. Men exhibited greater cell death at all time points ($P < 0.05$), whereas myofibrillar protein content and total DNA content decreased in both genders at 24 h after exercise. No changes in LDH were found ($P > 0.05$). Although more research is needed, differences between genders may provide greater endogenous protection against oxidative stress and apoptosis. Kerksick, C., Taylor, L., Harvey, A., and Willoughby, D. Med. Sci. Sports Exerc. 40(10), pp. 1772-1780, October 2008.

Heroin Transition Risk among Daily and Non-daily Cannabis Users Who are Non-injectors of Heroin

Non-injecting heroin use (NIU) has been identified as a potential precursor for the transition to injecting drug use (IDU). Heroin transition risks between two groups of Mexican American cannabis users (daily users (DU) vs. non-daily users (NDU)) who are NIUs were examined and compared. Three fourths of the cannabis NDU showed transition risk attributes. Heroin transition risk was positively associated with longer term heroin use. An inverse relationship was found with DU of cannabis and those reporting use of alcohol in the past month

being less likely to be associated with heroin transition risks. Findings tentatively indicate that DU of cannabis may be interpreted as a form of self-regulation and potentially deterring problematic heroin use among Mexican American NIUs and possibly other polydrug users in similar social environments. The authors discuss alternative interpretations of these findings. Valdez, A., Cepeda, A., Neaigus, A., and Russell, A. Int. J. Drug Policy, 19(6), pp. 442-449, December 2008.

Crack-Cocaine Use Accelerates HIV Disease Progression in a Cohort of HIV-Positive Drug Users

HIV infection is prevalent among substance abusers. The effects of specific illicit drugs on HIV disease progression have not been established. The authors evaluated the relationship between substances of abuse and HIV disease progression in a cohort of HIV-1-positive active drug users. A prospective, 30-month, longitudinal study was conducted on 222 HIV-1 seropositive drug users in Miami, FL. History of illicit drug, alcohol, and medication use, CD4+ cell count, and viral load were performed every 6 months. Crack-cocaine users were 2.14 times [95% confidence interval (CI): 1.08 to 4.25, P = 0.029] more likely to present a decline of CD4 to <=200 cells per microliter, independent of antiretroviral use. Viral load over 30 months was significantly higher in crack users ([beta] = 0.315, P = 0.037) independent of highly active antiretroviral therapy (HAART) over time. The only multidrug combination that significantly increased the risk of disease progression was crack cocaine with marijuana (hazard ratio = 2.42; 95% CI: 1.042 to 5.617, P = 0.04). Of those on HAART, a significantly lower proportion of crack-cocaine users versus nonusers had controlled viral load (P < 0.001), suggesting lower medication adherence, whereas crack-cocaine users not on HAART showed a greater risk for HIV disease progression than nonusers (hazard ratio = 3.946; 95% CI: 1.049 to 14.85, P = 0.042). The authors conclude that crack-cocaine use facilitates HIV disease progression by reducing adherence in those on HAART and by accelerating disease progression independently of HAART. Baum, M.K., Rafie, C., Lai, S., Sales, S., Page, B., and Campa, A. JAIDS, November 25, 2008.

Director's Report to the National Advisory Council on Drug Abuse - February, 2009

Research Findings - Services Research

Cost-Effectiveness of Genetic Testing for Initial Anti-Retroviral Therapy

This study evaluated the clinical impact and cost-effectiveness of HLA-B*5701 testing to guide selection of first-line HIV regimens in the United States. Cost-effectiveness analysis was done using a simulation model of HIV disease. The prevalence of HLA-B*5701 and the probabilities of confirmed and unconfirmed severe systemic hypersensitivity reaction among patients taking abacavir testing HLA-B-5701 positive and negative were from the Prospective Randomized Evaluation of DNA Screening in a Clinical Trial study. The monthly costs of abacavir-based and tenofovir-based regimens were $1135 and $1139, respectively; similar virologic efficacy was assumed and this assumption was varied in sensitivity analysis. The patients represented a simulated cohort initiating HIV therapy. The interventions are first-line abacavir, lamivudine, and efavirenz without pretreatment HLA-B-5701 testing; the same regimen with HLA-B-5701 testing; and first-line tenofovir, emtricitabine, and efavirenz. The main outcome measures were: Quality-adjusted life years and lifetime medical costs discounted at 3% per annum, cost-effectiveness ratios ($/QALY). Abacavir-based treatment without HLA-B-5701 testing resulted in a projected 30.93 years life expectancy, 16.23 discounted quality-adjusted life years, and $472 200 discounted lifetime cost per person. HLA-B-5701 testing added 0.04 quality-adjusted months at an incremental cost of $110, resulting in a cost-effectiveness ratio of $36 700/QALY compared with no testing. Initiating treatment with a tenofovir-based regimen increased costs without improving quality-adjusted life expectancy. HLA-B-5701 testing remained the preferred strategy only if abacavir-based treatment had equal efficacy and cost less per month than tenofovir-based treatment. Results were also sensitive to the cost of HLA-B-5701 testing and the prevalence of HLA-B-5701. It is concluded that pharmacogenetic testing for HLA-B-5701 is cost-effective only if abacavir-based treatment is as effective and costs less than tenofovir-based treatment. Schackman, B.R., Scott, C.A., Walenskyding, R.P., Losinar, E., Freedbergding, K.A., and Sax, P.E. The Cost-Effectiveness of HLA-B-5701 Genetic Screening to Guide Initial Antiretroviral Therapy for HIV. AIDS, 22(15), pp. 2025-2033, 2008.

Methadone Maintenance for Prisoners: Findings at 6 mos Post-Release

This study examined the effectiveness of methadone maintenance initiated prior to or just after release from prison at 6 months post-release. A three-group randomized controlled trial was conducted between September 2003 and June 2005. Two hundred and eleven adult pre-release inmates, in a Baltimore pre-release prison, who were heroin-dependent during the year prior to

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incarceration, were assigned randomly to the following: counseling only: counseling in prison, with passive referral to treatment upon release (n = 70); counseling + transfer: counseling in prison with transfer to methadone maintenance treatment upon release (n = 70); and counseling + methadone: methadone maintenance and counseling in prison, continued in a community-based methadone maintenance program upon release (n = 71). Counseling + methadone participants were significantly more likely than both counseling only and counseling + transfer participants to be retained in drug abuse treatment (P = 0.0001) and significantly less likely to have an opioid-positive urine specimen compared to counseling only (P = 0.002). Furthermore, counseling + methadone participants reported significantly fewer days of involvement in self-reported heroin use and criminal activity than counseling only participants. Methadone maintenance, initiated prior to or immediately after release from prison, increases treatment entry and reduces heroin use at 6 months post-release compared to counseling only. This intervention may be able to fill an urgent treatment need for prisoners with heroin addiction histories. Gordon, M., Kinlock, T., Schwartz, R., and O 'Grady, K. A Randomized Clinical Trial of Methadone Maintenance for Prisoners: Findings at 6 months Post-Release. Addiction, 103(8), pp. 1333-1342, 2008.

Epidemiology of Chronic Prescription Opioid Use: Results From a Major National, Population-Based Survey

Chronic pain occurs commonly and accounts for significant suffering and costs. Although use of opioids for treatment of chronic pain is increasing, little is known about patients who use opioids regularly. The researchers report data from the second wave of the Healthcare for Communities survey (2000-2001), a large, nationally representative household survey. They compared regular users of prescription opioids to nonusers of opioids and calculated the percentage of individuals within a given demographic or disease state that reported chronic opioid use. Approximately 2% of the 7,909 survey respondents reported use of opioid medications for at least a month, which the Healthcare for Communities survey defined as "regular use." It was found that opioid users were more likely than nonusers to report high levels of pain interference with their daily lives and to rate their health as fair or poor. Arthritis and back pain were the most prevalent chronic, physical health conditions among users of opioids, with 63% of regular users of opioids reporting arthritis and 59% reporting back pain. The majority of regular users of opioids had multiple pain conditions (mean=1.9 pain conditions). This study indicates that regular opioid users appear to have an overall lower level of health status and to have multiple, chronic physical health disorders. Hudson, T., Edlund, M., Steffick, D., Tripathi, S., and Sullivan, M. Epidemiology of Regular Prescribed Opioid Use: Results From a National, Population-Based Survey. J. Pain Symptom Manage., 36(3), pp. 280-288, 2008.

Trends in Use of Prescription Opioid Medication by the Type of Noncancer Pain, From 2000-2005, Among Arkansas Medicaid and HealthCore Enrollees: Results From the TROUP Study

Use of prescription opioids for noncancer pain has increased significantly in recent years, but it is not known if trends differ among the most common noncancer pain conditions. The researchers examined trends in opioid prescribing for the years 2000 through 2005 for individuals with arthritis/joint pain, back pain, neck pain, and headaches by type and number of pain diagnoses, using data from claims records from 2 health insurers: HealthCore commercially insured members (N = 3,768,223) and Arkansas Medicaid (N = 127,866). Rates of headache, back pain, and neck pain diagnoses increased significantly in Arkansas Medicaid enrollees but more modestly among HealthCore enrollees. Rates of opioid use increased in both groups, with long-

term use (>90 days '' supply per year) increasing at twice the rate of any use. It was found that rates of opioid use did not differ widely between noncancer pain conditions, but long-term opioid use rates doubled with each additional pain diagnosis. Mean days supply and cumulative yearly dose increased between 2000 and 2005 for all pain types and with increasing number of pain diagnoses, but dose per day supply remained relatively stable. The greatest increases in dose among all the pain conditions were seen in short-acting DEA Schedule II opioids. This study demonstrates increased use of opioids, particularly long-term use, in noncancer pain over a 6-year period among those with multiple pain types. These results appear to reflect a general increase in use of prescription opioids for noncancer pain rather than a condition-specific change in prescribing practices. Braden, J., Fan, M., Edlund, M., Martin, B., DeVries, A., and Sullivan, M. Trends in Use of Opioids by Noncancer Pain Type 2000-2005 Among Arkansas Medicaid and Health Core Enrollees: Results From the TROUP Study. J. Pain, 9(11), pp. 1026-1035, 2008.

The Adoption of Evidence-Based Practices in Public Sector Adolescent Addiction Treatment

This article examines the adoption and initial implementation phases of a statewide effort to narrow the gap between science and practice in the treatment of substance abuse disorders in adolescents. Although transporting evidence-based substance abuse services to community-based treatment settings has been described as a public health and federal research priority, the vast majority of substance abuse treatment services are not evidence-based, and relatively little research has examined the adoption and implementation of evidence-based practices. Four hundred thirty-two public sector therapists attended a workshop in contingency management (CM) and were interviewed monthly for the following 6 months to assess their adoption and initial implementation of CM to treat substance-abusing adolescent clients. Results showed that 58% (n = 131) of the practitioners with at least one substance-abusing adolescent client (n = 225) adopted CM. Rates of adoption varied with therapist service sector (mental health vs. substance abuse), educational background, professional experience, and attitudes toward treatment manuals and evidence-based practices. Competing clinical priorities and client resistance were most often reported as barriers to adopting CM, whereas unfavorable attitudes toward and difficulty in implementing CM were rarely cited as barriers. The fidelity of initial CM implementation among adopters was predicted by organizational characteristics as well as by several demographic, professional experience, attitudinal, and service sector characteristics. Fidelity, for example, was predicted by working in an organization with high motivational readiness for change, being certified in addiction counseling, having high caseloads and a high percentage of youth clients, being of younger age, and not holding negative attitudes toward treatment manuals. Overall, the findings support the amenability of public sector practitioners to adopt evidence-based practices and suggest that the predictors of adoption and initial implementation are complex and multifaceted. Future research may explore the conditions that support the fidelity of implementation of evidence-based practices or the sustainability of these innovations. Although research on these issues is costly and challenging to conduct, the authors argue that such work is critical for narrowing the gap between science and service. Henggeler, S., Chapman, J., Rowland, M., Halliday-Boykins, C., Randall, J., Shackelford, J., and Schoenwald, S. Statewide Adoption and Initial Implementation of Contingency Management for Substance-Abusing Adolescents. J. Consult. Clin. Psychol., 76(4), pp. 556-567, 2008.

Recovery Capital are Associated with Sustained Recovery, Higher Quality of Life, and Lower Stress

This study appears to be the first specifically designed to assess the differential

role of psychosocial factors as prospective predictors of recovery outcome. The authors build on previous cross-sectional findings that recovery capital (social supports, spirituality, religiousness, life meaning, and 12-step affiliation) enhances the ability to cope with stress and enhances life satisfaction. The authors state that many recovering persons report quitting their drug use because they are "sick and tired" of the drug life. There has been little research on the millions of recovering persons in the United States, and most research has focused on substance use outcomes rather than on broader functioning domains. This study (a) tests the hypothesis that higher levels of recovery capital prospectively predict sustained recovery, higher quality of life, and lower stress one year later, and (b) examines the differential effects of recovery capital on outcomes across the stages of recovery. Recovering persons (N = 312), mostly inner-city ethnic minority members whose primary substance had been crack or heroin, were interviewed twice at a one-year interval in New York City between April 2003 and April 2005. The sample was 55% male; 63% African-American, 15% non-Hispanic white, and 22% of other or mixed ethnic/racial background; 18% were of Hispanic origin. Participants were classified into one of four baseline recovery stages: under 6 months, 6-18 months, 18-36 months, and over 3 years. Multiple regression findings generally supported the central hypothesis and suggested that different domains of recovery capital were salient at different recovery stages. For example, twelve-step involvement was the only significant predictor of sustained recovery among individuals with 6 to 18 months of recovery at baseline. The study's limitations are noted and implications of findings for clinical practice and for future research are discussed, including the need for a theoretical framework to elucidate the recovery process. Identifying recovery patterns over time, as well as the factors that promote and hinder positive outcomes over the course of this process may assist in realizing recovery potential and help to minimize the risk of return to active addiction by informing clinicians, the recovery community, and family. Laudet, A., and White, W. Recovery Capital as Prospective Predictor of Sustained Recovery, Life Satisfaction, and Stress Among Former Poly-Substance Users. Subst. Use Misuse, 43(1), pp. 27-54, 2008.

Medical Severity at Chemical Dependency Admission and Receiving Integrated Treatment Both Positively Associated with Remission from Substance Abuse at 5 Years

Five-year outcomes of 589 adult chemical dependency clients in a private health plan were examined to determine the statistical association between having a substance abuse-related medical condition (SAMC, e.g. injury and poisonings, anxiety and nervous disorders, hypertension), severity of medical condition as measured by the Addiction Severity Index, having been randomized to integrated substance abuse and medical treatment, or receiving continuing primary care services and being in remission from substance abuse. Logistic regression models informed by the stress and coping model revealed that while clients with SAMCs or who received more than one primary care visits had similar odds of remitting within 5 years as others, those with higher ASI medical severity scores had higher odds of remission (OR = 2.0, 95% CI 1.14-3.54), as did those who had been randomized into integrated care (OR = 1.48, 95% CI 1.04 - 2.13). Among those with SAMCs (n=458), severity of medical condition and randomization into integrated care were also positively associated with the odds of remission, but those with 2-10 primary care visits also had higher odds of remitting when compared with those with no visits (OR = 1.23, 95% CI = 1.23-7.27). Mertens, J., Flisher, A., Satre, D., and Weisner, C. The Role of Medical Conditions and Primary Care Services in 5-Year Substance use Outcomes among Chemical Dependency Treatment Patients. Drug Alcohol Depend., 98(1-2), pp. 45-53, 2008.

Substance Abuse Treatment Outcomes

This longitudinal cohort study of 324 consecutive admissions to methadone maintenance treatment between August 1994 and September 1997 compared 1-year outcomes of opioid-dependent patients referred from a syringe exchange program (SEP; n = 81) versus other sources (n = 243). All participants received stepped-based counseling. The Addiction Severity Index was completed upon admission. Treatment outcomes were assessed using weekly urine testing and days in treatment. GEE regression models were used to evaluate the association between baseline variables and treatment outcomes. SEP referrals were older, included more males and African Americans, reported greater unemployment and heavier heroin, cocaine, and injection drug use at admission. During treatment, SEP referrals used more opioids (OR 2.57; 95% CI 1.86-3.56) and cocaine (OR 2.77; 95% CI 1.93-3.95), and were less likely to complete 1 year (35%) compared to other referrals (56%; hazard ratio 1.88; 95% CI 1.35-2.62). Nevertheless, referral source was not significantly associated with outcome when adjusted for baseline characteristics. Greater baseline frequency of substance and injection drug use, and younger age were positively associated with ongoing opioid and cocaine use. African American race and baseline unemployment were also associated with ongoing cocaine use. Younger age and greater baseline cocaine use were associated with poorer retention at 1 year. The poorer treatment response of SEP referrals is likely due to higher baseline problem severity. Specialized interventions may be required to reduce drug use and improve retention in this population. Neufeld, K., King, V., Peirce, J., Kolodner, K., Brooner, R., and Kidorf, M. A Comparison of 1-year Substance Abuse Treatment Outcomes in Community Syringe Exchange Participants Versus Other Referrals. Drug Alcohol Depend., 97, pp. 122-129, 2008.

An Examination of Attitudes Towards Opioid Substitution Therapies

Attitudes and beliefs about drug abuse treatment have long been known to shape response to that treatment. Two major pharmacological alternatives are available for opioid dependence: methadone, which has been available for the past 40 years, and buprenorphine, a recently introduced medication. This mixed-methods study examined the attitudes of opioid-dependent individuals toward methadone and buprenorphine. A total of 195 participants (n = 140 who were enrolling in one of six Baltimore area methadone programs and n = 55 who were out-of-treatment) were administered the Attitudes toward Methadone and toward Buprenorphine Scales, and a subset (n = 46) received an ethnographic interview. The majority of comments from out-of-treatment individuals regarding methadone were negative. Negative comments about methadone fell into four major categories: health effects, long-term nature of treatment with methadone, withdrawal symptoms upon discontinuation, and the impact of methadone on their peers who had entered treatment. The in-treatment group had significantly more positive attitudes toward methadone than did the out-of-treatment group ($p < .001$), while they did not differ in their attitudes toward buprenorphine. Participants believed that buprenorphine had fewer side effects than methadone. Both groups had significantly more positive attitudes toward buprenorphine than methadone. Addressing these attitudes may increase treatment entry and retention. Schwartz, R., Kelly, S., O 'Grady, K., Mitchell, S., Peterson, J., Reisinger, H., Agar, M., and Brown, B. Attitudes Toward Buprenorphine and Methadone Among Opioid-Dependent Individuals. Am. J. Addict., 17(5), pp. 396-401, 2008.

Expanding the Public Health Benefits of Syringe Exchange Programs

This study provides a brief history of community syringe exchange programs (SEPs), describes the clinical profile of those who attend them, identifies

factors interfering with the transition of SEP participants to more comprehensive substance abuse treatment services, reviews studies designed to improve rates of treatment seeking, and offers practical suggestions to facilitate links between SEPs and substance abuse treatment. Relevant articles were identified using a PubMed literature search of English-language journals from 1997 to 2007. Studies were included that evaluated the effectiveness of SEPs or methods for increasing treatment enrolment in SEP participants or other out-of-treatment intravenous drug users. Relevant articles prior to 1997 were identified using reference lists of identified articles. SEPs were found to have little impact on rates of drug use or injections. Substance abuse treatment reduces human immunodeficiency virus transmission through drug use reduction and psychosocial functioning improvement, yet SEP participants only infrequently engage in treatment. Psychological and pharmacological interventions delivered at the SEP setting can improve treatment seeking in SEP participants. Use of SEPs by substance abuse treatment programs can improve harm-reduction efforts at these settings. Efforts to improve the link between SEPs and substance abuse treatment should include interventions to enhance cooperation across programs, motivate treatment enrollment and SEP use, and expand access to treatment. A more fluent and bidirectional continuum of services can enhance the public health benefits of both of these health care delivery settings. Kidorf, M., and King, V. Expanding the Public Health Benefits of Syringe Exchange Programs. Can. J. Psychiatry, 53(8), pp. 487-495, 2008.

Cigarettes and Waterpipe Smoking Among Medical Students in Syria

The authors studied the tobacco use, beliefs and attitudes among medical students in Syria. The research conducted was a cross-sectional study of a random sample of 570 medical students (first and fifth year) registered at the Damascus University Faculty of Medicine in 2006-2007. A self-administered questionnaire was used to determine demographic information, smoking behavior (cigarette, water-pipe), family and peer smoking, attitudes and beliefs about smoking and future role in advising patients to quit smoking. The overall prevalence of tobacco use was 10.9% for cigarettes (15.8% men, 3.3% women), 23.5% for water-pipe (30.3% men, 13.4% women) and 7.3% for both (10.1% men, 3.1% women). Both smoking methods were more popular among the fifth year students (15.4% and 27%) compared to their younger counterparts (6.6% and 19.7%). Regular smoking patterns predominated for cigarettes (62%), while occasional use patterns predominated for water-pipes (83%). More than two thirds of students (69%) thought they might not address or would have difficulty addressing smoking in their future patients. This study shows that the level of tobacco use among Syrian medical students is alarming and highlights the rapidly changing patterns of water-pipe use, especially among female students. The need for medical schools to address this important public health problem and address it more efficiently in their curricula was highlighted. Almerie, M. Q., Matar, H. E., Salam, M., Morad, A., Abdulaal, M., and Koudsi, A. Cigarettes and Waterpipe Smoking Among Medical Students. Int. J. Tuberc. Lung Dis., 12(9), pp. 1085-1091, 2008.

Reducing HIV and Partner Violence Risk Among Women with Criminal Justice System Involvement

Women with histories of incarceration show high levels of risk for HIV and intimate partner violence (IPV). This randomized controlled trial with women at risk for HIV who had recent criminal justice system involvement (n = 530) evaluated two interventions based on Motivational Interviewing to reduce either HIV risk or HIV and IPV risk. Baseline and 3, 6, and 9-month follow-up assessments measured unprotected intercourse, needle sharing, and IPV. Generalized estimating equations revealed that the intervention groups had

significant decreases in unprotected intercourse and needle sharing, and significantly greater reductions in the odds and incidence rates of unprotected intercourse compared to the control group. No significant differences were found in changes in IPV over time between the HIV and IPV group and the control group. Motivational Interviewing-based HIV prevention interventions delivered by county health department staff appear helpful in reducing HIV risk behavior for this population. Weir, B.W., O'Brien, K., Bard, R.S., Casciato, C.J., Maher, J.E., Dent, C.W., Dougherty, J.A., and Stark, M.J. Reducing HIV and Partner Violence Risk Among Women with Criminal Justice System Involvement: A Randomized Controlled Trial of Two Motivational Interviewing-based Interventions. AIDS Behav., Online First 18 July 2008.

Gender: Post Traumatic Stress Syndrome

Patients with a chronic and severe substance use disorder who also have a history of post-traumatic stress disorder (PTSD) are thought to have a unique set of problems. The present study assessed psychiatric disorders, psychosocial problems, and traumatic events with structured interviews in 747 men and 693 women enrolling in urban opioid substitution treatment programs from 1995 to 2001. Participants with versus without a history of PTSD were more likely to have a history of many other psychiatric disorders and demonstrated more current and historical medical, employment, family/social, and psychiatric problems. PTSD was generally unrelated to substance use disorder severity or diagnoses, with the exception of an increased risk of alcohol dependence. Women were more likely than men to have experienced sexual assault, and less likely to have been physically assaulted, although these events precipitated PTSD at equivalent rates across gender. In contrast, witnessing or hearing about the death or injury of others was more likely to precipitate PTSD in women than men. Female gender, exposure to combat, sexual assault, or physical assault, and a history of major mood or anxiety disorder were the best predictors of PTSD in this group. Peirce, J.M., Kindbom, K.A., Waesche, M.C., Yuscavage, A.S., and Brooner, R.K. Posttraumatic Stress Disorder, Gender, and Problem Profiles in Substance Dependent Patients. Subst. Use Misuse, 43, pp. 596-611, 2008.

Clients May Be Willing to Pay for Methadone Maintenance, But Not Enough to Cover the Costs

This study examines how much clients would be willing to pay for methadone maintenance treatment and how the amount varies with the hypothetical effectiveness of treatment and availability of case management. It also estimates clients' likely responsiveness to price changes (elasticity of demand). 241 heroin users who had been referred to, but had not yet entered, methadone maintenance treatment in Baltimore, MD were asked to state a preference among three hypothetical treatment programs that varied across three domains: weekly fee paid by the client out-of-pocket ($5-$100), presence/absence of case management, and time spent heroin-free (3-24 months). Each subject was asked to complete 18 orthogonal comparisons. Subsequently each subject was asked if they likely would enroll in their preferred choice among the three hypothetical programs. Expected willingness to pay (WTP) was computed as the probability of enrollment times the fee considered in each choice from a multivariate logistic model that controlled for program attributes. The median fee subjects were willing to pay for a program offering 3 months heroin-free was $7.30, which rose to $17.11 per week for programs that offered 24 months heroin-free. The availability of case management increased the median amount clients would pay by $5.64 per week. The price elasticity was 0.39 (S.E. 0.042) meaning that the subjects were relatively unresponsive to price changes. These results suggest that clients are willing to pay for treatment but the median amount they likely will pay is far less than the average cost of $82 per week of treatment. Although

they will pay more for programs with higher rates of treatment success and for the presence of case management, it is still not enough to offset the costs. Bishai, D., Sindelar, J., Ricketts, E., Huettner, S., Cornelius, L., Lloyd, J., Havens, J., Latkin, C., and Strathdee, S. Willingness to Pay for Drug Rehabilitation: Implications for Cost Recovery. J. Health Econ., 27(4), pp. 959-972, 2008.

The Heterogeneity of Cannabis Use Disorders

DSM-IV criteria were examined to identify theoretically possible subtypes of cannabis dependence based on various combinations of the criteria. Prior research documented high homogeneity of alcohol use disorders (AUDs) as clinical entities. However, it is unknown whether this finding extends to other substance use disorders. The authors investigated this by examining the prevalence of all possible DSM-IV criteria-based clinical subtypes of current and lifetime cannabis use disorders in the general population. The number of possible (i.e., theoretical) clinical subtypes of cannabis abuse and dependence based on different combinations of the DSM-IV criteria was calculated using the combinatorial function. This number was compared with the subtypes actually observed in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a large U.S. national sample (N=43,093). Clinical and demographic correlates of the subtypes were examined with 2 tests whose target population was the United States civilian non-institutionalized population. All DSM-IV cannabis abuse and dependence criteria were assessed with the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV). Of all possible cannabis dependence subtypes, 29 (69%) were observed in the 12-month timeframe, and 41 (98%) in the lifetime timeframe. The corresponding numbers of subtypes for cannabis abuse were 12 (75%), current and 15 (100%), lifetime. These findings suggest that, in contrast to alcohol disorders, cannabis use disorders were highly heterogeneous. Diagnostically, these results underscore the need for clinicians to recognize the diverse symptom presentations of cannabis dependence. Future research should investigate whether there are differences in the course and treatment response of these clinical subtypes of cannabis use disorders, and the heterogeneity of other substance use disorders. Blanco, C., Ogburn, E., Perez de Los Cobos, J., Lujan, J., Nunes, E., Grant, B., Liu, S., and Hasin, D. DSM-IV Criteria-based Clinical Subtypes of Cannabis use Disorders: Results from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). Drug Alcohol Depend., 96(1-2), pp. 136-144, 2008.

HIV Sexual Risk Behaviors Among Ketamine and Non-Ketamine Using Criminal Offenders Prior to Prison Entry

This study is the first to examine ketamine use and its association with HIV sexual risk behaviors among a criminal offending population in the United States. Data were collected from 716 inmates as part of the Transitional Case Management (TCM) protocol within the Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) cooperative agreement. Bivariate analyses were used to identify differences between ketamine users (n=44) and nonketamine users (n=672). Three Poisson regression models were used to identify the significant correlates of high risk sexual behaviors in the 30 days prior to incarceration - (1) number of times had unprotected sex while high, (2) number of times had unprotected vaginal sex, and (3) number of times had unprotected anal sex. Results indicate that ketamine was a significant correlate in all of the Poisson regression models. Findings indicate that ketamine use may be a marker for engaging in HIV risk behaviors among criminal offenders. Oser, C., Havens, J., Staton-Tindal, M., Wong, C., Leukefeld, C., and Prendergast, M. HIV Sexual Risk Behaviors Among Ketamine and Non-Ketamine Using Criminal Offenders Prior to Prison Entry. Addiction Research and Theory, 16(3), pp. 289-302, 2008.

Substance Abuse Treatment in Human Immunodeficiency Virus: The Role of Patient Provider Discussions

Substance abuse treatment is associated with decreases in human immunodeficiency virus (HIV) risk behavior and can improve HIV outcomes. The purpose of this study was to examine factors associated with substance abuse treatment utilization, including patient-provider discussions of substance use issues. 951 HIV-infected adults receiving care at 14 HIV Research Network primary care sites were surveyed regarding drug and alcohol use, substance abuse treatment, and provider discussions of substance use issues. Although 71% reported substance use, only 24% reported receiving substance abuse treatment and less than half reported discussing substance use issues with their HIV providers. In adjusted logistic regression models, receipt of substance abuse treatment was associated with patient-provider discussions. Patient-provider discussions of substance use issues were associated with current drug use, hazardous or binge drinking, and Black race or ethnicity, though substance use was comparable between Blacks and Whites. These data suggest potential opportunities for improving engagement in substance abuse treatment services. Korthuis, P.T., Josephs, J.S., Fleishman, J.A., Hellinger, J., Himelhoch, S., Chander, G., Morse, E., and Gebo, K.A. Substance Abuse Treatment in Human Immunodeficiency Virus: The Role of Patient/Provider Discussions. J. Subst. Abuse Treat., 35 pp. 294-303, 2008.

Factors Associated with Early Therapeutic Alliance Among Adolescents in Substance Abuse Treatment

Given the importance of the therapeutic alliance in achieving positive treatment outcomes, research is needed to illuminate the factors that contribute to the development of this important relationship. The aim of this study was to expand upon the existing literature by examining predictors of the early therapeutic alliance among adolescents treated in two outpatient programs. Use of multilevel modeling techniques revealed that the majority of the variance in adolescents' ratings of the therapeutic alliance was due to adolescent factors (91%), while the variance in therapist ratings of alliance were nearly equally divided between adolescent and therapist factors (52% vs. 48%). Participant age was found to be the only significant predictor of therapist-rated alliance, with therapists reporting higher alliances with older adolescents. Adolescents reporting higher levels of social support, greater problem recognition, and more reasons for quitting also reported higher therapeutic alliance ratings. Future research is needed to examine if early identification of adolescents with low social support and problem recognition combined with brief treatment readiness interventions can be a promising approach to help improve therapeutic engagement and post-treatment substance use outcomes. Garner, B., Godley, S., and Funk, R. Predictors of Early Therapeutic Alliance Among Adolescents in Substance Abuse Treatment. J. Psychoactive Drugs, 40(1), pp. 55-65, 2008.

Violence Against Women

This research note examines the prevalence and correlates of intimate partner violence (IPV) and other violence (OV) among women (N = 529) at risk for HIV and with histories of criminal justice system involvement. The 3-month prevalences of IPV and OV were 31.2% and 18.7%, respectively. IPV was associated with having a current main partner, substance use, sexual risk behavior, trading sex, anxiety, depression, and lower self-esteem. OV was associated with no current employment or schooling, unstable housing, drug use, trading sex, anxiety, depression, and lower self-esteem. The high prevalence of violence demonstrates the need for intervention in this

population; the correlates show that effective interventions must address the complex issues in these women's lives. Weir, B., Bard, R., O'Brien, K., Casciato, C., and Stark, M. Violence Against Women with HIV Risk and Recent Criminal Justice System Involvement: Prevalence, Correlates, and Recommendations for Intervention. Violence Against Women, 14(8), pp. 944-960, 2008.

A National Survey of Psychiatric Disorders in Pregnant and Postpartum Women

Psychiatric disorders and substance use during pregnancy are associated with adverse outcomes for mothers and their offspring, and information about the epidemiology of these conditions in this population is lacking. The objective of this study is to examine sociodemographic correlates, rates of DSM-IV Axis I psychiatric disorders, substance use, and treatment seeking among past-year pregnant and postpartum women in the United States. The study's main outcome measures include the prevalence of 12-month DSM-IV Axis I psychiatric disorders, substance use, and treatment seeking. The study relied on face-to-face interviews conducted in the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), one of the largest nationally representative surveys to date to include information on psychiatric disorders in pregnant women. A total of 43,093 respondents were interviewed, of whom 14,549 were women 18 to 50 years old with known past-year pregnancy status. The analysis found that pregnant and postpartum women had significantly lower rates of alcohol use disorders and any substance use, except illicit drug use, than non-pregnant women. In addition, currently pregnant women had a lower risk of having any mood disorder than non-pregnant women. The only exception was the significantly higher prevalence of major depressive disorder in postpartum than in non-pregnant women. Age, marital status, health status, stressful life events, and history of traumatic experiences were all significantly associated with higher risk of psychiatric disorders in pregnant and postpartum women. Lifetime and past-year treatment-seeking rates for any psychiatric disorder were significantly lower among past-year pregnant than non-pregnant women with psychiatric disorders. It was interesting to note that most women with a current psychiatric disorder did not receive any mental health care in the 12 months prior to the survey regardless of pregnancy status. The authors' concluded that pregnancy per se is not associated with increased risk of the most prevalent mental disorders, although the risk of major depressive disorder may be increased during the postpartum period. In addition, groups of pregnant women with particularly high prevalence of psychiatric disorders were identified. Low rates of maternal mental health care underscore the need to improve recognition and delivery of treatment for mental disorders occurring during pregnancy and the postpartum period. Vesga-Lopez, O., Blanco, C., Keyes, K., Olfson, M., Grant, B., and Hasin, D. Psychiatric Disorders in Pregnant and Postpartum Women in the United States. Arch. Gen. Psychiatry, 65(7), pp. 805-815, 2008.

Organizational Structure and Therapist Adherence on Longer-Term Reduction of Behavior Problems of Youth

The current study investigated the relations among therapist adherence to an evidence-based treatment for youth with serious antisocial behavior (i.e., Multisystemic Therapy), organizational climate and structure, and improvement in youth behavior problems one-year post treatment. Participants were 1,979 youth and families treated by 429 therapists across 45 provider organizations in North America. Hierarchical Linear Modeling (HLM) results showed therapist adherence predicted improvement in youth behavior. Two structure variables and one climate variable predicted changes in youth behavior, and the climate variable also predicted therapist adherence. No statistical support for formal

mediation of organizational effects through adherence was found, though examination of changes in parameter estimates suggest a possible interplay of organizational climate with adherence and youth behavior change. The data suggest that adherence to an evidence-based treatment can be maintained largely irrespective of organizational structure. Additional research is needed to illuminate which aspects of the mental health service provider organizations in general, and of organizations implementing evidence-based treatments specifically, have the potential to affect the implementation and outcomes of evidence-based treatments. Schoenwald, S., Carter, R., Chapman, J., and Sheidow, A. Therapist Adherence and Organizational Effects on Change in Youth Behavior Problems One Year after Multisystemic Therapy. Adm. Policy Ment. Health, 35(5), pp. 379-394, 2008.

MI Cost-Effective for Relapse Prevention, But Not Smoking Cessation, Among Low-Income Pregnant Women

Study assesses the cost-effectiveness of a motivational intervention (MI) for smoking cessation and relapse prevention. Subjects were 302 low-income pregnant women recruited from multiple obstetrical sites in the Boston metropolitan area and randomized into the treatment versus control (UC - usual care) conditions. Outcomes included smoking cessation and relapse, maternal and infant outcomes, economic costs, life-years (LYs) and quality-adjusted life-years (QALYs) saved, and incremental cost-effectiveness ratios. The cost-effectiveness of MI for relapse prevention compared to UC was estimated to be $851/LY saved and $628/QALY saved. Including savings in maternal medical costs in sensitivity analyses resulted in cost savings for MI for relapse prevention compared to UC. For smoking cessation, MI cost more but did not provide additional benefit compared to UC, although a sensitivity analysis suggested that it may be cost-effective at conventional levels if it could induce 8-10% of smokers to quit. Ruger, J., Weinstein, M., Hammond, S., Kearney, M., and Emmons, K. Cost-Effectiveness of Motivational Interviewing for Smoking Cessation and Relapse Prevention among low-Income Pregnant Women: A Randomized Controlled Trial. Value Health, 11(2), pp. 191-198, 2008.

Quality-of-Life Tradeoffs for Hepatitis C Treatment

The authors investigated differences between how patients and providers evaluate the quality-of-life tradeoffs associated with HCV treatment in computer-assisted interviews. They interviewed 92 treatment-naive HCV patients at gastroenterology, methadone maintenance, and HIV clinics at 3 hospitals in New York City, and 23 physicians or nurses experienced in treating HCV at other hospitals in New York City. Subjects completed rating scale and standard gamble evaluations of current health and hypothetical descriptions of HCV symptoms and treatment side effects on a scale from 0 (death or worse than death) to 1 (best possible health). Treatment side effects were rated worse by patients than providers using the rating scale (moderate side effects 0.42 v. 0.62; severe side effects 0.24 v. 0.40) and standard gamble (moderate side effects 0.61 v. 0.91; severe side effects 0.52 v. 0.75) (all $P < \text{or} = 0.01$). A year of severe side effects was equivalent to 4.1 years of mild HCV symptoms avoided for patients if they returned to their current health after treatment compared with 2.0 years avoided if they achieved average population health. For patients with depression symptoms, HCV treatment with severe side effects had lower value unless it would also improve their current health. Patients have more concerns about treatment side effects than providers. Further research is warranted to develop HCV decision aids that elicit patient preferences and to evaluate how improved communication of the risks and benefits of HCV treatment and more effective treatment of depression may alter these preferences. Schackman, B., Teixeira, P., Weitzman, G., Mushlin, A., and Jacobson, I. Quality-of-life Tradeoffs for Hepatitis C Treatment: Do

Patients and Providers Agree? Med. Decis. Making, 28(2), pp. 233-242, 2008.

Ten-Year Trend in Addiction Treatment Shows a Decline in Special Population (Same-Race) Therapy

This work analyzes how trends in the provision of tailored treatment practices (TTPs) have changed between 1995 and 2005 across outpatient substance abuse treatment (OSAT) programs in the United States. Categories of interest include measures to capture needs assessment and treatment planning activities, treatment offerings for special populations, and case management activities. Results of national surveys conducted in 1995, 2000, and 2005 show that TTPs have diffused in an uneven fashion in the population of OSAT programs between 1995 and 2005. Specifically, needs assessment/treatment planning and case management remain a relatively common practice among OSAT programs, while treatment for special populations (especially same-race therapy) is less widely practiced and, indeed, experienced some decline over the study period. This trend is troublesome given that minority clients constitute a large proportion of those utilizing OSAT programs. Alexander, J.A., Nahra, T.A., Lemak, C.H., Pollack, H., and Campbell, C.I. Tailored Treatment in the Outpatient Substance Abuse Treatment Sector: 1995-2005. J. Subst. Abuse Treat., 34(3), pp. 282-292, 2008.

Generic Preference-Weighted Quality of Life Measures Correlated with Some, But Not All, ASI Subscales

Data collected from 574 subjects seeking substance abuse treatment as part of a clinical trial at one of seven centers in a medium-sized Midwestern City were used to assess the correlation between two generic preference-weighted quality of life scales, the Quality of Life Well-Being Scale - QWB-SA; and the Medical Outcomes Study SF-12 - SF-12SG - with Addiction Severity Index subscales. In unadjusted analyses, the QWB-SA measure was correlated significantly with six of seven ASI subscales and the SF-12 SG was correlated with four of seven. In adjusted analyses, both preference-weighted measures were correlated significantly with diagnostic, physical health, mental health and drug use measures, but not with legal or alcohol use measures. The QWB-SA was also correlated with employment problems and the SF-12 SG was correlated with family/social problems. This suggests that cost utility analyses (CUA) based on generic quality of life scores may reasonably capture the physical and mental health, and substance abuse improvements due to substance abuse interventions but not their full effect on the individual, family, or society, potentially leading to an underinvestment in substance abuse treatment. Pyne, J. M., McCollister, K., French, M., Tripathi, S., Rapp, R., and Booth, B. Preference-weighted Health-Related Quality of Life Measures and Substance Use Disorder Severity. Addiction, 103(8), pp. 1320-1329, 2008.

Substance Use and Delinquency in Criminal Justice Involved Youth Appear Temporally Interdependent in Models Accounting for Time in Controlled Environments

To assess the nature of the temporal association between substance use and delinquency in a sample of 449 ethnically-diverse youth recruited from the Los Angeles juvenile probation system, cross-lagged path models were estimated using full information maximum likelihood-robust estimation in MPlus 4.2. Participants were assessed using the Global Appraisal of Individual Needs (GAIN) at baseline (n=499), and at 3 month (n=406), 6 month (n=410) and 1 year (n=408) follow-ups. Substance use was measured using a continuous composite score equal to the sum of the standardized scores on the Substance Use Frequency Scale (SFS) and Substance Problem Scale (SPS). Delinquency was assessed using results from the Drug Crime Scale (DCS), Interpersonal

Crime Scale (ICS) and Property Crime Scale (PCS). The preferred model treated each of these crime scales as indicators of a latent delinquency variable and controlled for gender, age, ethnicity and crime spent in a controlled environment, the latter of which had not been controlled for in previous studies. Estimates of the standardized paths from substance use to criminal behavior ranged from 0.074 to 0.082 and from criminal behavior to substance use ranged from 0.075 to 0.124 across time lags, all of which were significantly different from zero. These results provide support for the hypothesis that the observed temporal relationship between substance use and delinquency is the result of a third causal factor such as a propensity for general deviance, suggesting that interventions could target either behavior and influence both. D 'Amico, E., Edelen, M., Miles, J., and Morral, A. The Longitudinal Association Between Substance Use and Delinquency Among High-Risk Youth. Drug Alcohol Depend., 93(1-2), pp. 85-92, 2008.

Sibling Outcomes from a Randomized Trial of Evidence-Based Treatments with Substance Abusing Juvenile Offenders

This study examined the substance use and delinquency outcomes for the nearest age siblings of substance abusing and delinquent adolescents that participated in a randomized clinical trial evaluating the effectiveness of integrating evidence-based practices into juvenile drug court. The sample of 70 siblings averaged 14.4 years of age, 50% were male, 71% were African-American, and 27% were white. Measures of sibling substance use and delinquency were collected at four points in time (i.e., pretreatment, 4, 12 and 18 months). Multilevel longitudinal models were used to evaluate whether changes in sibling substance use and delinquency paralleled the treatment effects observed for their substance abusing delinquent brothers and sisters in the juvenile drug court study. Parallel sibling outcomes were obtained for substance use but not for criminal behavior, and possible reasons for the divergence in these results were discussed. Rowland, M.D., Chapman, J. E., and Henggeler, S. W. Sibling Outcomes from a Randomized Trial of Evidence-Based Treatments with Substance Abusing Juvenile Offenders. J. Child and Adolescent Substance Use, 17(3), pp. 11-26, 2008.

Health Plans Use Multiple Methods to Maintain Provider Networks

Executives from a nationally-representative sample of 363 health plans with 812 insurance products were surveyed in 2003 on the methods they used to retain behavioral health care providers. These included methods applied to all providers and targeted methods applied to high-quality providers. Common methods applied to all providers included formal procedures for dealing with provider grievances (99.0% of products) and conducting provider satisfaction surveys (79.9% of plans). Among products with provider surveys topics commonly included were accuracy of claims payments (98.4%), satisfaction with utilization review and authorization decisions (95.9%), speed of response to treatment authorization requests (94.9%), and provider administrative burden (91.0%). Less common topics were the overall satisfaction with the fee schedule (59.0%), volume and type of referrals (44.0%), and collaboration and communication with primary care physicians (47.9%). Methods targeted at high-quality providers included reducing their administrative burden (53.8%), paying them higher fees (43.7%), and steering clients to their practices (16.5%). Annual bonuses and guaranteed volume were seldom used as methods to retain high-quality providers. Analysis by provider type revealed that compared with Health Maintenance Organizations (HMOs), Point of Service (POS) products were less likely to use any of the techniques while Preferred Provider Organizations (PPO) products were more likely to use higher fees or reduced administrative burden but less likely to steer referrals. Compared with products with specialty contracts with Managed Behavioral Health Care Organizations (MBHOs), those with internal management were considerably

less likely to use higher fees while those with comprehensive contracts with MBHOs were more likely to steer referrals. For-profit products were less likely to steer referrals but more likely to use decreased administrative burdens or higher fees than were not-for-profit products. Garnick, D., Horgan, C., Reif, S., Merrick, E., and Hodgkin, D. Management of Behavioral Health Provider Networks in Private Health Plans. J. Ambul. Care Manage., 31(4), pp. 330-341, 2008.

Problematic Use of Tobacco and Other Drugs High among Public Primary Care Patients in South Africa

Prevalence and risk and protective factors for the problematic use of tobacco, alcohol, and other drugs were assessed in a sample of 2,618 Black and mixed-race patients who received care at one of 14 public primary care clinics in Cape Town, South Africa. These 14 clinics comprised a stratified, random sample of the 49 such clinics in Cape Town. Subjects were interviewed in person in private rooms by trained research assistants matched for gender and language. Substance use was assessed using the WHO ASSIST instrument and those with a score indicating medium or high risk were coded as having problematic use. Risk and protective factor and other information were obtained by an instrument developed for the study. Included in that instrument was an assessment of stress from the International Classification of Primary Care, Second Edition which lists 23 stressors that may be reasons for encounters, as well as one additional question on unplanned pregnancy. As in other countries, prevalence rates for problematic substance use were higher for men than for women. For example, 43.1% of men in the sample reported using tobacco compared with only 19.5% of women. And while 7.4% of men reported using drugs other than tobacco and alcohol, only 1.1% of women did. Multivariate logistic analysis revealed those who were younger and those who had more stressors had higher odds of using tobacco, while those who were more highly educated and participated in religious activities had lower odds of using tobacco. In addition, black women reported extremely low rates of tobacco use (odds = 0.04 95% CI = 0.01-0.22) compared to other groups. Risk factors for problematic use of other drugs included being colored, being employed, and having more stressors, while protective factors again included religious involvement. Again, Black women had very low prevalence rates with only 3 respondents reporting other drug use. Ward, C., Mertens, J., Flisher, A., Bresick, G., Sterling, S., Little, F., and Weisner, C. Prevalence and Correlates of Substance Use Among South African Primary Care Clinic Patients. Subst. Use Misuse, 43(10), pp. 1395-1410, 2008.

Reactivity to Psychological and Pharmacological Stress Provocation: Gender Differences

The purpose of this study is to examine the influence of gender and smoking status on reactivity in two human laboratory stress paradigms. Participants were 46 (21 men, 25 women) healthy individuals who completed the Trier Social Stress Task (i.e., performed speech and math calculations in front of an audience) and a pharmacological stress provocation (i.e., administration of corticotrophin releasing hormone (CRH)) after an overnight hospital stay. Approximately half (53%) of the participants were smokers. Cortisol, adrenocorticotrophin hormone (ACTH), physiologic measures (heart rate, blood pressure), and subjective stress were assessed at baseline and at several time points post-task. Men demonstrated higher baseline ACTH and blood pressure as compared to women; however, ACTH and blood pressure responses were more pronounced in women. Women smokers evidenced a more blunted cortisol response as compared to non-smoking women, whereas smoking status did not affect the cortisol response in men. Finally, there was a more robust cardiovascular and subjective response to the Trier as compared to the CRH. Although preliminary, the findings suggest that women may be more

sensitive than men to the impact of cigarette smoking on cortisol response. In addition, there is some evidence for a more robust neuroendocrine and physiologic response to acute laboratory stress in women as compared to men. Investigation of relationships between stress response and mood/anxiety disorders in individuals with substance use disorders may provide important insights into mechanisms underlying gender differences in addiction. Back, S., Waldrop, A., Saladin, M., Yeatts, S., Simpson, A., McRae, A., Upadhyaya, H., Contini Sisson, R., Spratt, E., Allen, J., Kreek, M., and Brady, K. Effects of Gender and Cigarette Smoking on Reactivity to Psychological and Pharmacological Stress Provocation. Psychoneuroendocrino-logy, 33(5), pp. 560-568, 2008.

Adaptive Interventions in Drug Court: A Pilot Study

This pilot study (N 30) experimentally examines the accesptability and feasibility of using an adaptive intervention in a misdemeanor drug court. The adaptive algorithm adjusted the frequency of court hearings and case management sessions according to pre-specified criteria in response to participants' performance. Results reveal that the adaptive algorithm was acceptable to clients and staff, was feasible to implement with greater than 85% fidelity, and showed promise for eliciting substantial improvements in drug abstinence and graduation rates. Compared to drug court as usual, participants in the adaptive condition were more likely to receive responses from the drug court team for inadequate performance and received those responses after a shorter period. This suggests the adaptive algorithm more readily focused the team's attention on poorly performing individuals, allowing them to address problems before they developed too fully. This demonstration of acceptability and feasibility of implementing an adaptive intervention in drug court suggests that further research is warranted to test the efficacy of the adaptive intervention. Marlowe, D.B., Arabia, P.L., Dugosh, K.L., Benasutti, K.L., Croft, J.R., and McKay, J.R. Adaptive Interventions in Drug Court: A Pilot Experiment. Criminal Justice Review, 33(3), pp. 343-360, 2008.

Voluntary Screening of Recently Arrested Adolescents for Sexually Transmitted Diseases

Adolescent offenders may be at high risk for sexually transmitted diseases (STDs). With previous research and interventions focused on incarcerated adolescents, data are needed on STD prevalence and risk factors among newly arrested youth released to the community, a far larger subgroup. Participants were recruited from all arrested youth processed at the Hillsborough County, Florida Juvenile Assessment Center during the last half of 2006 (506 males, 442 females). Participants voluntarily providing urine samples for drug testing as part of standard protocol also consented to having their specimens split and tested for chlamydia and gonorrhea, using an FDA-approved nucleic acid amplification test. STD prevalence was found similar to those previously reported among incarcerated adolescents: 11.5% tested positive for chlamydia, 4.2% for gonorrhea, and 13.2% for either or both infections. Prevalence was significantly higher among females: 19.2% of females had either or both infections compared with 10.5% of males. Prevalence was higher for 17 to 18 year olds (15.2% of males, 25.5% of females), blacks, detained youths, drug users, and those engaged in sexual risk behaviors. Previous STD testing experience was limited. The study indicated that a voluntary STD screening protocol is feasible for arrested youth entering the juvenile justice system, and these offenders are at high risk for STDs. Because most arrested youths are released back to the community, routine testing and treatment of recently arrested youths, and expanded access to risk reduction and prevention programs, can yield substantial public health benefits. Belenko, S., Dembo, R., Weiland, D., Rollie, M., Salvatore, C., Hanlon, A., and Childs, K. Recently Arrested Adolescents are at High Risk for Sexually Transmitted Diseases. Sex.

Transm. Dis., 35(8), pp. 758-763, 2008.

Initial Subjective Effects of Opioids in Patients Treated for Pain as a Predector of Opioid Addiction

This pilot case-control study (n=40) retrospectively assessed between-groups differences in subjective opioid effects in patients treated for the first time with opioids for chronic pain. Cases were individuals in an inpatient substance abuse treatment center for primary prescription opioid addiction whose initial exposure to prescription opioids was reported for chronic pain. Controls had not developed prescription opioid addiction as measured in part by close monitoring on long-term opioid therapy at a pain management center. Twenty subjects in each group completed a battery of measures to capture data related to the individual's first exposure to prescription opioids. The Morphine Benzedrine Group subscale of an adapted 49-item Addiction Center Research Inventory (ARCI), designed to measure euphoria and other drug effects, showed an average score of 8.70 (+/- 4.18) in cases versus 2.55 (+/- 3.36) in controls ($p < 0.001$), indicating a significantly greater "euphoric" effect of opioids in the cases compared to the controls. Differences in the subjective response to opioids suggest that: (1) a subgroup of patients does develop euphoria when taking opioids for pain, which may be a risk factor for eventual development of prescription opioid addiction; and (2) subjective effects predictive of eventual addiction may include stimulation vs. sedation, and other experiences not typically associated with opioids. (PsycINFO Database Record (c) 2008 APA, all rights reserved). Bieber, C., Fernandez, K., Borsook, D., Brennan, M., Butler, S., Jamison, R., Osgood, E., Sharpe-Potter, J., Thomson, H., Weiss, R., and Katz, N. Retrospective Accounts of Initial Subjective Effects of Opioids in Patients Treated for Pain Who Do or Do Not Develop Opioid Addiction: A Pilot Case-Control Study. Exp. Clin. Psychopharmacol., 16(5), pp. 429-434, 2008.

Psychological Mediators of Buproprion Sustained-Release Treatment for Smoking Cessation

This study aimed to test simultaneously our understanding of the effects of bupropion sustained-release (SR) treatment on putative mediators and our understanding of determinants of post-quit abstinence, including withdrawal distress, cigarette craving, positive affect and subjective reactions to cigarettes smoked during a lapse. The specificity of bupropion SR effects was also tested in exploratory analyses. The study was performed using data from a randomized, placebo-controlled clinical trial of bupropion SR. Results were submitted to mediation analyses at the Center for Tobacco Research and Intervention, Madison, WI. A total of 403 adult, daily smokers without contraindications to bupropion SR use were studied. Participants were assigned randomly to receive a 9-week course of bupropion SR or placebo pill and to receive eight brief individual counseling sessions or no counseling. Ecological momentary assessment ratings of smoking behavior and putative mediators were collected pre- and post-quit. Results of structural equation and hierarchical linear models did not support the hypothesis that bupropion SR treatment improves short-term abstinence by reducing withdrawal distress or affecting the subjective effects of a lapse cigarette, but provided partial support for mediation by cigarette craving reduction and enhanced positive affect. Bupropion SR effects on point-prevalence abstinence at 1 month post-quit were also mediated partially by enhanced motivation to quit and self-efficacy. Results of this study provide some support for models of bupropion SR treatment and relapse and suggested that motivational processes may partially account for bupropion SR efficacy. McCarthy, D., Piasecki, T., Lawrence, D., Jorenby, D., Shiffman, S., and Baker, T. Psychological Mediators of Bupropion Sustained-Release Treatment for Smoking Cessation. Addiction, 103(9), pp. 1521-1533, 2008.

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Director's Report to the National Advisory Council on Drug Abuse - February, 2009

Research Findings - CTN-Related Research

A Step Forward in Teaching Addiction Counselors How to Supervise Motivational Interviewing Using a Clinical Trials Training Approach

A clinical trials training approach to supervision is a promising and empirically supported method for preparing addiction counselors to implement evidence-based behavioral treatments in community treatment programs. This supervision approach has three main components: (1) direct observation of treatment sessions; (2) structured performance feedback about counselors' treatment adherence and competence; and (3) coaching to improve the ability of counselors to implement psychosocial treatments proficiently. This article describes how to teach addiction counselors this approach to supervision as it is applied to Motivational Interviewing (MI) using a clinical supervision procedure called Motivational Interviewing Assessment: Supervisory Tools for Enhancing Proficiency (MIA-STEP). MIA-STEP is one of the NIDA/SAMHSA Blending Team Products and was based on protocol CTN-0005 ("MI (Motivational Interviewing) to Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse"), which found that MI improved both client attendance and retention during the first four weeks of outpatient care. The authors describe teaching points and strategies instructors may use to develop supervisory skills in each of the three main supervision components (performance observation, feedback, and coaching), how to supervise in an MI consistent manner, recommended qualifications for supervising MI, and future directions for MI supervision research. Martino, S., Gallon, S., Ball, S.A., and Carroll, K.M. Journal of Teaching in the Addictions. 6(2), pp. 39-67, 2008. [DOI: 10.1080/15332700802127946].

Community Program Therapist Adherence and Competence in Motivational Enhancement Therapy

The extent to which clinicians in addiction treatment programs can implement empirically validated therapies with adequate fidelity that can be discriminated from standard counseling has rarely been evaluated. The authors evaluated the treatment adherence and competence of 35 therapists from five outpatient community programs who delivered either a three-session adaptation of motivational enhancement therapy (MET) or an equivalent number of drug counseling-as-usual sessions to 461 clients within a National Institute on Drug Abuse Clinical Trial Network multi-site effectiveness protocol. MET therapists were carefully prepared to implement MET using a combination of expert-led intensive workshop training followed by program-based clinical supervision. Independent rating of sessions demonstrated that the adherence and competence items were very reliable (mean interclass correlation coefficients for adherence=.89 and competence=.81) and converged to form two a priori

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defined skill factors conceptually related to motivational interviewing. Moreover, the factors discriminated between MET therapists and those who delivered drug counseling-as-usual sessions in predicted ways, and were significantly related to in-session change in client motivation and some client treatment outcomes (percent negative drug urine screens). These findings demonstrate the reliability and validity of evaluating motivational interviewing fidelity and suggest that the combination of expert-led workshops followed by program-based clinical supervision may be an effective method for disseminating motivational interviewing in community treatment programs. Martino, S., Ball, S.A., Nich, C., Frankforter, T.L., and Carroll, K.M. Drug Alcohol Depend. 96(1-2), pp. 37-48, 2008. Epub 2008 March 6. PMID: 18328638 [PubMed - indexed for MEDLINE].

Quantifying Data Quality for Clinical Trials Using Electronic Data Capture

Historically, only partial assessments of data quality have been performed in clinical trials, for which the most common method of measuring database error rates has been to compare the case report form (CRF) to database entries and count discrepancies. Importantly, errors arising from medical record abstraction and transcription are rarely evaluated as part of such quality assessments. Electronic Data Capture (EDC) technology has had a further impact, as paper CRFs typically leveraged for quality measurement are not used in EDC processes. The National Institute on Drug Abuse Treatment Clinical Trials Network has developed, implemented, and evaluated methodology for holistically assessing data quality on EDC trials. The authors characterize the average source-to-database error rate (14.3 errors per 10,000 fields) for the first year of use of the new evaluation method. This error rate was significantly lower than the average of published error rates for source-to-database audits, and was similar to CRF-to-database error rates reported in the published literature. The authors attribute this largely to an absence of medical record abstraction on the trials they examined, and to an outpatient setting characterized by less acute patient conditions. Historically, medical record abstraction is the most significant source of error by an order of magnitude, and should be measured and managed during the course of clinical trials. Source-to-database error rates are highly dependent on the amount of structured data collection in the clinical setting and on the complexity of the medical record, dependencies that should be considered when developing data quality benchmarks. Nahm, M.L., Pieper, C.F., and Cunningham, M.M. PLoS ONE. 3(8), pp. e3049, 2008. PMID: 18725958 [PubMed - indexed for MEDLINE] PMCID: PMC2516178.

Effectiveness of HIV/STD Sexual Risk Reduction Groups for Women in Substance Abuse Treatment Programs: Results of NIDA Clinical Trials Network Trial

Because drug-involved women are among the fastest growing groups with AIDS, sexual risk reduction intervention for them is a public health imperative. The objective of this study was to test the effectiveness of HIV/STD safer sex skills building (SSB) groups for women in community drug treatment. The study design comprised a randomized trial of SSB versus standard HIV/STD Education (HE); assessments at baseline, 3 and 6 months. Women recruited from 12 methadone or psychosocial treatment programs in Clinical Trials Network of National Institute on Drug Abuse served as subjects. Five hundred fifteen women who reported unprotected vaginal or anal sex occasions (USO) with a male partner in the past 6 months were randomized. In SSB, five 90-minute groups used problem solving and skills rehearsal to increase HIV/STD risk awareness, condom use, and partner negotiation skills. In HE, one 60-minute group covered HIV/STD disease, testing, treatment, and prevention

information. The study's main outcome was the number of USOs at follow-up. A significant difference in mean USOs was obtained between SSB and HE over time ($F = 67.2$, $P < 0.0001$). At 3 months, significant decrements were observed in both conditions. At 6 months, SSB maintained the decrease and HE returned to baseline ($P < 0.0377$). Women in SSB had 29% fewer USOs than those in HE. The authors concluded that skills building interventions can produce ongoing sexual risk reduction in women in community drug treatment. Tross, S., Campbell, A.N., Cohen, L.R., Calsyn, D., Pavlicova, M., Miele, G.M., Hu, M.C., Haynes, L., Nugent, N., Gan, W., Hatch-Maillette, M., Mandler, R., McLaughlin, P., El-Bassel, N., Crits-Christoph, P., and Nunes, E.V. J. Acquir. Immune Defic. Syndr., 48(5), pp. 581-589, 2008. PMID: 18645513 [PubMed - indexed for MEDLINE].

Assessment and Treatment of Co-occurring Eating Disorders in Publicly Funded Addiction Treatment Programs

Publicly funded addiction treatment programs were surveyed to increase understanding of treatment options for persons with co-occurring eating and substance use disorders. Data were collected between 2002 and 2004 from face-to-face interviews with program directors of a nationally representative sample of 351 addiction treatment programs. Half of the programs screen patients for eating disorders; 29% admit all persons with eating disorders, and 48% admit persons with eating disorders of low severity. Few programs attempt to treat eating disorders. Programs that admit and treat patients with eating disorders are more likely to emphasize a medical-psychiatric model of addiction, use psychiatric medications, admit patients with other psychiatric disorders, and have a lower caseload of African-American patients. The authors conclude that generally, patients with co-occurring eating and substance use disorders do not appear to receive structured assessment or treatment for eating disorders in addiction treatment programs. These results highlight the need for education of addiction treatment professionals in assessment of eating disorders. Gordon, S.M., Johnson, J.A,, Greenfield, S.F., Cohen, L., Killeen, T., and Roman, P.M. Psychiatr. Serv. 59(9), pp. 1056-1059, 2008. PMID: 18757602 [PubMed - indexed for MEDLINE].

Informal Discussions in Substance Abuse Treatment Sessions

This study evaluated the extent to which counselors initiated informal discussions (i.e., general discussions and self-disclosures about matters unrelated to treatment) with their clients during treatment sessions within two National Institute on Drug Abuse Clinical Trial Network protocols involving adaptations of motivational interviewing (MI). Sixty counselors across the two protocols had 736 sessions independently rated for counselor treatment fidelity and the occurrence of informal discussions. The results showed that 88% of the counselors initiated informal discussions in their sessions and that most of these discussions involved counselors sharing personal information or experiences they had in common with their clients. The major finding was that counselor training in MI was associated with significantly less informal discussion across sessions. A higher frequency of informal discussion was (1) related to lower counselor MI proficiency and less in-session change in client motivation, and (2) unrelated to client program retention and substance use outcomes. The findings suggest that although some informal discussions may help build an alliance between counselors and clients, too much of it may hinder both counselors' proficient implementation of MI treatment strategies and clients' motivational enhancement process. Martino, S., Ball, S.A., Nich, C., Frankforter, T.L., and Carroll, K.M. J. Subst. Abuse Treat. 2008 October 3. [Epub ahead of print] PMID: 18835679 [PubMed - as supplied by publisher].

Extended vs. Short-Term Buprenorphine-Naloxone for Treatment

of Opioid-Addicted Youth: A Randomized Trial

The usual treatment for opioid-addicted youth is detoxification and counseling; however, extended medication-assisted therapy may be more helpful. To evaluate this question, the National Drug Abuse Treatment Clinical Trials Network study CTN-0010 evaluated the efficacy of continuing buprenorphine-naloxone for 12 weeks versus detoxification for opioid-addicted youth. The CTN-0010 clinical trial, held at six community treatment programs from July 2003 to December 2006, included 152 patients aged 15 to 21 years who were randomized to 12 weeks of buprenorphine-naloxone or a 14-day taper (detox). Patients in the 12-week buprenorphine/naloxone group were prescribed up to 24 mg per day for 9 weeks and then tapered to week 12; patients in the detox group were prescribed up to 14 mg a day and then tapered to day 14. All were offered weekly individual and group counseling. The main outcome measure was opioid-positive urine test results at weeks 4, 8, and 12. The number of patients younger than 18 years was too small to analyze separately, but overall, patients in the detox group had higher proportions of opioid-positive urine test results at weeks 4 and 8, but not at week 12. At week 4, 59 detox patients had positive results versus 58 12-week buprenorphine/naloxone patients. At week 8, 53 detox patients had positive results versus 52 12-week buprenorphine/naloxone patients. At week 12, 53 detox patients had positive results versus 49 12-week buprenorphine/naloxone patients. By week 12, 16 of 78 detox patients (20.5%) remained in treatment vs. 52 of 74 12-week buprenorphine/naloxone patients (70%). During weeks 1 through 12, patients in the 12-week buprenorphine/naloxone group reported less opioid use, less injecting, and less nonstudy addiction treatment. High levels of opioid use occurred in both groups at follow-up. Four of 83 patients who tested negative for hepatitis C at baseline were positive for hepatitis C at week 12. In conclusion, continuing treatment with buprenorphine/ naloxone improved outcome compared with short-term detoxification. Further research is necessary to assess the efficacy and safety of longer-term treatment with buprenorphine for young individuals with opioid dependence. Woody, G.E., Poole, S.A., Subramaniam, G., Dugosh, K., Bogenschutz, M., Abbott, P., Patkar, A., Publicker, M., McCain, K., Sharpe, P.J., Forman, R., Vetter, V., McNicholas, L., Blaine, J., Lynch, K.G., and Fudala, P. JAMA 300(17), pp. 2003-2011, 2008. PMID: 18984887 [PubMed - indexed for MEDLINE].

Serious Adverse Events in Randomized Psychosocial Treatment Studies: Safety or Arbitrary Edicts?

Human subjects protection policies developed for pharmaceutical trials are now being widely applied to psychosocial intervention studies. This study examined occurrences of serious adverse events (SAEs) reported in multicenter psychosocial trials of the National Institute on Drug Abuse Clinical Trials Network. Substance-abusing participants (N = 1,687) were randomized to standard care or standard care plus either contingency management or motivational enhancement. Twelve percent of participants experienced 1 or more SAEs during the 27,198 person-weeks of follow-up. Of the 260 SAEs recorded, none were judged by the data safety monitoring board to be study related, and there were no significant differences between experimental and control conditions in SAE incidence rates. These data underscore the need to reconsider the rationale behind, and appropriate methods for, monitoring safety during psychosocial therapy trials. Petry, N.M., Roll, J.M., Rounsaville, B.J., Ball, S.A., Stitzer, M., Peirce, J.M., Blaine, J., Kirby, K.C., McCarty, D., and Carroll, K.M. J. Consult. Clin. Psychol., 76(6), pp. 1076-1082, 2008. PMID: 19045975 [PubMed - in process].

Predictors of Outcome for Short-term Medically Supervised Opioid Withdrawal During a Randomized, Multicenter Trial of

Buprenorphine-naloxone and Clonidine in the NIDA Clinical Trials Network Drug and Alcohol Dependence

Few studies in community settings have evaluated predictors, mediators, and moderators of treatment success for medically supervised opioid withdrawal treatment. This report presents new findings about these factors from a study of 344 opioid-dependent men and women prospectively randomized to either buprenorphine-naloxone or clonidine in an open-label 13-day medically supervised withdrawal study. Subjects were either inpatient or outpatient in community treatment settings; however not randomized by treatment setting. Medication type (buprenorphine-naloxone versus clonidine) was the single best predictor of treatment retention and treatment success, regardless of treatment setting. Compared to the outpatient setting, the inpatient setting was associated with higher abstinence rates but similar retention rates when adjusting for medication type. Early opioid withdrawal severity mediated the relationship between medication type and treatment outcome with buprenorphine-naloxone being superior to clonidine at relieving early withdrawal symptoms. Inpatient subjects on clonidine with lower withdrawal scores at baseline did better than those with higher withdrawal scores; inpatient subjects receiving buprenorphine-naloxone did better with higher withdrawal scores at baseline than those with lower withdrawal scores. No relationship was found between treatment outcome and age, gender, race, education, employment, marital status, legal problems, baseline depression, or length/severity of drug use. Tobacco use was associated with worse opioid treatment outcomes. Severe baseline anxiety symptoms doubled treatment success. Medication type (buprenorphine-naloxone) was the most important predictor of positive outcome; however the paper also considers other clinical and policy implications of other results, including that inpatient setting predicted better outcomes and moderated medication outcomes. Ziedonis, D.M., Amass, L., Steinberg, M., Woody, G., Krejci, J., Annon, J.J., Cohen, A.J., Waite-O'Brien, N., Stine, S.M., McCarty, D., Reid, M.S., Brown, L.S. Jr., Maslansky, R., Winhusen, T., Babcock, D., Brigham, G., Muir, J., Orr, D., Buchan, B.J., Horton, T., and Ling, W. Drug Alcohol Depend. 99(1-3), pp. 28-36, 2009. Epub 2008 September 20.

What is Usual about "Treatment-as-Usual"? Data from Two Multisite Effectiveness Trials

Despite increased emphasis on broadening the implementation of empirically-supported therapies (ESTs) to improve standard clinical practice and patient outcomes, objective descriptions of what actually constitutes standard practice in community-based drug abuse treatment do not exist. The authors evaluated independent ratings of 379 audiotapes drawn from the "treatment-as-usual" arm of two multisite randomized effectiveness trials in the National Institute on Drug Abuse Clinical Trials Network. Fifteen independent tape raters were trained to assess clinician adherence and competence, and were blind to treatment protocol. The most frequently occurring strategies involved assessing the participant's substance use and social functioning, asking open-ended questions, discussing problems and feedback, and giving advice and direction. However, a number of interventions associated with ESTs were very rarely implemented in these early sessions. These data suggest missed opportunities for optimally engaging patients in the early stages of treatment and enhancing substance use outcomes and only moderate success to date of efforts to bridge the gap between research and practice. Santa Ana, E.J., Martino, S., Ball, S.A., Nich, C., Frankforter, T.L., and Carroll, K.M. What is Usual about "Treatment-as-Usual"? Data from Two Multisite Effectiveness Trials. Journal of Substance Abuse Treatment, 35(4), pp. 369-379, 2008.

Director's Report to the National Advisory Council on Drug Abuse - February, 2009

Research Findings - International Program-Related Research

Publications by Former NIDA Hubert H. Humphrey Fellows

Comparing Topiramate with Naltrexone in the Treatment of Alcohol Dependence
Baltieri, D.A., Daro, F.R., Ribeiro, P.L., and de Andrade, A.G.
Addiction. 2008 October 8; [Epub ahead of print].
HHH Fellow: Arthur Guerra de Andrade, Brazil
The aim of this study was to compare the efficacy of topiramate with naltrexone in the treatment of alcohol dependence. The investigation was a double-blind, placebo-controlled, 12-week study carried out at the University of Sao Paulo, Brazil. The sample comprised a total of 155 patients, 18-60 years of age, with an International Classification of Diseases (ICD-10) diagnosis of alcohol dependence. After a 1-week detoxification period, patients were assigned randomly to receive topiramate (induction to 300 mg/day), naltrexone (50 mg/day) or placebo. Time to first relapse (consumption of >60 g ethyl alcohol), cumulative abstinence duration and weeks of heavy drinking were measured. In intention-to-treat analyses, topiramate was statistically superior to placebo on a number of measures including time to first relapse (7.8 versus 5.0 weeks), cumulative abstinence duration (8.2 versus 5.6 weeks), weeks of heavy drinking (3.4 versus 5.9) and percentage of subjects abstinent at 4 weeks (67.3 versus 42.6) and 8 weeks (61.5 versus 31.5), but not 12 weeks (46.2 versus 27.8). Results remained significant after controlling for Alcoholics Anonymous attendance, which was higher in topiramate than in other groups. There were no significant differences between naltrexone versus placebo or naltrexone versus topiramate groups, but naltrexone showed trends toward inferior outcomes when compared to topiramate. The results of this study support the efficacy of topiramate in the relapse prevention of alcoholism. Suggestive evidence was also obtained for superiority of topiramate versus naltrexone, but this needs to be verified in future research with larger sample sizes.
PMID: 18855810 [PubMed - as supplied by publisher]

Young People's Blood Alcohol Concentration and the Alcohol Consumption City Law, Brazil
De Boni, R., Leukefeld, C., and Pechansky F. Rev. Saude Publica. 2008 Sepember 26; [Epub ahead of print].
HHH Fellow: Flavio Pechansky. Brazil
The paper assesses blood alcohol concentration and risk behaviors for traffic accidents before and after the implementation of a law which prohibits the use of alcoholic beverages at city gas stations. In Porto Alegre, Southern Brazil, young people go out at night and drive to gas station convenience stores to buy alcoholic beverages which are consumed on the premises of parking lots in gas stations. Data were obtained from self-administered questionnaires and breath analyzers in two cross-sectional collections with purposive samples of

youngsters in May and July 2006 (n=62, and n=50, respectively). There were no significant differences between the groups before and after the city law was passed. Blood alcohol concentration greater than 0.06% was found in 35.5% of pre-law group and 40% of post-law group (p=0.62). Results point out heavy alcohol use in both groups, which did not change after the law was passed.
PMID: 18833379 [PubMed - in process]

Development of a Questionnaire to Evaluate Sugar Abuse and Dependence
[Article in Portuguese] da Rosa, M.A., de Slavutzky, S.M., Pechansky, F., and Kessler, F.
Cad. Saude Publica. 2008 August;24(8):1869-76. Portuguese.
HHH Fellow: Flavio Pechansky. Brazil
This study describes the development of a questionnaire to evaluate the potential abuse of (and dependence on) non-milk extrinsic sugar (NMES). Recent studies have shown that excessive NMES consumption can cause alterations in the central nervous system due to the influence of these substances in the neurochemical reward system. The questionnaire was originally developed from a summary of reports from four focus groups utilizing the "L" module of the MINI-Plus questionnaire. Addiction specialists subsequently evaluated the draft of the questionnaire and altered the original instrument's content, substituting terms in order to better fit the substance used in this study. However, the original structure of 20 questions on abuse and dependence was maintained. It is hoped that an instrument to evaluate NMES abuse and dependence will help health professionals prevent and treat problems related to over-consumption of sugars. However, the diagnosis of sugar abuse and dependence and the instrument's potential psychometric properties require further study by the scientific community.
PMID: 18709227 [PubMed - in process]

High HIV Prevalence, Suboptimal HIV Testing, and Low Knowledge of HIV-Positive Serostatus Among Injection Drug Users in St. Petersburg, Russia
Niccolai, L.M., Toussova, O.V., Verevochkin, S.V., Barbour, R., Heimer, R., and Kozlov, A.P.
AIDS Behav. 2008 October 9; [Epub ahead of print]
HHH Fellow: Olga Toussova, Russia
The purpose of this analysis was to estimate human immunodeficiency virus (HIV) prevalence and testing patterns among injection drug users (IDUs) in St. Petersburg, Russia. HIV prevalence among 387 IDUs in the sample was 50%. Correlates of HIV-positive serostatus included unemployment, recent unsafe injections, and history/current sexually transmitted infection. Seventy-six percent had been HIV tested, but only 22% of those who did not report HIV-positive serostatus had been tested in the past 12 months and received their test result. Correlates of this measure included recent doctor visit and having been in prison or jail among men. Among the 193 HIV-infected participants, 36% were aware of their HIV-positive serostatus. HIV prevalence is high and continuing to increase in this population. Adequate coverage of HIV testing has not been achieved, resulting in poor knowledge of positive serostatus. Efforts are needed to better understand motivating and deterring factors for HIV testing in this setting.
PMID: 18843531 [PubMed - as supplied by publisher]

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Director's Report to the National Advisory Council on Drug Abuse - February, 2009

Research Findings - Intramural Research

Biomedical Informatics Section, Administrative Management Branch

Pharmacy Informatics in Controlled Substances Research
Pharmacies have become essential components in support of clinical research. Their operations become highly complex when preponderance of prescriptions is composed of controlled substances. Application of informatics will result in more efficient operations. IRP scientists present the Pharmacy Information Management System (PIMS) that includes a set of decision support systems to address the pharmacy challenges and is integrated into our electronic health record system. Lin, J.-L., Vahabzadeh, M., Mezghanni, M., Na, P.J., Leff, M., and Contoreggi, C. Proc. AMIA Annual Symposium on Biomedical and Health Informatics: From Foundations to Applications to Policy (American Medical Informatics Association-2008), pp. 1025, 2008.

Molecular Neurobiology Research Branch

Nicotine Abstinence Genotyping: Assessing the Impact on Smoking Cessation Clinical Trials
MNB workers and collaborators have used data from prior genome wide association studies and twin studies to provide the first estimate of the likely impact of application of molecular genetics to clinical trials for smoking cessation. Since this is one of the areas of addiction in which efficacies of a number of pharmacologic therapeutics have been established from well described clinical trials, this data also provides a substantial impetus for application of molecular genetics to trials for pharmacological treatments for other addictions as well. Uhl, G.R., Drgon, T., Johnson, C., and Rose, J.E. Pharmacogenomics J. Sepember 9, 2008.

Brain-derived Neurotrophic Factor and Obesity in the WAGR Syndrome
MNB investigators have aided collaborators from the NIH in elucidating clear-cut effects of human BDNF deletion on human obesity. While these comparisons of WGAR individuals who have vs. those who do not have obesity provides direct insight into a limited number of individuals, this human data and data from knockout mice both combine to provide a compelling implication of BDNF in obesity. Han, J.C., Liu, Q.R, Jones, M., Levinn, R. L., Menzie, C.M., Jefferson-George, K.S., Adler-Wailes, D.C., Sanford, E.L., Lacbawan, F L., Uhl, G.R., Rennert, O.M., and Yanovski, J.A.. N. Engl. J. Med. 359(9), pp. 918-27, 2008.

Molecular Genetics of Successful Smoking Cessation: Convergent Genome-wide Association Study Results
MNB investigators have provided the first genome wide association data that is

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remarkably replicated for smoking cessation. These data should provide many clues to individual differences in ability to quit use of other substances as well. Uhl, G.R., Liu, Q.R,, Drgon, T., Johnson, C., Walther, D., Rose, J.E, David, S.P., Niaura, R., and Lerman, C. Arch. Gen. Psychiatry 65(6), pp. 683-693, 2008.

OKCAM: An Ontology-based, Human-centered Knowledgebase for Cell Adhesion Molecules
MNB investigators, in collaboration with Beijing University investigators, have provided a novel database that, for the first time, enumerates the universe of human "cell adhesion" related genes. Prior MNB success in identifying GWA signals in large number of these genes implicate many of them in addiction mechanisms. Li, C.Y., Liu, Q.R, Zhang, P.W., Li, X.M., Wei, L., and Uhl, G.R. Nucleic Acids Res. 2008 Sepember 12.

Genome-wide Association for Methamphetamine Dependence: Convergent Results from 2 Samples
MNB investigators, in collaborations with Japanese JGIDA and Taiwan methamphetamine group investigators provide novel genome wide association results for methamphetamine dependence in two replicate, carefully studied samples. Uhl, G.R., Drgon, T., Liu, Q.R., Johnson, C., Walther, D., Komiyama, T., Harano, M., Sekine, Y., Inada, T., Ozaki, N., Iyo, M., Iwata, N., Yamada, M., Sora, I., Chen, C.K., Liu, H.C., Ujike, H., and Lin, S.K. Arch. Gen. Psychiatry, 65(3), pp. 345-355, 2008.

Neural Protection and Regeneration Section, Molecular Neurobiology Research Branch

Bone Morphogenetic Protein-7 Reduces Toxicity Induced by High Doses of Methamphetamine in Rodents
Methamphetamine (MA) is a drug of abuse as well as a dopaminergic neurotoxin. IRP investigators have previously demonstrated that pretreatment with bone morphogenetic protein 7 (BMP7) reduced 6-hydroxydopamine-mediated neurodegeneration in a rodent model of Parkinson's disease. In this study, the authors examined the neuroprotective effects of BMP7 against MA-mediated toxicity in dopaminergic neurons. Primary dopaminergic neurons, prepared from rat embryonic ventral mesencephalic tissue, were treated with MA. High doses of MA decreased tyrosine hydroxylase immunoreactivity (THir) while increasing terminal deoxynucleotidyl transferase-mediated dNTP nick end labeling. These toxicities were significantly antagonized by BMP7. Interaction of BMP7 and MA in vivo was first examined in CD1 mice. High doses of MA (10 mg/kgx4 s.c.) significantly reduced locomotor activity and THir in striatum. I.c.v. administration of BMP7 antagonized these changes. In BMP7 +/- mice, MA suppressed locomotor activity and reduced TH immunoreactivity in nigra reticulata to a greater degree than in wild type BMP7 +/+ mice, suggesting that deficiency in BMP7 expression increases vulnerability to MA insults. Since BMP7 +/- mice also carry a LacZ-expressing reporter allele at the BMP7 locus, the expression of BMP7 was indirectly measured through the enzymatic activity of beta-galactosidase (beta-gal) in BMP7 +/- mice. High doses of MA significantly suppressed beta-gal activity in striatum, suggesting that MA may inhibit BMP7 expression at the terminals of the nigrostriatal pathway. A similar effect was also found in CD1 mice in that high doses of MA suppressed BMP7 mRNA expression in nigra. In conclusion, these data indicate that MA can cause lesioning in the nigrostriatal dopaminergic terminals and that BMP7 is protective against MA-mediated neurotoxicity in central dopaminergic neurons. Chou, J., Lu, Y., Kuo, C.C., Powers, K., Shen, H., Harvey, B.K., Hoffer, B.J., and Wang, Y. Neuroscience, 151, pp. 92-103, 2008.

Nigrostriatal Alterations in Bone Morphogenetic Protein Receptor II Dominant Negative Mice
IRP scientists previously demonstrated that exogenous application of bone morphogenetic protein 7 (BMP7) reduced 6-hydroxydopamine-mediated

neurodegeneration in a rodent model of Parkinson's disease. The purpose of this study is to examine the endogenous neurotrophic properties of BMP Receptor II in dopaminergic neurons of the nigrostriatal pathway. Adult male BMPRII dominant negative (BMPRIIDN) mice and their wild type controls (WT) were placed in the activity chambers for 3 days to monitor locomotor activity. Animals were sacrificed for tyrosine hydroxylase (TH) immunostaining. A subgroup of BMPRIIDN and WT mice were injected with high doses of methamphetamine (MA) and were sacrificed for terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) histochemistry at 4 days after injection. The authors found that BMPRIIDN mice had lower locomotor activity than the WT. There is a significant decrease in TH neuronal number in substantia nigra compacta, TH fiber density in the substantia nigra reticulata, and TH immunoreactivity in striatum in the BMPRIIDN mice, suggesting that deficiency in endogenous BMP signaling reduces dopaminergic innervation and motor function in the nigrostriatal pathway. Administration of MA increased TUNEL labeling in the substantia nigra in the BMPRIIDN mice. In conclusion, these data suggest that endogenous BMPs have trophic effects on nigrostriatal dopaminergic neurons. Deficiency in BMP signaling increases vulnerability to insults induced by high doses of MA. Chou, J., Harvey, B.K., Ebendal, T., Hoffer, B.J., and Wang, Y. Acta Neurochir. Suppl 101, pp. 93-98, 2008.

BMP7 Reduces Synergistic Injury Induced by Methamphetamine and Ischemia in Mouse Brain

Previous studies have indicated that methamphetamine (MA) potentiates neurodegeneration induced by ischemia in brain. IRP scientists, and others, have reported that bone morphogenetic protein 7 (BMP7) is protective against MA and ischemic brain injury. The purpose of this study was to examine whether BMP7 reduces synergistic injury induced by both MA and cerebral ischemia. Adult CD-1 mice were treated with MA (10 mg/kg x 4, each dose two hours apart) or saline. Using the quantitative real time polymerase chain reaction, the authors found that MA suppressed the expression of BMP7 mRNA in the cerebral cortex one day after injection. Ischemic and reperfusional injuries were introduced by ligation of the right middle cerebral artery for 90 min after MA injection. Animals were sacrificed for caspase 3/7 activity assay and tri-phenyl-tetrazolium chloride staining at 1 hour and 2 days after reperfusion, respectively. Cerebral infarction and caspase-3/7 activity were enhanced in the stroke animals pretreated with MA; both responses were attenuated by pretreatment with BMP7. In conclusion, these data suggest that MA facilitates cerebral infarction after ischemia possibly mediated, in part, through the suppression of BMP7. Shen, H., Luo, Y., Kuo, C.C., and Wang, Y. Neurosci. Lett., 442, pp. 15-18, 2008.

Tropism and Toxicity of Adeno-associated Viral Vector Serotypes 1, 2, 5, 6, 7, 8, and 9 in Rat Neurons and Glia in vitro

Recombinant adeno-associated viral (rAAV) vectors are frequently used for gene delivery to the central nervous system and are capable of transducing neurons and glia in vitro. In this study, seven serotypes of a rAAV vector expressing green fluorescent protein (GFP) were characterized for tropism and toxicity in primary cortical cells derived from embryonic rat brain. At 2 days after transduction, serotypes 1 and 5 through 8 expressed GFP predominately in glia, but by 6 days post-transduction expression was neuronal except for AAV5. AAV2 and 9 produced minimal GFP expression. Using cell viability assays, toxicity was observed at higher multiplicities of infection (MOI) for all serotypes except AAV2 and 9. The toxicity of AAV1 and 5-8 affected mostly glia as indicated by a loss of glial-marker immunoreactivity. A frameshift mutation in the GFP gene reduced overall toxicity for serotypes 1, 5 and 6, but not 7 and 8 suggesting that the toxicity was not solely due to the overexpression of GFP. Collectively, a differential tropism and toxicity was observed among the AAV serotypes on primary cortical cultures with an overall preferential glial transduction and toxicity. These studies facilitate experimentation of mechanistic actions of genes in models of neurodegeneration using primary

neuronal cultures. Howard, D., Powers, K., Wang, Y., and Harvey, B. Virology, 372, pp. 24-34, 2008.

Molecular Neuropsychiatry Research Branch

Growth Factor Signals in Neural Cells: Coherent Patterns of Interaction Control Multiple Levels of Molecular and Phenotypic Responses

Individual neurons express receptors for several different growth factors that influence the survival, growth, neurotransmitter phenotype and other properties of the cell. While there has been considerable progress in elucidating the molecular signal transduction pathways and physiological responses of neurons and other cells to individual growth factors, little is known about if and how signals from different growth factors are integrated within a neuron. In this study, IRP investigators determined the interactive effects of nerve growth factor (NGF), insulin-like growth factor 1 (IGF-1) and epidermal growth factor (EGF) on the activation status of downstream kinase cascades and transcription factors, cell survival, and neurotransmitter production in neural cells that express receptors for all three growth factors. The authors document considerable differences in the quality and quantity of intracellular signaling and eventual phenotypic responses that are dependent on whether cells are exposed to either single or multiple growth factors. Their findings suggest that in true physiological settings where multiple growth factors are present, activation of one receptor type may result in molecular and phenotypic responses that are different from what is observed in typical experimental paradigms in which cells are exposed to only a single growth factor at a time. Martin, B., Brenneman, R., Golden, E., Walent, T., Becker, K.G,, Prabhu, V.V., Wood, W. 3rd, Ladenheim, B., Cadet, J.L., and Maudsley, S. J. Biol. Chem, E-pub 2008.

Heavy Marijuana Users Show Increased Serum Apolipoprotein C-III Levels: Evidence from Proteomic Analyses

Marijuana (MJ) is the most commonly used illicit drug in the United States. Its abuse is associated with cognitive dysfunctions and increased resistance to blood flow in the cerebral vasculature. In addition, MJ abuse is associated with increased risks of potentially serious cardiovascular disorders. In the present study, IRP scientists used the protein chip platform based on surface-enhanced laser desorption/ionization time-of-flight mass spectroscopy (SELDITOF-MS) to test the possibility that MJ abuse might be associated with changes in serum protein levels. Indeed, MJ users showed significant increases in three protein peaks, which were identified as three isoforms of apolipoprotein (apo) C-III. Immunoprecipitation using an apoC-III antibody also validated the identification of the proteins. Marijuana-induced increases in apoC-III levels might occur through chronic stimulation of hepatic cannabinoid receptors (CB1 and/or CB2) by its active ingredient, D-9-tetrahydrocannibol (THC). Thus, chronic MJ abuse might cause increased transcription and/or translation of apoC-III in the liver with corresponding changes reflected in the plasma of these patients. In any case, because apoC-III is a cardiovascular risk factor, the increased levels observed in MJ users might explain, in part, the cardiac and cerebral abnormalities reported in these patients. Jayanthi, S., Buie, S., Moore, S., Herning, R.I., Better, W., Wilson, N.M., Contoreggi, C., and Cadet, J.L. Mol. Psychiatry E-pub 2008.

Office of the Scientific Director

Signal-Averaged Electrocardiogram in Physically Healthy, Chronic 3,4-Methylene-dioxymethamphetamine (MDMA) Users

3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) use has been associated with cardiac arrhythmias. Markers of ventricular late potentials (VLP), which may be a precursor to malignant ventricular arrhythmias, can be detected by signal-averaged electrocardiography (SA-ECG), but not by

standard ECG. This study evaluated SA-ECG parameters in 21 physically healthy, recently abstinent MDMA users who also used cannabis, 18 physically healthy cannabis users, and 54 non-drug-using controls. All subjects were > 18 years old. IRP researchers analyzed three SA-ECG parameters considered markers of VLPs: duration of filtered QRS complex (fQRS), duration of low amplitude potentials during terminal 40 ms of QRS complex (LAS40), and root mean square voltage during terminal 40 ms of QRS complex (RMS40). MDMA users, cannabis users, and non-drug-using controls did not differ significantly from each other in fQRS, LAS40, or RMS40 values or in the proportion of subjects with abnormal SA-ECG parameters. There were significant gender differences among controls, but not among MDMA users. These findings suggest that chronic MDMA use or cannabis use by physically healthy adults is not associated with a high prevalence of electrophysiological risk factors for cardiac ventricular arrhythmias. Kanneganti, P.., Huestis, M.A., Kolbrich, E.A., Goodwin, R., Ziegelstein, R.C., and Gorelick, D.A. American Journal of Drug and Alcohol Abuse, 34, pp. 712-720, 2008.

Brain Mu-Opioid Receptor Binding: Relationship to Relapse to Cocaine Use After Monitored Abstinence

Cocaine users have increased regional brain mu-opioid receptor (mOR) binding which correlates with cocaine craving. The relationship of mOR binding to relapse is unknown. This study evaluated regional brain mOR binding as a predictor of relapse to cocaine use in 15 non-treatment-seeking, adult cocaine users who were housed on a closed research ward for 12 weeks of monitored abstinence, then followed for up to one year after discharge. Regional brain mOR binding was measured after one and 12 weeks using positron emission tomography (PET) with [11C]carfentanil (a selective mOR agonist). Time to first cocaine use (lapse) and to first two consecutive days of cocaine use (relapse) after discharge was based on self-report and urine toxicology. A shorter interval before relapse was associated with increased mOR binding in frontal and temporal cortical regions at one and 12 weeks of abstinence and with a lesser decrease in binding between one and 12 weeks. There were significant positive correlations between mOR binding at 12 weeks and % days of cocaine use during the first month after relapse. In multiple linear regression analysis, mOR binding contributed significantly to the prediction of time to relapse ($R2 = 0.79$, $P < 0.001$), even after accounting for clinical variables. These findings show that increased brain mOR binding in frontal and temporal cortical regions is a significant independent predictor of time to relapse to cocaine use, suggesting an important role for the brain endogenous opioid system in cocaine addiction. Gorelick, D.A., Kim, Y.-K., Bencherif, B., Boyd, S.J., Nelson, R., Copersino, M.L., Dannals, R.F., and Frost J.J. Psychopharmacology, 200, pp. 475-486, 2008.

Clinical Psychopharmacology Section, Chemical Biology Research Branch

Tolerance to 3,4-Methylenedioxymethamphetamine in Rats Exposed to Single High-Dose Binges

3,4-Methylenedioxymethamphetamine (MDMA or ecstasy) stimulates the transporter-mediated release of monoamines, including 5-HT. High-dose exposure to MDMA causes persistent 5-HT deficits (e.g. depletion of brain 5-HT) in animals, yet the functional and clinical relevance of such deficits are poorly defined. Here IRP scientists examine functional consequences of MDMA-induced 5-HT depletions in rats. Male rats received binges of three i.p. injections of MDMA or saline, one injection every 2 h; MDMA was given at a threshold pharmacological dose (1.5 mg/kgx3, low dose) or at a fivefold higher amount (7.5 mg/kgx3, high dose). One week later, jugular catheters and intracerebral guide cannulae were implanted. Two weeks after binges, rats received acute i.v. challenge injections of 1 and 3 mg/kg MDMA. Neuroendocrine effects evoked by i.v. MDMA (prolactin and corticosterone

secretion) were assessed via serial blood sampling, while neurochemical effects (5-HT and dopamine release) were assessed via microdialysis in brain. MDMA binges elevated core temperatures only in the high-dose group, with these same rats exhibiting approximately 50% loss of forebrain 5-HT 2 weeks later. Prior exposure to MDMA did not alter baseline plasma hormones or dialysate monoamines, and effects of i.v. MDMA were similar in saline and low-dose groups. By contrast, rats pretreated with high-dose MDMA displayed significant reductions in evoked hormone secretion and 5-HT release when challenged with i.v. MDMA. As tolerance developed only in rats exposed to high-dose binges, hyperthermia and 5-HT depletion are implicated in this phenomenon. These results suggest that MDMA tolerance in humans may reflect 5-HT deficits which could contribute to further dose escalation. Baumann, M.H., Clark, R.D., Franken, F.H., Rutter, J.J., and Rothman, R.B. Neuroscience, 152, pp. 773-784, 2008.

Herkinorin Analogues with Differential beta-Arrestin-2 Interactions
Salvinorin A is a psychoactive natural product that has been found to be a potent and selective kappa opioid receptor agonist in vitro and in vivo. The activity of salvinorin A is unusual compared to other opioids such as morphine in that it mediates potent kappa opioid receptor signaling yet leads to less receptor down-regulation than observed with other kappa agonists. IRP scientists' initial chemical modifications of salvinorin A have yielded one analogue, herkinorin (1c), with high affinity at the muOR. They recently reported that 1c does not promote the recruitment of beta-arrestin-2 to the muOR or receptor internalization. Here they describe three new derivatives of 1c (3c, 3f, and 3i) with similar properties and one, benzamide 7b, that promotes recruitment of beta-arrestin-2 to the muOR and receptor internalization. When the important role mu opioid receptor regulation plays in determining physiological responsiveness to opioid narcotics is considered, mu opioids derived from salvinorin A may offer a unique template for the development of functionally selective mu opioid receptor-ligands with the ability to produce analgesia while limiting adverse side effects. Tidgewell, K., Groer, C.E., Harding, W.W., Lozama, A., Schmidt, M., Marquam, A., Hiemstra, J., Partilla, J.S., Dersch, C.M., Rothman, R.B., Bohn, L.M., and Prisinzano, T.E. J. Med. Chem., 51, pp. 2421-2431, 2008.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

Effects of Chronic Caffeine Exposure on Adenosinergic Modulation of the Discriminative-stimulus Effects of Nicotine, Methamphetamine, and Cocaine in Rats
Adenosine receptors are involved in cocaine and methamphetamine discrimination and exposure to caffeine can affect behavioral effects of nicotine in rats. Here IRP researchers investigated the relative involvement of adenosine A(1) and A(2A) receptors in nicotine, cocaine, and methamphetamine discrimination, before and/or during chronic caffeine exposure. The nonselective adenosine receptor antagonist caffeine, the A(1)-receptor antagonist cyclopentyltheophylline (CPT), and the A(2A)-receptor antagonist MSX-3 were evaluated in rats trained to discriminate 0.4 mg/kg nicotine from saline under a fixed-ratio schedule of food delivery. Effects of adenosine receptor antagonists were then compared in rats discriminating nicotine, methamphetamine, or cocaine from saline during chronic caffeine exposure in their drinking water. Caffeine, CPT, and MSX-3 partially generalized to nicotine and shifted nicotine dose-response curves leftwards. During chronic caffeine exposure, however, all three ligands failed to generalize to nicotine and failed to shift nicotine dose-response curves. In previous experiments, CPT and MSX-3 partially generalized to methamphetamine and cocaine and shifted dose-response curves leftwards. In the present experiments, CPT neither generalized nor shifted dose-response curves for

methamphetamine or cocaine during chronic caffeine exposure. However, MSX-3 partially generalized to both psychostimulants and shifted their dose-response curves leftwards. Caffeine partially generalized to cocaine, but not methamphetamine, and shifted both dose-response curves leftwards. The authors conclude that both adenosine A(1) and A(2A) receptors are capable of modulating the discriminative-stimulus effects of nicotine. Chronic caffeine exposure produces complete tolerance to both A(1)- and A(2A)-mediated effects in nicotine-trained rats. In contrast, chronic caffeine exposure produces tolerance to adenosine A(1)-mediated, but not A(2A)-mediated, effects in methamphetamine- and cocaine-trained rats. Justinova, Z., Ferre, S., Barnes, C., Wertheim, C.E., Pappas, L.A., Goldberg, S.R., and Le Foll, B. Psychopharmacology (Berl), August 8, 2008, Epub ahead of print, PMID: 18688601.

Looking for the Role of Cannabinoid Receptor Heteromers in Striatal Function

The introduction of two concepts, "local module" and "receptor heteromer", facilitates the understanding of the role of interactions between different neurotransmitters in the brain. In artificial cell systems, cannabinoid CB(1) receptors form receptor heteromers with dopamine D(2), adenosine A(2A) and mu opioid receptors. There is indirect but compelling evidence for the existence of the same CB(1) receptor heteromers in striatal local modules centered in the dendritic spines of striatal GABAergic efferent neurons, particularly at a postsynaptic location. Their analysis provides new clues for the role of endocannabinoids in striatal function, which cannot only be considered as retrograde signals that inhibit neurotransmitter release. Recent studies using a new method to detect heteromerization of more than two proteins, which consists of sequential BRET-FRET (SRET) analysis, has demonstrated that CB(1), D(2) and A(2A) receptors can form heterotrimers in transfected cells. It is likely that functional CB(1)-A(2A)-D(2) receptor heteromers can be found where they are highly co-expressed, in the dendritic spines of GABAergic enkephalinergic neurons. The functional properties of these multiple receptor heteromers and their role in striatal function need to be determined. Ferre, S., Goldberg, S.R., Lluis, C., and Franco, R. Neuropharm., July 19, 2008, Epub ahead of print, PMID: 18691604.

Dopamine D(2) and Adenosine A(2A) Receptors Regulate NMDA-Mediated Excitation in Accumbens Neurons through A(2A)-D(2) Receptor Heteromerization

Bursting activity of striatal medium spiny neurons results from membrane potential oscillations between a down- and an upstate that could be regulated by G-protein-coupled receptors. Among these, dopamine D(2) and adenosine A(2A) receptors are highly enriched in striatal neurons and exhibit strong interactions whose physiological significance and molecular mechanisms remain partially unclear. More particularly, respective involvements of common intracellular signaling cascades and A(2A)-D(2) receptor heteromerization remain unknown. Here IRP scientists show, by performing perforated-patch-clamp recordings on brain slices and loading competitive peptides, that D(2) and A(2A) receptors regulate the induction by N-methyl-D-aspartate of a depolarized membrane potential plateau through mechanisms relying upon specific protein-protein interactions. Indeed, D(2) receptor activation abolished transitions between a hyperpolarized resting potential and a depolarized plateau potential by regulating the Ca(V)1.3a calcium channel activity through interactions with scaffold proteins Shank1/3. Noticeably, A(2A) receptor activation had no effect per se but fully reversed the effects of D(2) receptor activation through a mechanism in which A(2A)-D(2) receptors heteromerization is strictly mandatory, demonstrating therefore a first direct physiological relevance of these heteromers. These results show that membrane potential transitions and firing patterns in striatal neurons are tightly controlled by D(2) and A(2A) receptors through specific protein-protein interactions including A(2A)-D(2) receptors heteromerization. Azdad, K., Gall,

D., Woods, A.S., Ledent, C., Ferre, S., and Schiffmann, S.N. Neuropsychopharm., September 17, 2008, Epub ahead of print, PMID: 18800071.

Anandamide-Induced Behavioral Disruption through a Vanilloid-dependent Mechanism in Rats

Endocannabinoids are involved in a variety of behavioral and physiological processes that are just beginning to be understood. In the five-choice serial reaction-time task, exogenous cannabinoids have been found to alter attention, but endocannabinoids such as anandamide have not been studied. IRP scientists used this task to evaluate the effects of anandamide in rats. Since anandamide is a ligand for not only cannabinoid receptors but also transient receptor potential vanilloid 1 (TRPV1) receptors, and as recently suggested, peroxisome proliferator-activated nuclear receptor-alpha (PPARalpha), the authors also determined whether anandamide's effects in this task were mediated by each of these receptors. Whenever one of five holes was illuminated for 2 s, a food pellet was delivered if a response occurred in that hole during the light or within 2 s after the light. Anandamide increased omission errors and decreased responding during inter-trial intervals. These effects were blocked by the TRPV1 antagonist capsazepine, but not by the cannabinoid-receptor antagonist rimonabant or the PPARalpha antagonist MK886. Testing with open-field activity and food-consumption procedures in the same rats suggested that the disruption of operant responding observed in the attention task was not due to motor depression, anxiety, decreased appetite, or an inability to find and consume food pellets. The vanilloid-dependent behavioral disruption induced by anandamide was specific to the operant attention task. These effects of anandamide resemble effects of systemically administered dopamine antagonists and might reflect changes in vanilloid-mediated dopamine transmission. Panlilio, L. V., Mazzola, C., Medalie, J., Hahn, B., Justinova, Z., Drago, F., Cadet, J.L., Yasar, S., and Goldberg, S.R. Psychopharmacology (Berl.), 18 Nov 2008, Epub ahead of print, PMID: 19015836.

Diminished Iron Concentrations Increase Adenosine A(2A) Receptor Levels in Mouse Striatum and Cultured Human Neuroblastoma Cells

Brain iron insufficiency has been implicated in several neurological disorders. The dopamine system is consistently altered in studies of iron deficiency in rodent models. Changes in striatal dopamine D(2) receptors are directly proportional to the degree of iron deficiency. In light of the unknown mechanism for the iron deficiency-dopamine connection and because of the known interplay between adenosinergic and dopaminergic systems in the striatum IRP investigators examined the effects of iron deficiency on the adenosine system. They first attempted to assess whether there is a functional change in the levels of adenosine receptors in response to this low iron. Mice made iron-deficient by diet had an increase in the density of striatal adenosine A(2A) (A(2A)R) but not A(1) receptor (A(1)R) compared to mice on a normal diet. Between two inbred murine strains, which had 2-fold differences in their striatal iron concentrations under normal dietary conditions, the strain with the lower striatal iron had the highest striatal A(2A)R density. Treatment of SH-SY5Y (human neuroblastoma) cells with an iron chelator resulted in increased density of A(2A)R. In these cells, A(2A)R agonist-induced cyclic AMP production was enhanced in response to iron chelation, also demonstrating a functional upregulation of A(2A)R. A significant correlation (r(2)=0.79) was found between a primary marker of cellular iron status (transferrin receptor (TfR)) and A(2A)R protein density. In conclusion, the A(2A)R is increased across different iron-insufficient conditions. The relation between A(2A)R and cellular iron status may be an important pathway by which adenosine may alter the function of the dopaminergic system. Gulyani, S., Earley, C.J., Camandola, S., Maudsley, S., Ferre, S., Mughal, M.R., Martin, B., Cheng, A., Gleichmann, M., Jones, B.C., Allen, R.P., and Mattson, M.P. Experimental Neurology, October 28, 2008, Epubmed ahead of print, PMID: 19013457.

Fatty Acid Amide Hydrolase Inhibition Heightens Anandamide Signaling without Producing Reinforcing Effects in Primates

CB(1) cannabinoid receptors in the brain are known to participate in the regulation of reward-based behaviors. However, the contribution of each of the endocannabinoid transmitters, anandamide and 2-arachidonoylglycerol (2-AG), to these behaviors remains undefined. To address this question, IRP researchers assessed the effects of URB597, a selective anandamide deactivation inhibitor, as a reinforcer of drug-seeking and drug-taking behavior in squirrel monkeys. They investigated the reinforcing effects of the fatty acid amide hydrolase (FAAH) inhibitor URB597 in monkeys trained to intravenously self-administer Delta(9)-tetrahydrocannabinol (THC), anandamide, or cocaine and quantified brain endocannabinoid levels using liquid chromatography/mass spectrometry. They measured brain FAAH activity using an ex vivo enzyme assay. URB597 (.3 mg/kg, intravenous) blocked FAAH activity and increased anandamide levels throughout the monkey brain. This effect was accompanied by a marked compensatory decrease in 2-AG levels. Monkeys did not self-administer URB597, and the drug did not promote reinstatement of extinguished drug-seeking behavior previously maintained by THC, anandamide, or cocaine. Pretreatment with URB597 did not modify self-administration of THC or cocaine, even though, as expected, it significantly potentiated anandamide self-administration. In the monkey brain, the FAAH inhibitor URB597 increases anandamide levels while causing a compensatory down-regulation in 2-AG levels. These effects are accompanied by a striking lack of reinforcing properties, which distinguishes URB597 from direct-acting cannabinoid agonists such as THC. These results reveal an unexpected functional heterogeneity within the endocannabinoid signaling system and suggest that FAAH inhibitors might be used therapeutically without risk of abuse or triggering of relapse to drug abuse. Justinova, Z., Mangieri, R.A., Bortolato, M., Chefer, S.I., Mukhin, A.G., Clapper, J.R., King, A.R., Redhi, G.H., Yasar, S., Piomelli, D., and Goldberg, S.R. Biological Psychiatry, 64(11), pp. 930-937, 2008.

Inhibition of Anandamide Hydrolysis by Cyclohexyl Carbamic Acid 3'-carbamoyl-3-yl ester (URB597) Reverses Abuse-related Behavioral and Neurochemical Effects of Nicotine in Rats

Emerging evidence suggests that the rewarding, abuse-related effects of nicotine are modulated by the endocannabinoid system of the brain. For example, pharmacological blockade or genetic deletion of cannabinoid CB(1) receptors can reduce or eliminate many abuse-related behavioral and neurochemical effects of nicotine. Furthermore, doses of Delta(9)-tetrahydro-cannabinol and nicotine that are ineffective when given alone can induce conditioned place preference when given together. These previous studies have used systemically administered CB(1) receptor agonists and antagonists and gene deletion techniques, which affect cannabinoid CB(1) receptors throughout the brain. A more functionally selective way to alter endocannabinoid activity is to inhibit fatty acid amide hydrolase (FAAH), thereby magnifying and prolonging the effects of the endocannabinoid anandamide only when and where it is synthesized and released on demand. Here, IRP scientists combined behavioral and neurochemical approaches to evaluate whether the FAAH inhibitor URB597 (cyclohexyl carbamic acid 3'-carbamoyl-3-yl ester) could alter the abuse-related effects of nicotine in rats. They found that URB597, at a dose (0.3 mg/kg) that had no behavioral effects by itself, prevented development of nicotine-induced conditioned place preference (CPP) and acquisition of nicotine self-administration. URB597 also reduced nicotine-induced reinstatement in both CPP and self-administration models of relapse. Furthermore, in vivo microdialysis showed that URB597 reduced nicotine-induced dopamine elevations in the nucleus accumbens shell, the terminal area of the brain's mesolimbic reward system. These findings suggest that FAAH inhibition can counteract the addictive properties of nicotine and that FAAH may serve as a new target for development of medications for treatment of tobacco

dependence. Scherma, M., Panlilio, L.V., Fadda, P., Fattore, L., Gamaleddin, I., Le Foll, B., Justinova, Z., Mikics, E., Haller, J., Medalie, J., Stroik, J., Barnes, C., Yasar, S., Tanda, G., Piomelli, D., Fratta, W., and Goldberg, S.R. JPET, 327(2), pp. 482-490, 2008.

Effects of Baclofen on Conditioned Rewarding and Discriminative Stimulus Effects of Nicotine in Rats

Neurochemical studies suggest that baclofen, an agonist at GABA(B) receptors, may be useful for treatment of nicotine dependence. However, its ability to selectively reduce nicotine's abuse-related behavioral effects remains in question. IRP researchers assessed effects of baclofen doses ranging from 0.1 to 3mg/kg on nicotine-induced conditioned place preferences (CPPs), nicotine discrimination, locomotor activity and food-reinforced behavior in male Sprague-Dawley rats. The high dose of baclofen (3mg/kg) totally eliminated food-reinforced responding and significantly decreased locomotor activity. Lower doses of baclofen did not have nicotine-like discriminative effects in rats trained to discriminate 0.4mg/kg nicotine from saline under a fixed-ratio 10 schedule of food delivery. Lower doses of baclofen also did not reduce discriminative stimulus effects of the training dose of nicotine and did not significantly shift the dose-response curve for nicotine discrimination. Rats treated with the high 3mg/kg dose of baclofen did not express nicotine-induced CPP. These experiments, along with previous reports that baclofen can reduce intravenous nicotine self-administration behavior, confirm the potential utility of baclofen as a tool for smoking cessation. Le Foll, B., Wetheim, C.E., and Goldberg, S.R. Neuroscience Letters, 443(3), pp. 236-240, 2008.

Sleep Deprivation Decreases Binding of [11C]Reclopride to Dopamine D2/D3 Receptors in the Human Brain

Sleep deprivation did not affect dopamine transporters (target for most wake-promoting medications) and thus dopamine increases are likely to reflect increases in dopamine cell firing and/or release rather than decreases in dopamine reuptake. Because dopamine-enhancing drugs increase wakefulness, IRP researchers postulate that dopamine increases after sleep deprivation is a mechanism by which the brain maintains arousal as the drive to sleep increases but one that is insufficient to counteract behavioral and cognitive impairment. Sleep deprivation can markedly impair human performance contributing to accidents and poor productivity. The mechanisms underlying this impairment are not well understood, but brain dopamine systems have been implicated. Here, they test whether one night of sleep deprivation changes dopamine brain activity. The authors studied 15 healthy subjects using positron emission tomography and [11C]raclopride (dopamine D2/D3 receptor radioligand) and [11C]cocaine (dopamine transporter radioligand). Subjects were tested twice: after one night of rested sleep and after one night of sleep deprivation. The specific binding of [11C]raclopride in the striatum and thalamus were significantly reduced after sleep deprivation and the magnitude of this reduction correlated with increases in fatigue (tiredness and sleepiness) and with deterioration in cognitive performance (visual attention and working memory). In contrast, sleep deprivation did not affect the specific binding of [11C]cocaine in the striatum. Because [11C]raclopride competes with endogenous dopamine for binding to D2/D3 receptors, the authors interpret the decreases in binding to reflect dopamine increases with sleep deprivation. However, they could not rule out the possibility that decreased [11C]raclopride binding reflects decreases in receptor levels or affinity. Sleep deprivation did not affect dopamine transporters (target for most wake-promoting medications) and thus dopamine increases are likely to reflect increases in dopamine cell firing and/or release rather than decreases in dopamine reuptake. Because dopamine-enhancing drugs increase wakefulness, the authors postulate that dopamine increases after sleep deprivation is a mechanism by which the brain maintains arousal as the drive to sleep increases but one that is insufficient to counteract behavioral and cognitive impairment. Volkow, N.D., Wang, G.J., Telang, F., Fowler, J.S., Logan, J.,

Wong, C., Ma, J., Pradhan, K., Tomasi, D., Thanos, P.K., Ferre, S., and Jayne, M. Journal of Neuroscience, August 20, 2008, 28(34), pp. 8454-8461, 2008.

Plasma Membrane Diffusion of g Protein-coupled Receptor Oligomers

G protein-coupled receptors are known to form homo-and heteromers at the plasma membrane, but the molecular properties of these oligomers are relatively unknown. Here, IRP scientists show a method that allows the diffusion of G protein-coupled receptors oligomers in the plasma membrane to be monitored in single cells by combining Bimolecular Fluorescence Complementation and Fluorescence Correlation Spectroscopy. With this approach they have measured, for the first time, the membrane diffusional characteristics of adenosine A(1) and A(2A) receptor homo-and heterodimers in Chinese Hamster Ovary cells. Interestingly, both homodimers display similar diffusion co-efficients (D) when expressed in living cells (D=5.0 and 4.8x10(-9) cm(2)/s, respectively) but the heterodimer formed by these receptors exhibit a significantly faster plasma membrane diffusion co-efficent (D=5.6x10(-9) cm(2)/s) when compared to the adenosine A(1) receptor tagged with the full-length yellow fluorescent protein (D=4.0x10(-9) cm(2)/s). Overall, these results demonstrate differences in plasma membrane diffusion between adenosine receptor homo-and heterodimers, providing new insights into the molecular plasticity of G protein-coupled receptor oligomerization. Briddon, S.J., Gandia, J., Amarol, O.B., Ferre, S., Lluis, C., Franco, R., Hill, S.J., and Ciruela, F. Biochimica Biophysica Acta, 1783(12), pp. 2262-2268, 2008.

Detection of Heteromerization of More than Two Proteins by Sequential BRET-FRET

Identification of higher-order oligomers in the plasma membrane is essential to decode the properties of molecular networks controlling intercellular communication. IRP scientists combined bioluminescence resonance energy transfer (BRET) and fluorescence resonance energy transfer (FRET) in a technique called sequential BRET-FRET (SRET) that permits identification of heteromers formed by three different proteins. In SRET, the oxidation of a Renilla luciferase (Rluc) substrate by an Rluc fusion protein triggers acceptor excitation of a second fusion protein by BRET and subsequent FRET to a third fusion protein. The authors describe two variations of SRET that use different Rluc substrates with appropriately paired acceptor fluorescent proteins. Using SRET, they identified complexes of cannabinoid CB(1), dopamine D(2) and adenosine A(2A) receptors in living cells. SRET is an invaluable technique to identify heteromeric complexes of more than two neurotransmitter receptors, which will allow us to better understand how signals are integrated at the molecular level. Carriba, P., Navarro, G., Ciruela, F., Ferre, S., Casado, V., Agnati, L., Cortes, A., Mallol, J., Fuxe, K., Canela, E.I., Lluis, C., and Franco, R. Nature Methods, 5(8), pp. 727-733, 2008.

Potential Therapeutic Interest of Adenosine A2A Receptors in Psychiatric Disorders

The interest on targeting adenosine A(2A) receptors in the realm of psychiatric diseases first arose based on their tight physical and functional interaction with dopamine D(2) receptors. However, the role of central A(2A) receptors is now viewed as much broader than just controlling D(2) receptor function. Thus, there is currently a major interest in the ability of A(2A) receptors to control synaptic plasticity at glutamatergic synapses. This is due to a combined ability of A(2A) receptors to facilitate the release of glutamate and the activation of NMDA receptors. Therefore, A(2A) receptors are now conceived as a normalizing device promoting adequate adaptive responses in neuronal circuits, a role similar to that fulfilled, in essence, by dopamine. This makes A(2A) receptors particularly attractive targets to manage psychiatric disorders since adenosine may act as go-between glutamate and dopamine, two of the key players in mood processing. Furthermore, A(2A) receptors also control glia function and brain metabolic adaptation, two other emerging mechanisms to understand abnormal processing of mood, and A(2A) receptors are important

players in controlling the demise of neurodegeneration, considered an amplificatory loop in psychiatric disorders. Current data only provide an indirect confirmation of this putative role of A(2A) receptors, based on the effects of caffeine (an antagonist of both A(1) and A(2A) receptors) in psychiatric disorders. However, the introduction of A(2A) receptor antagonists in clinics as anti-parkinsonian agents is hoped to bolster our nowledge on the role of A(2A) receptors in mood disorders in the near future. Cunha, R.A., Ferre, S., Vaugeois, J.M., and Chen, J.F. Curr. Pharm. Des., 14(15), pp. 1512-1524, 2008.

Identification of Dopamine D1-D3 Receptor Heteromers: Indications for a Role of Synergistic D1-D3 Receptor Interactions in the Striatum

The function of dopamine D3 receptors present in the striatum has remained elusive. In the present study evidence is provided for the existence of dopamine D1-D3 receptor heteromers and for an intramembrane D1-D3 receptor cross-talk in living cells and in the striatum. The formation of D1-D3 receptor heteromers was demonstrated by Fluorescence Resonance Energy Transfer (FRET) and Bioluminescence Resonance Energy Transfer (BRET) techniques in transfected mammalian cells. In membrane preparations from these cells, a synergistic D1-D3 intramembrane receptor-receptor interaction was observed, by which D3 receptor stimulation enhances D1 receptor agonist affinity, indicating that the D1-D3 intramembrane receptor-receptor interaction is a biochemical characteristic of the D1-D3 receptor heteromer. The same biochemical characteristic was also observed in membrane preparations from brain striatum, demonstrating the striatal colocalization and heteromerization of D1 and D3 receptors. According to the synergistic D1-D3 intramembrane receptor-receptor interaction, experiments in reserpinized mice showed that D3 receptor stimulation potentiates D1 receptor-mediated behavioral effects by a different mechanism than D2 receptor stimulation. The present study shows that a main functional significance of the D3 receptor is to obtain a stronger dopaminergic response in the striatal neurons that co-express the two receptors. Marcellino, D., Ferre, S., Casado, V., Cortes, A., Le Foll, B., Mazzola, C., Drago, F., Saur, O., Stark, H., Soriano, A., Barnes, C., Goldberg, S.R., Lluis, C., Fuxe, K., and Franco, R. Journal of Biological Chemistry, July 25, 2008, Epub ahead of print, PMID: 18644790.

Interactions between Histamine H(3) and Dopamine D(2) Receptors and the Implications for Striatal Function

The striatum contains a high density of histamine H(3) receptors, but their role in striatal function is poorly understood. Previous studies have demonstrated antagonistic interactions between striatal H(3) and dopamine D(1) receptors at the biochemical level, while contradictory results have been reported about interactions between striatal H(3) and dopamine D(2) receptors. In this study, by using reserpinized mice, IRP researchers demonstrate the existence of behaviorally significant antagonistic postsynaptic interactions between H(3) and D(1) and also between H(3) and dopamine D(2) receptors. The selective H(3) receptor agonist imetit inhibited, while the H(3) receptor antagonist thioperamide potentiated locomotor activation induced by either the D(1) receptor agonist SKF 38393 or the D(2) receptor agonist quinpirole. High scores of locomotor activity were obtained with H(3) receptor blockade plus D(1) and D(2) receptor co-activation, i.e., when thioperamide was co-administered with both SKF 38393 and quinpirole. Radioligand binding experiments in striatal membrane preparations showed the existence of a strong and selective H(3)-D(2) receptor interaction at the membrane level. In agonist/antagonist competition experiments, stimulation of H(3) receptors with several H(3) receptor agonists significantly decreased the affinity of D(2) receptors for the agonist. This kind of intramembrane receptor-receptor interactions are a common biochemical property of receptor heteromers. In fact, by using Bioluminescence Resonance Energy Transfer techniques in co-transfected HEK-293 cells, H(3) (but not H(4)) receptors were found to form heteromers with D(2) receptors. This study demonstrates an important role of

postsynaptic H(3) receptors in the modulation of dopaminergic transmission by means of a negative modulation of D(2) receptor function. Ferrada, C., Ferre, S., Casado, V., Cortes, A., Justinova, Z., Barnes, C., Canela, E.I., Goldberg, S.R., Leurs, R., Lluis, C., and Franco, R. Neuropharmacology, May 16, 2008, Epub ahead of print, PMID 18547596.

Blocking Cannabinoid CB1 Receptors for the Treatment of Nicotine Dependence: Insights from Pre-clinical and Clinical Studies

Tobacco use is one of the leading preventable causes of death in developed countries. Since existing medications are only partially effective in treating tobacco smokers, there is a great need for improved medications for smoking cessation. It has been recently proposed that cannabinoid CB(1) receptor antagonists represent a new class of therapeutic agents for drug dependence, and notably, nicotine dependence. Here, IRP scientists reviewed current evidence supporting the use of this class of drugs for smoking cessation treatment. Pre-clinical studies indicate that nicotine exposure produces changes in endocannabi-noid content in the brain. In experimental animals, N-piperidinyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl) -4-methylpyrazole-3-carboxamide (rimonabant, SR141716) and N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide (AM251), two cannabinoid CB(1) receptor antagonists, block nicotine self-administration behavior, an effect that may be related to the blockade of the dopamine-releasing effects of nicotine in the brain. Rimonabant also seems efficacious in decreasing the influence of nicotine-associated stimuli over behavior, suggesting that it may act on two distinct neuronal pathways, those implicated in drug-taking behavior and those involved in relapse phenomena. The utility of rimonabant has been evaluated in several clinical trials. It seems that rimonabant is an efficacious treatment for smoking cessation, although its efficacy does not exceed that of nicotine-replacement therapy and its use may be limited by emotional side effects (nausea, anxiety and depression, mostly). Rimonabant also appears to decrease relapse rates in smokers. These findings indicate significant, but limited, utility of rimonabant for smoking cessation. Le Foll, B., Forget, B., Aubin, H.J., and Goldberg, S.R. Addiction Biology, 13, pp. 239-252, 2008.

The Endocannabinoid System in Brain Reward Processes

Food, drugs and brain stimulation can serve as strong rewarding stimuli and are all believed to activate common brain circuits that evolved in mammals to favour fitness and survival. For decades, endogenous dopaminergic and opioid systems have been considered the most important systems in mediating brain reward processes. Recent evidence suggests that the endogenous cannabinoid (endocannabinoid) system also has an important role in signalling of rewarding events. First, CB(1) receptors are found in brain areas involved in reward processes, such as the dopaminergic mesolimbic system. Second, activation of CB(1) receptors by plant-derived, synthetic or endogenous CB(1) receptor agonists stimulates dopaminergic neurotransmission, produces rewarding effects and increases rewarding effects of abused drugs and food. Third, pharmacological or genetic blockade of CB(1) receptors prevents activation of dopaminergic neurotransmission by several addictive drugs and reduces rewarding effects of food and these drugs. Fourth, brain levels of the endocannabinoids anandamide and 2-arachidonoylglycerol are altered by activation of reward processes. However, the intrinsic activity of the endocannabinoid system does not appear to play a facilitatory role in brain stimulation reward and some evidence suggests it may even oppose it. The influence of the endocannabinoid system on brain reward processes may depend on the degree of activation of the different brain areas involved and might represent a mechanism for fine-tuning dopaminergic activity. Although involvement of the various components of the endocannabinoid system may differ depending on the type of rewarding event investigated, this system appears to play a major role in modulating reward processes. Solinas, M., Goldberg, S.R., and Piomelli, D. British Journal of Pharmacology, 154, pp. 369-

383, 2008.

Novel Pharmacological Targets Based on Receptor Heteromers
Studies performed in the last 10 years have provided solid evidence indicating that G-protein-coupled receptors are expressed on the plasma membrane as homo and heterodimers. The first consequence of this fact is that homo and heterodimers are the true targets of natural (hormones, neurotransmitters) and synthetic drugs. Furthermore a given receptor in a heteromer may display a different functional and/or pharmacological profile than the same receptor characterized as monomer or as homodimer. Recent evidence indicates that receptor heteromers are sensors that lead to a fine-tuning in neurotransmission or hormone regulation; mainly this is achieved by a modification of the signaling pathways activated via a given receptor when it is forming a given heteromer. Quite often antagonists display variable affinities when a given receptor is expressed with different heteromeric partners. This fact should be taken into account in the development of new drugs. Finally it should be pointed out that radioligand binding data has to be analyzed by a model that considers receptors as dimers and not as monomers. This model provides a novel approach to characterize drugs interacting with the orthosteric center (agonists/antagonists) or with allosteric centers (allosteric regulators). Franco, R., Casado, V., Cortes, A., Perez-Capote, K., Mallol, J., Canela, E., Ferre, S., and Lluis, C. Brain Research Review, June 20, 2008, Epub ahead of print, PMID: 18620000.

How Calmodulin Interacts with the Adenosine A2A and the Dopamine D2 Receptors
Receptor heteromerization is a mechanism used by G protein-coupled receptors to diversify their properties and function. IRP researchers previously demonstrated that these interactions occur through salt bridge formation between epitopes of the involved receptors. Recent studies claim that calmodulin (CaM) binds to an Arg-rich epitope located in the amino-terminus of the dopamine D 2 receptor third intracellular loop. This is the same epitope involved in adenosine A 2A-D 2 receptor heteromerization, through Coulombic interaction between the Arg residues and a phosphorylated serine (pS) located in the medial segment of the C-terminus of the A 2A receptor. Mass spectrometric analysis indicates that an electrostatic interaction involving the D 2 receptor Arg-rich epitope and several CaM acidic epitopes are mainly responsible for the D 2 receptor-CaM binding. CaM could also form multiple noncovalent complexes by means of electrostatic interactions with an epitope localized in the proximal segment of the C-terminus of the A 2A receptor. Ca (2+) disrupted the binding of CaM to the D 2 but not to the A 2A receptor epitope, and CaM disrupted the electrostatic interactions between the D 2 receptor epitope and the more distal A 2A receptor epitope. A model is introduced with the possible functional implications of A 2A-D 2-CaM interactions. These in vitro findings imply a possible regulatory role for CaM in receptor heteromers formation. Woods, A.S., Marcellino, D., Jackson, S.N., Franco, R., Ferre, S., Agnati, L.F., and Fuxe, K. Journal of Proteomic Research, July 1, 2008, Epub ahead of print, PMID: 18590318.

Future Medications for Tobacco and Cannabis Dependence
Worldwide more than 3 million deaths a year are attributable to smoking, and tobacco use is on the rise in developing countries. Consequently, smoking is one of the few causes of mortality that is increasing, with deaths projected to reach 10 million annually in 30-40 years. Cannabinoids, which are usually used in the form of marijuana, have become the most frequently used illicit drugs, but there is no pharmacological treatment for marijuana dependence. Although the dopaminergic system plays a critical role in reinforcing the effects of drugs of abuse, other neurotransmitter systems are also involved. Here IRP scientists review recent results obtained with antagonists targeting cannabinoid CB1 receptors, dopamine D3 receptors and opioid receptors, that directly or indirectly modulate dopaminergic transmission. These promising approaches

warrant clinical trials in the treatment of tobacco and marijuana dependence. Le Foll, B,, Justinova, Z., Tanda, G., and Goldberg, S.R. Bulletin of the Academy of National Medicine, 192, pp. 45-56; discussion 56-57, 2008. PMID: 18663981.

Behavioral Neuroscience Research Branch

Acetylcholine Release in the Mesocorticolimbic Dopamine System During Cocaine Seeking: Conditioned and Unconditioned Contributions to Reward and Motivation

Microdialysis was used to assess the contribution to cocaine-seeking of cholinergic input to the mesocortico-limbic dopamine system in ventral tegmental area (VTA). VTA acetylcholine (ACh) was elevated in animals lever-pressing for IV cocaine and in cocaine-experienced and cocaine-naive animals passively receiving similar "yoked" injections. In cocaine-trained animals, the elevations comprised an initial (first hour) peak to about 160% of baseline and a subsequent plateau of 140% of baseline for the rest of the cocaine intake period. In cocaine-naive animals, yoked cocaine injections raised ACh levels to the 140% plateau but did not cause the initial 160% peak. In cocaine-trained animals that received unexpected saline (extinction conditions) rather than the expected cocaine, the initial peak was seen but the subsequent plateau was absent. VTA ACh levels played a causal role and were not just a correlate of cocaine-seeking. Blocking muscarinic input to the VTA increased cocaine intake; the increase in intake offset the decrease in cholinergic input, resulting in the same VTA dopamine levels as were seen in the absence of the ACh antagonists. Increased VTA ACh levels (resulting from 10 uM VTA neostigmine infusion) increased VTA dopamine levels and reinstated cocaine-seeking in cocaine-trained animals that had undergone extinction; these effects were strongly attenuated by local infusion of a muscarinic antagonist and weakly attenuated by a nicotinic antagonist. These findings identify two cholinergic responses to cocaine self-administration--an unconditioned response to cocaine itself and a conditioned response triggered by cocaine-predictive cues--and confirm that these cholinergic responses contribute to the control of cocaine-seeking. You, Z.-B., Wang, B., Zitzman, D., and Wise, RA. Journal of Neuroscience, 28, pp. 9021-9029, 2008.

Cocaine Serves as a Peripheral Interoceptive Conditioned Stimulus for Central Glutamate and Dopamine Release

Intravenous injections of cocaine HCl are habit-forming because, among their many actions, they elevate extracellular dopamine levels in the terminal fields of the mesocorticolimbic dopamine system. This action, thought to be very important for cocaine's strong addiction liability, is believed to have very short latency and is assumed to reflect rapid brain entry and pharmacokinetics of the drug. However, while intravenous cocaine HCl has almost immediate effects on behavior and extracellular dopamine levels, recent evidence suggests that its central pharmacological effects are not evident until 10 or more seconds after IV injection. Thus the immediate effects of a given intravenous cocaine injection on extracellular dopamine concentration and behavior appear to occur before there is sufficient time for cocaine to act centrally as a dopamine uptake inhibitor. To explore the contribution of peripheral effects of cocaine to the early activation of the dopamine system, IRP researchers used brain microdialysis to measure the effects of cocaine methiodide (MI)--a cocaine analogue that does not cross the blood brain barrier--on glutamate (excitatory) input to the dopamine cells. IP injections of cocaine MI were ineffective in cocaine-naive animals but stimulated ventral tegmental glutamate release in rats previously trained to lever-press for cocaine HCl. This peripherally triggered glutamate input was sufficient to reinstate cocaine-seeking in previously trained animals that had undergone extinction of the habit. These findings offer an explanation for short-latency behavioral responses and immediate dopamine elevations seen following cocaine injections in cocaine-

experienced but not cocaine-naive animals. Wise, R.A., Wang, B., and You, Z.-B. Public Library of Science One, 3, e2846.

Medicinal Chemistry Section, Medications Discovery Research Branch

Structure-Activity Relationships for a Novel Series of Dopamine D2-like Receptor Ligands

Discovering dopamine D2-like receptor subtype-selective ligands has been a focus of significant investigation. The D2R-selective antagonist L741,626 (Ki D2R:D3R 11.2:163 nM) has previously provided a lead template for chemical modification. In the present study, a series of analogues was synthesized wherein the piperidine of L741,626 was replaced by a tropane ring that reversed the selectivity seen in the parent compound, in human hD2LR- or hD3R-transfected HEK 293 cells (Ki D2R:D3R 33.4:15.5 nM). Further exploration of both N- and aryl ring-substituted analogues resulted in the discovery of several high affinity D2R/D3R ligands with 3-benzofurylmethyl-substituents that induced high affinity not achieved in similarly N-substituted piperidine analogues, and significantly (470-fold) improved D3R binding affinity compared to the parent ligand. X-Ray crystallographic data revealed a distinctive spatial arrangement of pharmacophoric elements in the piperidinol vs tropine analogues that provide clues for the diversity in structure-activity relationships at the D2 and D3 receptor subtypes. Paul, N.M., Taylor, M., Kumar, R., Dechamps, J.R., Luedtke, R.R., and Newman, A.H. Journal of Medicinal Chemistry, 51, pp. 6095-6109, 2008.

Director's Report to the National Advisory Council on Drug Abuse - February, 2009

Program Activities

New NIDA PAs and RFAs

On August 27, 2008, NIDA reissued an RFA entitled **Medications Development Centers of Excellence (P50)**. This Funding Opportunity Announcement (FOA) encourages grant applications for Medications Development Centers of Excellence (MDCEs) that conduct drug abuse and addiction research, and that have outstanding innovative science and are multidisciplinary, thematically integrated, synergistic, and are/will be serving as national resources for the NIDA research fields. The MDCEs should be dedicated to clinical research directed towards the identification, evaluation, and development of safe and effective medications for treatment of substance related disorders, alone or with comorbid conditions.

In 2008, NIDA issued a new SBIR Contract Proposal entitled **Development of Therapeutic Agents for Substance Use Disorders (105)**. The purpose of this FOA is to support pilot clinical studies of medications for investigation as possible treatments for Substance Related Disorders (SRDs). The neurophysiological underpinnings of substance abuse appear to involve numerous neurotransmitter systems including opioid, dopamine, serotonin, GABA and glutamate across multiple brain regions. Small businesses have used government grant programs to conduct basic research and early preclinical testing; however, many of these projects are still in an early drug development stage and are not yet candidates for capital funding. Thus, the short-term goal of this SBIR contract is to create a mechanism of 'bridge funding' whereby novel therapeutic agents or immunotherapies that have demonstrated promising pre-clinical findings can be further evaluated in clinical trials. It is anticipated that these funds, long term, will help shepherd promising products from 'bench to bedside'.

On October 2, 2008, NIDA issued a Program Announcement entitled **Drug Abuse Epidemiology and Services Research in Cooperation with the Clinical and Translational Science Awards Consortium (R01) PAS-09-001**. Through this program announcement with set aside (PAS), NIDA invites applicants to develop innovative drug abuse epidemiology or health services research in cooperation with academic centers supported through the NIH Clinical and Translational Science Awards (CTSA) consortium. A major NIH initiative, the CTSA consortium is transforming how clinical and translational research is conducted, building an infrastructure for multidisciplinary researchers and clinicians to perform research and develop new treatments more efficiently. As a part of this infrastructure, CTSA sites have established partnerships with a range of clinical settings and have access to large, multi-generational population cohorts. These features of the CTSA sites offer a unique opportunity for researchers to integrate drug abuse epidemiology and health services research in these settings. Applicants are asked to propose innovative drug abuse research which builds upon the resources available at CTSA sites, resources which would include CTSA efforts to strengthen networks of clinical sites and to establish innovative information technologies, phenotyping systems, and biobanks. A broad range of drug abuse epidemiology and health services research areas will be supported under the auspices of this FOA.

On October 21, 2008, NIDA issued a Program Announcement entitled **Diversity-promoting Institutions Drug Abuse Research Program (DIDARP) (R24) PAR-09-011**. This FOA encourages Research Project Grant (R24) applications from institutions that historically and/or currently serve students from diverse and disadvantaged backgrounds that aim to increase their capacity to conduct drug abuse and addiction research. The applications should propose to foster the research career

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development of a diverse cadre of faculty, students and staff who are currently underrepresented in drug abuse research, and to enhance research infrastructure at the institution.

On October 29, 2008, NIDA issued a Program Announcement entitled **International Research Collaboration on Drug Abuse and Addiction Research (R01) PA-09-020**. This Program Announcement (PA) solicits collaborative research proposals on drug abuse and addiction that take advantage of special opportunities that exist outside the United States. Special opportunities include access to unusual talent, resources, populations, or environmental conditions in other countries that will speed scientific discovery. Projects must have relevance to the mission of NIDA and where feasible should address NIDA's scientific priority areas. While the priorities will change from year to year, in FY09 priority areas include: linkages between HIV/AIDS and drug abuse, methamphetamine abuse, inhalant abuse, smoking during pregnancy, and drugs and driving.

On October 29, 2008, NIDA issued a Program Announcement entitled **International Research Collaboration on Drug Abuse and Addiction Research (R21) PA-09-021**. This Funding Opportunity Announcement (FOA) solicits collaborative research proposals on drug abuse and addiction that take advantage of special opportunities that exist outside the United States. Special opportunities include access to unusual talent, resources, populations, or environmental conditions in other countries that will speed scientific discovery. Projects must have relevance to the mission of NIDA and where feasible should address NIDA's scientific priority areas. While the priorities will change from year to year, in FY09 priority areas include: linkages between HIV/AIDS and drug abuse, methamphetamine abuse, inhalant abuse, smoking during pregnancy, and drugs and driving.

On October 29, 2008, NIDA issued a Program Announcement entitled **International Research Collaboration on Drug Abuse and Addiction Research (R03) PA-09-022**. This Funding Opportunity Announcement (FOA) solicits collaborative research proposals on drug abuse and addiction that take advantage of special opportunities that exist outside the United States. Special opportunities include access to unusual talent, resources, populations, or environmental conditions in other countries that will speed scientific discovery. Projects must have relevance to the mission of NIDA and where feasible should address NIDA's scientific priority areas. While the priorities will change from year to year, in FY09 priority areas include: linkages between HIV/AIDS and drug abuse, methamphetamine abuse, inhalant abuse, smoking during pregnancy, and drugs and driving.

On December 12, 2008, NIDA issued a Program Announcement entitled **Pre-Application for the 2009 NIDA Avant-Garde Award Program for HIV/AIDS Research (X02) PAR-09-044**. The NIDA Avant-Garde Award Program for HIV/AIDS Research is meant to complement NIDA's traditional investigator-initiated grant programs by supporting individual scientists of exceptional creativity who propose high-impact research that will open new avenues for prevention and treatment of HIV/AIDS among drug abusers. The term "avant-garde" is used to describe highly innovative approaches that have the potential to be transformative-- open new areas of research or lead to new avenues of treatment and prevention for HIV/AIDS among drug abusers. The proposed research should reflect ideas substantially different from those already being pursued by the investigator or others. The research proposed must be in an area described in the Trans - NIH Plan for HIV-Related Research. The purpose of this FOA is to solicit applications for the Avant-Garde Award. The X02 application will be reviewed by external reviewers to identify the most outstanding applications (applications from individuals of exceptional creativity who propose highly significant and innovative projects that are not appropriate for traditional grant mechanisms). Those investigators whose submissions are judged to be the most outstanding will be notified of the opportunity to submit full applications under RFA-DA-09-011. All awards will be made under RFA-DA-09-011. No awards will be made under this announcement.

On December 10, 2008, NIDA issued an RFA entitled **2009 NIDA Avant-Garde Award Program for HIV/AIDS Research (DP1) RFA-DA-09-011**. The NIDA Avant-Garde Award Program for HIV/AIDS Research is meant to complement NIDA's traditional investigator-initiated grant programs by supporting individual scientists of exceptional creativity who propose high-impact research that will open new avenues for prevention and treatment of HIV/AIDS among drug abusers. The term "avant-garde" is used to describe highly innovative approaches that have the potential to be transformative-- open new areas of research or lead to new avenues of treatment and prevention for HIV/AIDS among drug abusers. The proposed research should reflect

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ideas substantially different from those already being pursued by the investigator or others. The research proposed must be in an area described in the Trans - NIH Plan for HIV-Related Research. The 2009 Avant-Garde Award competition will proceed in two phases. The first phase is a pre-application phase in response to PAR-09-044. 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 2009 Avant-Garde awardees will be selected from this group of applicants. Application Due Date for this RFA: June 2, 2009.

On January 7, 2009, NIDA issued a Program Announcement entitled **Imaging - Science Track Award for Research Transition (I/START) [R03] PAR-09-073**. This funding opportunity announcement (FOA) encourages Small Research Grant (R03) applications to facilitate the entry of investigators to the area of neuroimaging, including both new investigators and established investigators seeking to adopt neuroimaging methodologies in their research programs. The R03 is intended to support small research projects that can be carried out in a short period of time with limited resources.

On September 12, 2008, NIDA issued an RFA entitled **The Interaction of HIV, Drug Use, and the Criminal Justice System (R01) RFA-DA-09-007**. This initiative solicits R01 applications that link drug abuse, HIV/AIDS prevention and the criminal justice system. Applications responsive to this FOA should conduct intervention research or propose descriptive research that can clearly lead to effective new interventions. Letters of Intent Receipt Date for this RFA: October 27, 2008; Application Due Date: November 25, 2008.

On September 12, 2008, NIDA issued an RFA entitled **Exploratory Centers for Translational Research on the Clinical Neurobiology of Drug Addiction (P20) RFA-DA-09-012**. This solicitation invites applications for the development of Exploratory Translational Research Centers on the clinical neurobiology of drug abuse and addiction. For purposes of this FOA, an Exploratory Translational Research Center is defined as an entity with a strong primary human neurobiology focus in which preclinical research is included to directly inform or provide a mechanistic foundation for the human neuroscience/neurobiological research. Letters of Intent Receipt Date for this RFA: January 27, 2009; Application Receipt Date: February 27, 2009.

On October 1, 2008, NIDA issued an RFA entitled **Behavioral Pharmacology and Genetics: Translating and Targeting Individual Differences (R03) RFA-DA-09-016**. Individual differences in response to drugs of abuse may confer vulnerability or resistance to drug abuse or the development of addiction. Several lines of evidence indicate that genetic variation contributes to drug abuse and addiction as well as to the propensity to use specific classes of drugs, such as psychostimulants, opiates, marijuana and nicotine. Recently developed genetic methodologies make it possible to better understand drug abuse phenotypes in terms of underlying genetic factors. This FOA seeks applications that use controlled, human laboratory-based experimental techniques for the measurement of behavior, combined with genetic analyses, to study drug abuse phenotypes and/or endophenotypes, and their relationship to (a) individual differences in response to drugs of abuse; (b) individual differences in the consequences of repeated abuse; or (c) pharmacogenetic differences in response to putative or currently used pharmacotherapeutic agents for treating addiction. Research in these areas may identify genetic variations that will help define the biochemical mechanisms underlying drug effects and the associated biological and/or behavioral processes responsible for individual differences, and may suggest genetically targeted pharmacotherapeutic approaches for treating addiction. Letters of Intent Receipt Date for this RFA: December 29, 2008; Application Due Date: January 27, 2009.

On October 1, 2008, NIDA issued an RFA entitled **Biosignatures of Chronic Drug Exposure (R21) RFA-DA-09-022**. The goal of this funding Opportunity Announcement (FOA) is to discover peripheral biosignatures of drug exposure. In relation to this FOA, biosignatures are defined as biological indicators obtainable through assays, which can be used to ascertain facts about an individual's past exposure to drugs of abuse. Biosignature could be comprised of more than one biomarker. The total number of biomarkers must be reasonably limited to address the developability of the screening assay. This FOA would support high risk projects to search for peripheral, not associated with the central nervous system, biosignatures (not drug or drug metabolites) that could serve as surrogates to monitor changes that are taking place in the brain in response to illicit and licit drug exposure, withdrawal or relapse. These projects are intended to be feasibility projects using animal models

only to identify appropriate clinically accessible biomaterial (e.g., blood, lymphocytes, bladder epithelial cells, stem cells) and to identify the best class or classes of molecules (proteins, peptides, RNA, miRNA, etc.) suitable for assay development . These feasibility projects are intended to address technical issues such as sensitivity and signal-to-noise ratio, in addition to predictive validity. Letters of Intent Receipt Date for this RFA: December 29, 2008; Application Due Date: January 27, 2009.

On October 16, NIDA issued an RFA entitled **Interactions between Physical Activity and Drug Abuse (R01) RFA-DA-09-013**. The goal of this Funding Opportunity Announcement (FOA) is to stimulate investigations, using animal models or human subjects, of neurobiological and behavioral mechanisms that underlie the effects of physical activity on brain function across the lifespan as well as research designed to improve the translation of existing knowledge of the effects of exercise and physical activity into strategies for the prevention and treatment of drug abuse. The proposed line of investigation may focus on any neurobiological, behavioral or cognitive process that has been demonstrated to be affected by drugs of abuse or behaviors related to drug abuse. The research may be conducted in healthy individuals or, if scientifically appropriate, may include substance-abusing populations. All applications, however, must address how the proposed investigations are relevant to the understanding and/or treatment of substance abuse or how they may be implemented in substance abusing populations. Letters of Intent Receipt Date for this RFA: December 29, 2008; Application Due Date: January 28, 2009.

On October 17, 2008, NIDA issued an RFA entitled **Interactions between Physical Activity and Drug Abuse (R03) RFA-DA-09-014**. The goal of this Funding Opportunity Announcement (FOA) is to stimulate investigations (using animal models or human subjects) of neurobiological and behavioral mechanisms that underlie the effects of physical activity on brain function across the lifespan as well as research designed to improve the translation of existing knowledge of the effects of exercise and physical activity into strategies for the prevention and treatment of drug abuse. The proposed line of investigation may focus on any neurobiological, behavioral or cognitive process that has been demonstrated to be affected by drugs of abuse or behaviors related to drug abuse. The research may be conducted in healthy individuals or, if scientifically appropriate, may include substance-abusing populations. All applications, however, must address how the proposed investigations are relevant to the understanding and/or treatment of substance abuse or how they may be implemented in substance abusing populations. Letters of Intent Receipt Date: December 29, 2008; Application Due Date: January 28, 2009.

On November 5, 2008, NIDA issued an RFA entitled **Brain Imaging Studies of Negative Reinforcement in Humans (R01) RFA-DA-09-008**. This FOA solicits Research Project Grant (R01) applications from institutions/organizations that propose to investigate brain processes in humans underlying how aversive events control behavior in order to stimulate a program of clinical neuroscience research on negative reinforcement/avoidance learning. On the basis of pre-clinical studies, negative reinforcement has re-emerged as a contributing factor in the basic processes of substance abuse. The range of processes engaged by the human brain to avoid aversive outcomes are much less well understood than that of brain processes engaged by positive outcomes. For the purpose of this FOA negative reinforcement and avoidance learning are considered synonymous and refer to behaviors and cognitive strategies that are learned and maintained in order to minimize or eliminate the occurrence of aversive events. Aversive events may be either environmental stimuli or internal states. Applications for this FOA are expected to propose hypotheses-testing studies regarding the brain regions or processes in humans that underlie avoidance learning including behaviors and cognitive strategies maintained by negative reinforcement. The studies proposed in response to this FOA may be conducted in healthy individuals, substance-abusing populations (current or abstinent) or individuals at risk for substance abuse. However, all applications must address how the proposed investigations are relevant to advancing the understanding of substance abuse. Letters of Intent Receipt Date for this RFA: January 19, 2009; Application Due Date: February 19, 2009.

On November 5, 2008, NIDA issued an RFA entitled **Brain Imaging Studies of Negative Reinforcement in Humans (R21) RFA-DA-09-009**. This FOA issued by National Institute on Drug Abuse, National Institutes of Health, solicits Exploratory/Developmental Grant (R21) applications from institutions/ organizations that propose to investigate brain processes in humans underlying how aversive events control behavior in order to stimulate a program of clinical neuroscience research on negative reinforcement / avoidance learning. On the basis of pre-clinical studies, negative reinforcement has re-emerged as a contributing factor in the basic

processes of substance abuse. The range of processes engaged by the human brain to avoid aversive outcomes are much less well understood than that of brain processes engaged by positive outcomes. For the purpose of this FOA negative reinforcement and avoidance learning are considered synonymous and refer to behaviors and cognitive strategies that are learned and maintained in order to minimize or eliminate the occurrence of aversive events. Aversive events may be either environmental stimuli or internal states. Applications for this FOA are expected to propose exploratory, hypotheses-generating or proof of concept studies regarding the brain regions or processes in humans that underlie avoidance learning including behaviors and cognitive strategies maintained by negative reinforcement. This FOA is also appropriate for the development of new tasks in humans that may be used in future brain imaging studies to target specific brain processing areas affected by negative reinforcement/avoidance learning. The studies proposed in response to this FOA may be conducted in healthy individuals, substance-abusing populations (current or abstinent) or individuals at risk for substance abuse. However, all applications must address how the proposed investigations are relevant to advancing the understanding of substance abuse. Letters of Intent Receipt Date for this RFA: January 19, 2009; Application Due Date: February 19, 2009.

On November 5, 2008, NIDA issued an RFA entitled **Secondary Data Analyses for Substance Abuse Research (R21/R33) RFA-DA-09-020**. This funding opportunity announcement (FOA), invites Phased Innovation (R21/R33) grant applications from organizations/institutions that propose to conduct secondary analyses of rich biological data sets related to substance abuse research and to advance data and computational infrastructure relevant to the proposed analyses. Letters of Intent Receipt Date for this RFA: December 29, 2008; Application Due Date: January 28, 2009.

PAs and RFAs Issued with Other NIH Components/Agencies

On October 6, 2008, NIDA, in collaboration with a number of other NIH components, issued a Program Announcement entitled **Short Courses on Mathematical, Statistical, and Computational Tools for Studying Biological Systems (R25) PA-09-002**. This FOA encourages applications for Research Education Grants (R25) from institutions and organizations to conduct workshops and short courses to improve integration of mathematical, statistical, and computational approaches into biological and/or behavioral research. Support will be limited to activities that reach a wide audience of researchers. The program announcement is NOT intended for university course or curriculum development.

On December 12, 2008, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement entitled **NIH Pathway to Independence Award (K99/R00) PA-09-036**. The overall goal of NIH-supported career development programs is to help ensure that a diverse pool of highly trained scientists are available in adequate numbers and in appropriate research areas to address the Nation's biomedical, behavioral, and clinical research needs. The primary purpose of the Pathway to Independence Award (K99/R00) program is to increase and maintain a strong cohort of new and talented NIH-supported independent investigators. The program is designed to facilitate a timely transition from a mentored postdoctoral research position to a stable independent research position with independent NIH or other independent research support at an earlier stage than is currently the norm.

On December 11, 2008, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement entitled **Midcareer Investigator Award in Patient-Oriented Research (K24) PA-09-037**. The overall goal of NIH-supported career development programs is to help ensure that a diverse pool of highly trained scientists are available in adequate numbers and in appropriate research areas to address the Nation's biomedical, behavioral, and clinical research needs. The purpose of the NIH Midcareer Investigator Award in Patient-Oriented Research (K24) is to provide support to mid-career health-professional doctorates or equivalent who are typically at the Associate Professor level or the equivalent for protected time to devote to patient-oriented research (POR) and to act as research mentors primarily for clinical residents, clinical fellows and/or junior clinical faculty.

On December 11, 2008, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement entitled **Independent Scientist Award (K02) PA-09-038**. The overall goal of NIH-supported career development programs is to help ensure that a diverse pool of highly trained scientists are available in adequate numbers and in appropriate research areas to address the Nation's biomedical, behavioral, and clinical research needs. The purpose of the NIH Independent Scientist Award (K02) is to foster the development of outstanding scientists and enable them

to expand their potential to make significant contributions to their field of research. The K02 award provides three, four, or five years of salary support and "protected time" for newly independent (see IC provisions) scientists who can demonstrate the need for a period of intensive research focus as a means of enhancing their research careers. Each independent scientist career award program must be tailored to meet the individual needs of the candidate.

On December 11, 2008, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement entitled **Mentored Quantitative Research Development Award (K25) PA-09-039**. The overall goal of NIH-supported career development programs is to help ensure that a diverse pool of highly trained scientists are available in adequate numbers and in appropriate research areas to address the Nation's biomedical, behavioral, and clinical research needs. The purpose of the Mentored Quantitative Research Career Development Award (K25) is to attract to NIH-relevant research those investigators whose quantitative science and engineering research has thus far not been focused primarily on questions of health and disease. The K25 award will provide support and "protected time" for a period of supervised study and research for productive professionals with quantitative (e.g., mathematics, statistics, economics, computer science, imaging science, informatics, physics, chemistry) and engineering backgrounds to integrate their expertise with NIH-relevant research.

On December 11, 2008, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement entitled **Mentored Research Scientist Development Award (K01) PA-09-040**. The overall goal of NIH-supported career development programs is to help ensure that a diverse pool of highly trained scientists are available in adequate numbers and in appropriate research areas to address the Nation's biomedical, behavioral, and clinical research needs. The purpose of the NIH Mentored Research Scientist Development Award (K01) is to provide support and "protected time" (three, four, or five years) for an intensive, supervised career development experience in the biomedical, behavioral, or clinical sciences leading to research independence. Although all of the participating NIH Institutes and Centers (ICs) use this mechanism to support career development experiences that lead to research independence, some ICs use the K01 award for individuals who propose to train in a new field or for individuals who have had a hiatus in their research career because of illness or pressing family circumstances. Other ICs utilize the K01 award to increase research workforce diversity by providing enhanced research career development opportunities.

On December 11, 2008, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement entitled **Mentored Clinical Scientist Research Career Development Award (K08) PA-09-042**. The overall goal of NIH-supported career development programs is to help ensure that a diverse pool of highly trained scientists are available in adequate numbers and in appropriate research areas to address the Nation's biomedical, behavioral, and clinical research needs. The primary purpose of the NIH Mentored Clinical Scientist Research Career Development Awards (K08) program is to prepare qualified individuals for careers that have a significant impact on the health-related research needs of the Nation. This program represents the continuation of a long-standing NIH program that provides support and "protected time" to individuals with a clinical doctoral degree for an intensive, supervised research career development experience in the fields of biomedical and behavioral research, including translational research.

On December 11, 2008, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement entitled **Mentored Patient-Oriented Research Career Development Award (K23) PA-09-043**. The overall goal of NIH-supported career development programs are to help ensure that a diverse pool of highly trained scientists are available in adequate numbers and in appropriate research areas to address the Nation's biomedical, behavioral, and clinical research needs. The purpose of the NIH Mentored Patient-Oriented Research Career Development Award (K23) is to support the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research.

On September 30, 2008 NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Replication and Fine-Mapping Studies for the Genes Environment and Health Initiative (GEI) (R01) RFA-CA-09-003**. This funding opportunity announcement (FOA), administered by the National Cancer Institute, is a part of the Genes, Environment, and Health Initiative (GEI) sponsored by the National Institutes of Health (NIH). The purpose of this FOA is to provide support for replication and fine-mapping studies of genetic regions that are putatively associated

with common complex traits, primarily those identified by genome-wide association studies (GWAS). The proposed projects should aim to enhance the identification of causal variants influencing complex diseases. Any phenotype may be appropriate for these projects (i.e., studies need not be oriented on cancer or cancer-related phenotypes). This FOA will not support recruitment of human subjects, collection of human specimens, collection of medical or phenotype data, studies using animal models, or discovery genome-wide association efforts. Letters of Intent Receipt Date for this RFA: October 24, 2008; Application Due Date: December 1, 2008.

On October 9, 2008, NIDA, in collaboration with NIDDK and NIBIB, issued an RFA entitled Neuroimaging in Obesity Research (R01) RFA-DK-08-009. This FOA solicits Research Project Grant (R01) applications from institutions/ organizations that propose to use neuroimaging approaches in obesity research in human subjects and animal models. Many areas of the brain interact or communicate with other organs to control eating behavior, physical activity and energy metabolism, and functional neuroimaging holds enormous promise for expanding our understanding of how food intake and energy expenditure are mismatched in a setting of abundantly available nutrients, leading to excessive fat storage. Letters of Intent Receipt Date for this RFA: February 18, 2009; Application Due Date: March 18, 2009.

On October 20, 2008, NIDA, in collaboration with NIAAA, issued an RFA entitled **The Mouse Gene Development Initiative (R01) RFA-DA-09-015**. This funding opportunity announcement (FOA), requests research grant applications that propose to 1) map traits associated with addiction by varying environmental factors at different states of development across inbred strains of mice including using, but not limited to, selective breeding strategies, recombinant inbred mice, the collaborative cross, and haplotype associative mapping with inbred strains; or 2) Identify epigenetic and genetic modifiers that under different environmental and developmental conditions produces different phenotypic outcomes in mice carrying a defined genetic variant, (e.g., knockout, CNVs). A separate paragraph in the section on Specific Requirements, Objectives, and Scope addresses the interest of NIAAA. Letters of Intent Receipt Date for this RFA: December 29, 2008; Application Due Date: January 27, 2009.

On October 24, 2008, NIDA, in collaboration with NINDS, issued an RFA entitled **Central Nervous System Intersections of Drug Addiction, Chronic Pain and Analgesia (R01) RFA-DA-09-017**. The purpose of this Funding Opportunity Announcement (FOA) is to encourage investigations of CNS changes that occur with chronic pain, and how these changes parallel those that occur with drug addiction. Of interest will be how chronic pain changes the CNS, how analgesics of various classes impact pain-induced CNS changes, and how analgesics in the absence of pain (some of which have abuse potential) produce CNS changes. The temporal course of these changes will also be of interest. A focus of this research will be comparing and contrasting these CNS changes in an effort to identify shared and unique mechanisms involved in pain, analgesia and drug abuse, as well as environmental and genetic factors that influence these changes. Letters of Intent Receipt Date for this RFA: December 29, 2008: Application Due Date: January 28, 2009.

On October 24, 2008, NIDA, in collaboration with NINDS, issued an RFA entitled **Central Nervous System Intersections of Drug Addiction, Chronic Pain and Analgesia (R21) RFA-DA-09-018**. The purpose of this Funding Opportunity Announcement (FOA) is to encourage investigations of CNS changes that occur with chronic pain and how these changes parallel those that occur with drug addiction. Of interest will be how chronic pain changes the CNS, how analgesics of various classes impact pain-induced CNS changes, and how analgesics in the absence of pain (some of which have abuse potential) produce CNS changes. The temporal course of these changes will also be of interest. A focus of this research will be comparing and contrasting these CNS changes in an effort to identify shared and unique mechanisms involved in pain, analgesia and drug abuse, as well as environmental and genetic factors that influence these changes. Letters of Intent Receipt Date for this RFA: December 29, 2008; Application Due Date: January 28, 2009.

On October 24, 2008, NIDA, in collaboration with NINDS, issued an RFA entitled **Central Nervous System Intersections of Drug Addiction, Chronic Pain and Analgesia (R03) RFA-DA-09-019**. The purpose of this Funding Opportunity Announcement (FOA) is to encourage investigation of CNS changes that occur with chronic pain, and how these changes parallel those that occur with drug addiction. Of interest will be how chronic pain changes the CNS, how analgesics of various classes impact pain-induced CNS changes, and how analgesics in the absence of pain (some of which have abuse potential) produce CNS changes. The temporal course of these

changes will also be of interest. A focus of this research will be comparing and contrasting these CNS changes in an effort to identify shared and unique mechanisms involved in pain, analgesia and drug abuse, as well as environmental and genetic factors that influence these changes. Letters of Intent Receipt Date for this RFA: December 29, 2008; Application Due Date: January 28, 2009.

On November 13, 2008, NIDA, in collaboration with NIMH, issued an RFA entitled **Education Programs of Excellence in Scientifically Validated Behavioral Treatment (R25) RFA-MH-09-110**. The purpose of this Funding Opportunity Announcement (FOA) is to support curriculum development to train clinician-scientists who can develop, test, and rapidly translate into practice innovative learning-based treatments in the addictive and mental disorders. A clinician-scientist is skilled in both clinical practice and clinical research. The goals in establishing the Programs of Excellence Award are to recognize and enhance current clinical training programs that teach and develop research-based clinical practices and to provide a model for clinician education nationwide. Letters of Intent Receipt Date for this RFA: December 14, 2008; Application Due Date: January 14, 2009.

On December 12, 2008 NIDA, in collaboration with NIAAA, issued an RFA entitled **Support Opportunity for Addiction Research (SOAR) for New Investigators (R03) RFA-DA-09-021**. This Funding Opportunity Announcement (FOA) is intended to support new investigator's on-going basic or clinical alcohol, drug abuse and/or related co-morbidity research. The primary goal of this Support Opportunity for Addiction Research (SOAR) is for new investigators to leverage existing research programs in order to strengthen, possibly expand, and/or further develop alcohol, drug abuse, and co-morbidity research. Letters of Intent Receipt Date for this RFA: February 3, 2009; Application Due Date: March 3, 2009.

On December 30, 2008, NIDA, in collaboration with NINDS and NIAAA, issued an RFA entitled **Optimization of Small Molecule Probes for the Nervous System (R21) RFA-NS-09-003**. The aim of this FOA is to facilitate the discovery of new small molecule probes for investigating biological function in the nervous system by providing funding for advanced medicinal chemistry and the biological testing of compounds. Eligible Investigators will have identified probe candidates via screening of small molecule collections, using in vitro assays of biological activity developed to interrogate these collections, and be able to show that the structural features of these small molecules are related to their biological activity. Project proposals should nominate small molecule probe candidates from distinct structural series for the further, iterative design and testing of analogues in structure-activity relationship studies, using in vitro assays of biological function adapted to the medium throughput screening requirements of this work. These studies should have the goal of developing a small molecule probe possessing the attributes (eg: affinity, selectivity, activity) required for its use in future pharmacological studies proposed by the investigator. Applicants are strongly encouraged to utilize publicly available cheminformatic capabilities for the acquisition of compounds, and semi-custom synthesis of analogues, which is required of these studies. Letters of Intent Receipt Date for this RFA: February 3, 2009; Application Due Date: March 3, 2009.

On January 13, 2009, NIDA, in collaboration with NIAAA, issued a Program Announcement entitled **Senior Scientist Research and Mentorship Award (K05) (PA-09-076)**. The purpose of the Senior Scientist Research and Mentorship Award (K05) is intended to provide protected time for outstanding senior scientists who have demonstrated a sustained high level of productivity conducting biomedical research relevant to the scientific mission of the appropriate institute to focus on their research and to provide mentoring of new investigators. The overall goal of NIH-supported career development programs is to help ensure that a diverse pool of highly trained scientists are available in adequate numbers and in appropriate research areas to address the Nation's biomedical, behavioral, and clinical research needs.

On January 22, 2009, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement entitled **PHS 2009-02 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42]) (PA-09-081)**. This FOA invites eligible United States small business concerns (SBCs) to submit Small Business Technology Transfer (STTR) grant applications. United States SBCs that have the research capabilities and technological expertise to contribute to the R&D mission(s) of the NIH awarding components identified in this FOA are encouraged to submit STTR grant applications in response to identified topics.

On January 22, 2009, NIDA, in collaboration with numerous other DHHS components, issued a Program Announcement entitled **PHS 2009-02 Omnibus Solicitation of**

the NIH, CDC, FDA and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44]) (PA-09-080). This FOA invites eligible United States small business concerns (SBCs) to submit Small Business Innovation Research (SBIR) grant applications. United States SBCs that have the research capabilities and technological expertise to contribute to the R&D mission(s) of the NIH, CDC, FDA and ACF awarding components identified in this FOA are encouraged to submit SBIR grant applications in response to identified topics.

Other Program Activities

The Recruitment & Training Program for Under-represented Populations is now accepting applications for Summer 2009. The NIDA IRP Recruitment & Training Program for Under-represented Populations (RTURP) is an intramural program that provides training opportunities for students from under-represented groups who are interested in the scientific basis of drug abuse. In this program, students gain basic science and/or clinical laboratory experience, attend student seminars and participate in a summer poster presentation. The goal of this program is to expose students to the realities of research, from experimental design to data analysis, interpretation and presentation. To request an application or to receive additional information, contact: Christie Brannock at cbrann@intra.nida.nih.gov.

Clinical Trials Network (CTN) Update

Protocols: A total of 39 protocols have been initiated since 2001, including multi-site clinical trials (26), multi-site surveys (3), studies in special populations (5), and secondary analyses of data across various trials (5). Twenty trials have completed data lock; two are in the follow-up, data-lock phase; two are currently enrolling and two will enroll patients in 2009. In addition, 18 ancillary studies have been supported by CTN and non-CTN funds. Seven protocols are in the development phase. Nearly 9,500 participants have enrolled in studies.

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

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

Primary outcome papers are published or in press for:

- Protocol CTN 0003, Bup/Nx: Comparison of Two Taper Schedules
- Protocol CTN 0004, MET (Motivational Enhancement Treatment) To Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse
- Protocol CTN 0008, A Baseline for Investigating Diffusion of Innovation
- Protocol CTN 0009, Smoking Cessation Treatment with Transdermal Nicotine Replacement Therapy in Substance Abuse Rehabilitation Programs
- Protocol CTN 0011, A Feasibility Study of a Telephone Enhancement Procedure (TELE) to Improve Participation in Continuing Care Activities
- Protocol CTN 0012, Characteristics of Screening, Evaluation, and Treatment of HIV/AIDS, Hepatitis C Viral Infection, and Sexually Transmitted Infections in Substance Abuse Treatment Programs
- Protocol CTN 0013 (Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome In Pregnant Substance Abusers)
- Protocol CTN 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)

In addition, the following protocols have submitted primary papers:

- Protocol CTN 0015 (Women's Treatment for Trauma and Substance Use Disorder: A Randomized Clinical Trial)
- 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 Attention Deficit Hyperactivity Disorder (ADHD)

The following protocol has locked the data:

- Protocol CTN 0014, Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT)

The following protocols have ended new enrollment, and are in the follow-up or data-lock phase:

- 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) (anticipate lock January 2009)
- 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 is being carried out in 9 sites, and reached its enrollment target of 648 participants. The last participant into phase 1 was randomized on November 11, 2008. Randomization of enrolled patients into phase 2 continues.
- CTN 0030A1, Collection of Economic Data for the Prescription Opioid Addiction Treatment Study. This ancillary study is conducted in collaboration with NIDA DESPR.
- CTN 0030A2, Effects of Chronic Opioids is conducted in collaboration with NIDA DCNBR to obtain anatomical MR scans in subjects with a history of opioid use to evaluate neural changes that may occur with such use and compare with age/gender healthy controls.
- CTN 0030A3, POATS Long-Term Follow Up Study (LTFU) is being developed to examine long-term outcomes for individuals with opioid analgesic (OA) dependence who participated in CTN-0030.

Two protocols are currently enrolling:

- 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). Enrollment began in April 2006. As of November 30, 2008, there were 943 randomized participants.
- CTN 0027A1, START Pharmacogenetics: Exploratory Genetic Studies In Starting Treatment With Agonist Replacement Therapies.
- 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.
- 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. As of November 30, 2008, all ten sites (three Wave 1, seven Wave 2) are actively recruiting and have randomized a total of 111 participants to either the STAGE-12 or the TAU condition.
- CTN 0031A1, An Evaluation of Neurocognitive Function, Oxidative

Damage, and Their Association with Treatment Outcomes in Methamphetamine and Cocaine Abusers. Potential participants are being recruited at six sites. As of November 30, 2008, 58 participants have been enrolled in this ancillary study.

- CTN 0031A2, The Role of Alcohol Consumption in Classifications of Alcohol Use Disorders: A Clinical Study. It investigates the utility of adding a frequency measure of alcohol consumption (i.e., the first three items of the Alcohol Use Disorders Identification Test [AUDIT-C]), to the DSM-IV diagnostic criteria for alcohol use disorders. This study is funded by an MOU between NIDA and NIAAA. Data will be collected for this study throughout the life of the main STAGE-12 study.
- 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 will form the foundation for an R01 grant application.

The following protocols are in the development phase:

- Protocol CTN 0032, HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the U.S. This study seeks 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 seeks to enroll more than 1,200 participants across approximately 12 sites in the US. Dr. Lisa Metsch is the PI at the Florida Node, and Dr. Grant Colfax is the co-PI at the CA/AZ node. All 12 sites have been selected, seven of which have received IRB approval through a central mechanism. An eight center received approval by the local IRB, and the four other centers are expected to have local IRB approval by the end of this 2008. Centers are located in Missouri, New Mexico, Arizona, South Carolina, North Carolina, Connecticut, Maryland, Virginia, Pennsylvania and Oregon. Mandatory national training took place in Bethesda, MD from September 9 through September 12, with continuous post-training sessions by Webinar and face-to-face counselor training sessions. The electronic instruments, including Web-based ACASI have been completed and are being tested. Patient enrollment is planned to start on January 5, 2009.
- CTN 0032A1, Economic Analysis of HIV Rapid Testing in Drug Abuse Treatment Programs. This is an ancillary study to protocol CTN 0032, to conduct 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 Schakman. The project is in collaboration with NIDA's DESPR.
- Protocol CTN 0033, 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. Investigators plan to start data collection in the fall.
- Protocol CTN 0034, 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, 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 will be conducted in the CA-AZ Node.
- Protocol CTN 0036, 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 will be conducted in the Texas Node.

- 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 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. The trial will randomize individuals entering outpatient treatment for substance use disorders to receive 24 weeks of either: (1) Treatment as Usual (TAU), reflecting standard treatment at the outpatient programs in which participants are enrolled, or (2) TAU plus the Therapeutic Education System (TES), a computerized psychosocial intervention with incentives targeting abstinence from one's primary drug of abuse. The primary outcome measure is drug abstinence (as measured via urine testing and confirmed via self-report) and will also evaluate if improved outcomes are maintained at 3 and 6 months post-intervention. Additionally, the study will perform a comprehensive economic analysis of adding TES to TAU.

In addition to the primary CTN trials, there are currently five secondary analyses using data across several of the completed 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 40 funded studies supported by independent grants that use CTN studies as a platform.

NIDA's New and Competing Continuation Grants Awarded Since September 2008

Aizenman, Elias -- University of Pittsburgh at Pittsburgh
Methamphetamine Induces a Complex Microglia-Neuronal Crosstalk

Alexander-Eitzman, Ben E. -- Washington University
Substance Abuse, Marginalization, and Homelessness: A Bayesian Perspective

Altice, Frederick L. -- Yale University
Intervention of HIV, Drug Use and the Criminal Justice System in Malaysia

Beeler, Jeff A. -- University of Chicago
Pharmacological Targets Facilitating Non-Drug Reward and Extinction of Drug-Seeking

Benoit, Ellen -- National Development and Research Institutes
Feasibility of Recruiting Nondisclosing Black MSM/W for Drug Use /HIV Research

Berwid, Olga G. -- Queens College
Impact of Stimulant Treatment on Neural Reward Circuitry Functioning in ADHD

Bilbo, Staci D. -- Duke University
Early Life Origins of Risk and Resilience to Drugs of Abuse: Role of Glial Priming

Borrelli, Emiliana -- University of California, Irvine

Presynaptic Versus Postsynaptic Functions of Dopamine D2 Receptors in the Response

Botvin, Gilbert J. -- Weill Medical College of Cornell University
A Collaborative System Approach for the Diffusion of Evidence-Based Prevention

Brady, Kathleen T. -- Medical University of South Carolina
The Impact of Real-Time fMRI Feedback on Response to Nicotine Cues

Brenhouse, Heather C. -- McLean Hospital (Belmont, MA)
Facilitating Extinction in Adolescents

Brisson, Anne Elizabeth -- Columbia University, New York Morningside
Shield Central Asia: HIV Prevention with Injection Drug Users in Kyrgyzstan

Brouwer, Kimberly C. -- University of California, San Diego
HIV and STI Transmission Dynamics along Transport Routes Linking the Americas

Buch, Shilpa J. -- University of Kansas Medical Center
PLGA/Antisense IL-10: Gene Therapy for Cocaine Abusers with HAD

Burke, Jessica G. -- University of Pittsburgh at Pittsburgh
Patterns of Substance Use Among HIV Positive and Negative Aging MSM

Carroll, Frank I. -- Research Triangle Institute
Development of Ligands for Nicotinic Receptors

Carvelli, Lucia -- Vanderbilt University
Amphetamine Regulation of DAT Function in C Elegans

Cassidy, Jude A. -- University of Maryland, College Park Campus
Distress Tolerance: Links with Family Emotional Climate and Adolescent HIV Risk

Castillo, Pablo -- Yeshiva University
Presynaptic Forms of Long-Term Plasticity in the CNS

Chartoff, Elena H. -- McLean Hospital (Belmont, MA)
Role of AMPA Receptors in the Nucleus Accumbens Shell in Morphine Dependence

Chavkin, Charles -- University of Washington
The Role of Kappa Opioid Receptor-Induced Activation of Astrocytes

Chen, Chu -- Louisiana State University HSC, New Orleans
Astroglial Cells in Marijuana-Altered Synaptic Plasticity

Childress, Anna R. -- University of Pennsylvania
1 of 2: Real-Time fMRI Pattern Training for Treatment of Craving and Addiction

Chiu, Pearl H. -- Baylor College of Medicine
Localized and Distributed Real-Time fMRI Approaches to Facilitate Self Control

Chung, Hwan -- Michigan State University
A New Approach for the Analysis of Stage-Sequential Process in Substance Use Behavior

Cohen, Mark S. -- University of California, Los Angeles
Real-Time Automated Detection of Craving States with fMRI and EEG

Corso, Phaedra S. -- University of Georgia (UGA)
Economic Evaluation of Drug Abuse Prevention with Rural African American Youth

Cristea, Ileana M. -- Princeton University
Proteomic Tools to Uncover the Role of Chromatin Remodeling in HIV-1 Infection

De Lecea, Luis -- Stanford University
Optogenetic Manipulation of Brain Reward

Deleo, Joyce A. -- Dartmouth College
Microglial Regulation in Opioid Tolerance, Hyperalgesia and Addiction

Dewhurst, Stephen -- University of Rochester
Cerebrovascular Mechanisms in Methamphetamine-Mediated Exacerbation of NeuroAIDS

Dobs, Adrian S. -- Johns Hopkins University
Serum Sex Hormones and Cardiovascular Risk in the MACS

Dodge, Tonya -- Skidmore College
Steroid Use in Adolescents

D'onofrio, Gail -- Yale University
Models of SBIRT for Opioid Dependent Patients in the Emergency Department

Eby, Lillian T. -- University of Georgia (UGA)
Understanding the Adoption and Implementation of Tobacco-Free Regulation

Eisch, Amelia J. -- University of Texas, SW Medical Center/Dallas
Opiates and Adult Neurogenesis

El-Bassel, Nabila -- Columbia University, New York Morningside
Multimedia HIV/STI Prevention for Drug-Involved Female Offenders

Elmer, Gregory I. -- University of Maryland, Baltimore
Pattern Array: In Vivo Mining for Novel Psychoactive Drug Discovery

Foa, Edna B. -- University of Pennsylvania
Treatment of Smoking among Individuals with PTSD

Fountain, Stephen B. -- Kent State University at Kent
Adolescent Nicotine Exposure and Adult Cognitive Processes in Rats

Fox, Howard S. -- University of Nebraska Medical Center
Proteomic Strategies for AIDS and Drug Abuse - HIV and METH CNS Synergy

Friedmann, Peter D. -- Rhode Island Hospital (Providence, RI)
Treatment Study Using Depot Naltrexone (2/6) Rhode Island Protocol Treatment Site

Frost, Simon David William -- University of California, San Diego
Examining the Role of Venues in Structuring Sexual and Drug-Use Networks

Gabuzda, Dana H. -- Dana-Farber Cancer Institute
LPS and Monocyte Activation in HIV Neuropathogenesis

Gould, Thomas J. -- Temple University
Genetic, Behavioral, and Neurobiological Substrates of Nicotine Withdrawal

Groopman, Jerome E. -- Beth Israel Deaconess Medical Center
Inhibition of HIV at the Immune Synapse Utilizing Novel Ligands and Receptors

Gu, Howard H. -- Ohio State University
Mechanism of Drug Addiction

Hammond, Donna L. -- University of Iowa
Role of Medullary Substance P in Acute and Persistent Nociception

Hammond, Donna L. -- University of Iowa
Opioid Mechanisms of Analgesia

Haydon, Philip G. -- Tufts University, Boston
Roles for Gliotransmission in Substance Abuse

Hien, Denise A. -- City College of New York
A Randomized Trial of Concurrent Treatment for PTSD and Substance Dependence

Ho, Wenzhe -- Children's Hospital of Philadelphia
Methamphetamine and HIV Infection

Ho, Wenzhe -- Children's Hospital of Philadelphia
Drug Abuse, Sustance P and HIV

Hobrath, Judith Varady -- Southern Research Institute
Development of Opioid Receptor Models for Rational Design of Bifunctional Ligands

Hser, Yih-Ing -- University of California, Los Angeles
Reducing HIV/AIDS and Drug Abuse: Linking Compulsory Rehabilitation to Methadone

Hughes, John R. -- University of Vermont and State Agricultural College
Natural History of Attempts to Stop Smoking

Hughes, John R. -- University of Vermont and State Agricultural College
Attempts to Stop/Reduce Marijuana among Dependent Users

Jiang, Faming -- Sri International

Development of Photoaffinity Ligands for the Alpha3beta4 Nicotinic Acetylcholine

Johnson, Eric O. -- Research Triangle Institute
Genome-Wide Association Study of HIV-1 Host Genetics among Injection Drug Users

Kandel, Denise B. -- Columbia University Health Sciences
Nicotine Dependence in Early Adulthood

Keefe, Kristen A. -- University of Utah
Long-Term Consequences of Methamphetamine Toxicity

Kenny, Paul J. -- Scripps Research Institute
Role of Micrornas in the Mechanisms of Drug Dependence

Kharasch, Evan D. -- Washington University
Methadone and HIV Drug Interactions

Knackstedt, Lori A. -- Medical University of South Carolina
Striatal Glutamate Homeostasis and Cocaine Relapse

Knopik, Valerie S. -- Brown University
Prenatal Tobacco Exposure: Effects on Neuropsychological Outcomes and ADHD

Koek, Wouter -- University of Texas Health Science Center, San Antonio
Vulnerability to Opioids: A Mouse Model

Kosten, Thomas R. -- Baylor College of Medicine
Multisite Controlled Trial of Cocaine Vaccine (1of 6) Lead Site/Houston Treatment

Kral, Alexander H. -- Research Triangle Institute
International Feasibility Study of Pharmacy-Based HIV Prevention: San Francisco

Kumar, Anil -- University of Missouri, Kansas City
Methamphetamine and AIDS in a Non-Human Primate Model

Lai, Shenghan -- Johns Hopkins University
HIV Infection, Cocaine Use and Coronary Artery Disease In HIV+ African Americans

Lattal, Kennon Matthew -- Oregon Health and Science University
Behavioral and Epigenetic Mechanisms in Extinction of Cocaine-Induced Memories

Leonard, Noelle R. -- National Development and Research Institutes
Prevention Intervention for Drug Use and Related Behaviors with Incarcerated Youth

Letourneau, Elizabeth J. -- Medical University of South Carolina
Targeting HIV Risk Behaviors in Juvenile Drug Court-Involved Youth

Levin, Frances R. -- Columbia University Health Sciences
Multi-Site Controlled Trial of Cocaine Vaccine (6 of 6) Columbia University Site

Lile, Joshua Anthony -- University of Kentucky
GABA Drugs for Cannabis-Use Disorders: Initial Mechanistic Studies in Humans

Lochman, John E. -- University of Alabama in Tuscaloosa
Individual and Group Intervention Formats with Aggressive Children

Lyons, Thomas M. -- University of Illinois at Chicago
HIV Prevention for MSM Stimulant Users Focused on Healthy Sexuality

Mains, Richard E. -- University of Connecticut School of Medicine/Dentistry
Dissecting the Role of One Neuronal RhoGEF amongst Many: The Kalirin-7 Null Mouse

Markham, Richard B. -- Johns Hopkins University
Effect of Cocaine and LTR Polymorphism on HIV-1 Pathogenesis

Marlowe, Douglas B. -- Treatment Research Institute, Inc. (TRI)
Adaptive Services in Drug Court

Mason, Graeme F. -- Yale University
GABA Effects of Nicotine in Men and Women

McCance-Katz, Elinore F. -- University of California, San Francisco
Disulfiram Interactions with HIV Medications: Clinical Implications

McClernon, Francis Joseph -- Duke University
Brain Substrates of Extinction-Based Treatment for Nicotine Dependence

McCurdy, Sheryl A. -- University of Texas Health Science Center, Houston
Tanzania Aids Prevention Project - Vijana Wateja (Young Injectors) Study

McKay, Mary M. -- Mount Sinai School of Medicine of NYU
Family-Based Intervention for HIV+ Youth in Argentina

Mello, Nancy K. -- McLean Hospital (Belmont, MA)
Sex/Gender Factors in Nicotine Addiction

Meyer, Jerrold S. -- University of Massachusetts, Amherst
Neurobehavioral Effects of Combined MDMA (Ecstasy) and THC Exposure

Mocchetti, Italo -- Georgetown University
HIV Drug Abusers, Polymorphisms and Brain Plasticity

Monks, Terrence J. -- University of Arizona
Hepatic Metabolism and Susceptibility to Ecstasy Toxicity

Montaner, Julio Sergio Gonzalez -- University of California, San Diego
Seek and Treat for Optimal Outcomes and Prevention in HIV & AIDS in IDU

Moron-Concepcion, Jose A. -- University of Texas Medical Branch, Galveston
Mechanisms Underlying Opiate-Induced Neuroplasticity at the Synapse

Morral, Andrew R. -- Rand Corporation
Case-Mix-Adjustment for Adolescent Treatment

Murai, Keith Kazuo -- McGill University
Role of TNFalpha in Synaptic Homeostasis in Response to Drugs of Abuse

Nader, Michael A. -- Wake Forest University Health Sciences
Dopamine D2 Receptors in Primate Models of Cocaine Abuse

Nair, Madhavan P. -- Florida International University
Role of Cocaine in Neuro-AIDS by HIV 1B and C Clades

Nichols, David E. -- Purdue University, West Lafayette
Stereochemical Aspects of Hallucinogenesis

Nikulina, Ella M. -- University of Arizona
BDNF in Frontal Cortex and Social Stress-Induced Sensitization

Nunes, Edward V. -- New York State Psychiatric Institute
Treatment Studies Using Depot Naltrexone (4/6) Columbia Protocol Treatment Site

Otto-Salaj, Laura L. -- University of Wisconsin, Milwaukee
Etiology of Sexual Risk, Substance Abuse, and Trauma: A Bioecological Systems Model

Paige, Mikell A. -- Georgetown University
Design and Synthesis of New Neuronal nAChR Silent Desensitizers for Drug Abuse

Pentel, Paul R. -- Minneapolis Medical Research Foundation, Inc.
Multivalent Vaccine for Opiate Addiction

Perrone-Bizzozero, Nora Irma -- University of New Mexico
Role of Micrornas and RNA-Binding Proteins in Addiction-Related Gene Expression

Pleasure, Samuel Jeremy -- University of California, San Francisco
Defective Forebrain Development in Mutant Mice

Poduska, Jeanne Marie -- American Institutes for Research
Scaling-Up Prevention Services for Early Drug Abuse Risk in School Systems

Polcin, Douglas L. -- Public Health Institute
Intensive Motivational Interviewing for Methamphetamine Dependence

Potts, Jeffrey Thomas -- University of North Texas Health Science Center
Hybrid Atomic Force-Optical Imaging System to Investigate Prenatal Nicotine

Potula, Raghava -- Temple University
Meth-Induced T Cell Dysfunction: Role in HIV-1 Immunopathogenesis

Prado, Guillermo -- University of Miami School of Medicine
Familias Unidas Stage III Study: Preventing Substance Abuse in Hispanic Youth

Prochaska, James O. -- University of Rhode Island
Comparing Population Cessation Services with Emphasis on Unmotivated Smokers

Rakic, Pasko -- Yale University
Origin of Cortical Species-Specific Distinctions

Ramsay, Douglas S. -- University of Washington
Drug-Induced Allostasis and Its Motivational Effects during Adolescence

Renshaw, Perry F. -- University of Utah
Longitudinal Neuroimaging of Metamphetamine-Dependent Adolescents

Resnick, Heidi S. -- Medical University of South Carolina
Prevention of Postrape Drug Abuse: Replication Study

Rogers, Thomas J. -- Temple University
Opioid Modulation of Inflammatory Monocyte Activity Involved in HIV Susceptibility

Roitman, Jamie D. -- University of Illinois at Chicago
Neural Basis of Decisions about Uncertain Rewards

Ruger, Jennifer P. -- Yale University
Economic Evaluation of Drug Abuse Treatment and HIV Prevention Services

Rush, Craig R. -- University of Kentucky
GABAA Modulation as a Target for Developing Medications for Methamphetamine Abuse

Rush, Craig R. -- University of Kentucky
Agonist Replacement Therapy for Methamphetamine Dependence: Human Lab Studies

Salvemini, Daniela -- Saint Louis University
Role of Ceramide in Morphine Hyperalgesia and Tolerance

Schoenbaum, Geoffrey M. -- University of Maryland, Baltimore
Corticolimbic Encoding of Conditioned Reinforcers: Relevance to Addiction

Shafer, Michael S. -- Arizona State University-Tempe Campus
The Arizona Network for the Study of Implementation Effectiveness

Shedlin, Michele G. -- University of Texas, El Paso
Substance Abuse and Health Vulnerability: Colombian Refugees in Ecuador

Simpson, D. D. -- Texas Christian University
Sustainable HIV Risk Reduction Strategies for CJ Systems

Smith, Richard D. -- Battelle Pacific Northwest Laboratories
HIV Proteomic Center for Host-Viral Response Characterization

Staley, Julie K. -- Yale University
Tobacco Smoking, Genes and Nicotinic Receptors

Sterk, Claire E. -- Emory University
Neighborhood Effects on HIV Risk-Taking

Stitzer, Maxine L. -- Johns Hopkins University
Multi-site Controlled Trial of Cocaine Vaccine (3 of 6) Baltimore Treatment Site

Sulkowski, Mark S. -- Johns Hopkins University
HCV Disease Management in HIV- HCV Coinfected IDUS

Sun, Wenlin -- University of Tennessee Health Science Center
Neural Mechanisms of Extinction-Mediated Inhibition of Relapse to Cocaine-Seeking

Surratt, Hilary L. -- University of Delaware
The Diversion of Antiretroviral Medications to Street Markets

Svikis, Dace S. -- Virginia Commonwealth University
Computer vs Therapist-Delivered Brief Intervention for Drug Abuse in Primary Care

Swartz, James Anthony -- University of Illinois at Chicago
A Life Course Perspective Model of HIV Risk and Substance Use Patterns among MSM

Szumlinski, Karen K. -- University of California, Santa Barbara
Homer-Mediated Signaling and Cocaine Addiction

Thio, Chloe L. -- Johns Hopkins University
Liver Disease and Drug Use in the HAART

Traube, Dorian E. -- University of Southern California
Drugs, Sexual Impulsivity, HIV: Psychosocial and Cognitive Risk Factors of YMSM

Valdez, Avelardo -- University of Houston
At Risk Hispanic Gangs: Long-Term Consequences for HIV, Hepatitis and STI

Van Der Kouwe, Andre Jan Willem -- Massachusetts General Hospital
Functional Spectroscopy with Real-Time Feedback for Altering Preferences in Addicts

Vandrey, Ryan G. -- Johns Hopkins University
Effects of Zolpidem Extended-Release on Withdrawal and Sleep in Cannabis Users

Velasquez, Mary Marden -- University of Texas, Austin
Multidisciplinary Approach to Reduce Injury and Substance Abuse

Vijayaraghavan, Sukumar -- University of Colorado, Denver
Nicotinic Receptors in Glia-Neuron Interactions

Vijayaraghavan, Sukumar -- University of Colorado, Denver
Nicotinic Signaling in the Brain

Watson, Stanley J. -- University of Michigan at Ann Arbor
Cocaine Regulation of miRNAs in Rats with Differing Vulnerability to Drug Abuse

Webster, John Matthew -- University of Kentucky
A Web-Based Employment Intervention for Drug Court Participants

White, Fletcher A. -- Loyola University Chicago
Chemokine-Mediated Modulaton of Opioid-Induced Pain

White, William -- University of Connecticut School of Medicine/Dentistry
Contingency Management for Initiating Smoking Abstinence

Wiebe, Sandra A. -- University of Nebraska, Lincoln
Prenatal Tobacco Exposure, Self Regulation, Externalizing Behaviors in Early Childhood

Woodward, John J. -- Medical University of South Carolina
Neural Actions of Toluene

Yankee, Thomas M. -- University of Kansas Medical Center
The Effects of Morphine on the Immune Responses against HIV in Vivo

Yu, Xiao-Fang -- Johns Hopkins University
A Novel Allele Influencing HIV Infection among Injection Drug Users

Zahniser, Nancy R. -- University of Colorado, Denver
Individual Differences in Cocaine Activation/Reward and the Dopamine Transporter

Zhang, Yan -- Virginia Commonwealth University
Non-Peptide Mu Opioid Receptor Selective Antagonists

Zubieta, Jon-Kar -- University of Michigan at Ann Arbor
Development and Use of rtfMRI for Self-control of Nicotine Craving

Director's Report to the National Advisory Council on Drug Abuse - February, 2009

Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 944 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 733 applications.

OEA arranged and managed 17 grant review meetings in which 182 applications were evaluated. OEA's reviews included applications in chartered, standing review committees and Special Emphasis Panels (SEPs). In addition, OEA's Contract Review Branch (CRB) arranged and managed 10 contract proposal review meetings.

NIDA's chartered committees consist of NIDA-E (Treatment Review Committee), NIDA-F (Health Services Review Committee), NIDA-L (Medications Development Committee), and NIDA-K (Training Committee). In addition to meetings of each of these committees, OEA staff held 13 Special Emphasis Panels to review grant applications for a variety of reasons:

Conflicts with the chartered committees
Program Project grant applications
Behavioral Science Track Award for Rapid Transition (B/START)
Imaging Science Track Award for Research Transition (I/START)
Cutting-Edge Basic Research Awards (CEBRA) (R21)
Conference Grants (R13)
Mechanism for Time-Sensitive Research Opportunities
Minority Institutions' Drug Abuse Research Development Program (MIDARP)
Requests for Applications (RFAs)

OEA managed the following RFA review:

- DA09-006: Criminal Justice Drug Abuse Treatment Studies 2 (CJ-DATS 2) (U01)

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

R&D and non-R&D Contract Reviews

- NO1DA-9-8882: Drug Testing for Clinical Trials
- NO1DA-9-8883: Non-Clinical ADME Studies

Phase II SBIR Contract Reviews

N44DA-9-2213: Web Based training for Pain Management Providers

Phase I SBIR Contract Reviews

- N43DA-9-5543: Electronic Drug Abuse Treatment Referral Systems for Physicians
- N43DA-9-5544: Virtual Reality Simulations to Train Caregivers/Providers
- N43DA-9-8886: Design and Synthesis of Treatment Agents for Drug Abuse
- N43DA-9-8888: Web Based Cognitive/Neuropsychological Testing for Substance Abuse
- N43DA-9-8884: Development of Therapeutic Agents for Substance Use Disorders
- N43DA-9-8885: Pharmaceutical Approaches for Development of Pharmacotherapies for Drug Addiction
- N43DA-9-7768: Screening, Characterization and Validation Assays for Protein Capture Reagents

CTN Data and Safety Monitoring Board(s) Meetings

- September 12, 2008 for the final report on the CTN 0029 study "A Pilot Study of Osmotic-Release Methylphenidate (OROS MPH) in Initiating and Maintaining Abstinence in Smokers with Attention Deficit Hyperactivity Disorder (ADHD)."
- September 26, 2008 to review the rationale and design of the study CTN 0037: Exercise as a Treatment for Substance Use Disorders.
- October 24, 2008 to discuss the progress of study protocols CTN 0027: Starting Treatment with Agonist Replacement Therapies (START) and CTN 0031: Stimulant Abuser Groups to Engage in 12-Step (STAGE-12).

Certificates of Confidentiality

Between August 5 and December 4, 2008, OEA processed 109 Certificate applications, including 28 amendments for either extension of expiration date or protocol change.

Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued through the summer. Activities included open forums for discussions and presentations that included NIH GWAS policies, Enhancing Peer Review Update, NIH staff training on handling financial COI, The Program Leadership Committee, the Program Module Users Group, Updates to the Program Module, and NIH/NSF collaborations.

Activities

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Director's Report to the National Advisory Council on Drug Abuse - February, 2009

Congressional Affairs (Prepared January 21, 2009)

Appropriations

NIDA continues to operate under a continuing resolution, with funding at the FY 2008 level (enacted at $1.001 billion). Congress is working on legislation that will fund the remainder of FY 2009. As a reminder: last June, the House Appropriations Subcommittee on Labor, HHS, Education marked up its draft bill for FY2009, including a 3.9 percent or $1.15 billion increase for NIH programs. The full Committee met but adjourned before taking action on the FY2009 Labor, HHS, Education appropriations bill. In the Senate, the Appropriations Committee passed its Labor/HHS bill for FY 2009. This bill included an increase of $1.025 billion for NIH, for a total of $30,254,524,000. Final Congressional action is expected prior to the March 6, 2009 expiration of the continuing resolution.

Transition - Executive Branch

HHS Secretary-Designate **Tom Daschle** had a confirmation hearing on January 8, 2009 in the Senate's Committee on Health, Education, Labor and Pensions. He also must testify in front of the Committee on Finance; as of this writing that hearing is not scheduled.

William Corr has been nominated to be Deputy Secretary of HHS. Since early 2000, Mr. Corr has been the Executive Director of the Campaign for Tobacco Free Kids. Prior to that, he was Chief Counsel and Policy Director for former Senator Tom Daschle. Before that Senate role, Mr. Corr was the HHS Chief of Staff for Secretary Donna Shalala. At HHS, he also served as Deputy Assistant Secretary for Health and Counselor to the Secretary.

As of this writing, we are still waiting to hear who will be nominated by President Obama to be the **NIH Director**, as well as the **Director of the Office of National Drug Control Policy**.

Legislation of Particular Interest

Parity Legislation enacted into law. In October, 2008, after 12 years of effort, Congress passed and the President signed legislation designed to ensure parity for substance abuse and mental health in insurance coverage. The legislative language, the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act of 2008, was included in the economic recovery bill that moved through Congress last fall.

Bills of Interest

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[For the full text and additional information about any bill, go to the Library of Congress website at http://thomas.loc.gov].

H.R. 2 - On January 13, Representative Frank Pallone (D-NJ) introduced the Children's Health Insurance Program Reauthorization Act of 2009, to amend Title XXI of the Social Security Act to extend and improve the Children's Health Insurance Program, and for other purposes. Section 502 of this bill includes substance abuse and mental health parity for insurance coverage. The bill was passed by the House on January 14. See S. 275.

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. 193 - On January 6, Representative Pete Stark (D-CA) introduced the AmeriCare Health Care Act of 2009, to amend the Social Security Act and Internal Revenue Service Code of 1986 to provide for an AmeriCare that assures the provision of health insurance coverage to all residents, and for other purposes. Section 2221(h) of this Act would provide benefits for "mental health services and for substance abuse treatment in the same manner as such benefits are made available for medical and surgical services. The bill was referred to three committees: Energy and Commerce; Ways and Means; and Education and Labor.

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.

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.

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. See H.R. 2 and S. 275.

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. 275 - On January 16, Senator Max Baucus (D-MT) introduced the Children's Health Insurance Program Reauthorization Act of 2009, to amend Title XXI of the Social Security Act to extend and improve the Children's Health Insurance Program, and for other purposes. Section 502 of this bill includes substance abuse and mental health parity for insurance coverage. The bill is currently under consideration by the full Senate. See H.R. 2.

111th Congress

As a result of the November 2008 elections, Democrats have strengthened their majorities in both the Senate and House of Representatives. The most relevant committee-related information for NIDA is listed below.

Senate: In the Senate, primary focus is on the
Committee on Appropriations (Subcommittee on Labor, Health and Human Services, and Education; Financial Services; and Commerce, Justice, Science;
Committee on Health, Education, Labor, and Pensions (HELP);
Committee on the Judiciary; and the Caucus on International Narcotics Control (this is an officially recognized Caucus, established by law in 1985).

House: In the House, primary focus is on the
Committee on Appropriations (Subcommittee on Labor, Health and Human Services, Education, and Related Agencies; Financial Services; and Commerce, Justice, Science and Related Agencies);
Committee on Energy and Commerce (Subcommittee on Health); and the Committee on Oversight and Government Reform (Subcommittee on Domestic Policy).

Committee and subcommittee rosters are being finalized. More details will be provided in the May 2009 Report to Council.

Director's Report to the National Advisory Council on Drug Abuse - February, 2009

International Activities

Funding Initiatives

Supplements Support US-Netherlands Binational Collaborative Research

NIDA will provide up to $300,000 to support up to three 1-year administrative supplements to ongoing NIDA grants for U.S. researchers working with Dutch partners. The Dutch Addiction Program (DAP) will provide matching funds to support the Dutch researchers. Dutch applicants needed to submit a letter of intent by December 9, 2008. U.S. applications are due on or before April 7, 2009.

NIDA, CDRF Support Two HIV/AIDS and Drug Abuse Research Teams

With funding provided by NIDA and administered by the U.S. Civilian Research & Development Foundation (CRDF), two teams of U.S. and Eurasian scientists have earned support for innovative projects in HIV/AIDS and drug abuse research. The grant competition was a follow-up activity to the joint NIDA/CRDF April 2008 proposal development workshop in Kiev, Ukraine, which focused on identifying a research agenda and developing regional collaborative research proposals. The first team will investigate HIV transmission among injecting and non-injecting drug users in Tallinn, Estonia. Dr. Anneli Uuskula, University of Tartu, Estonia, is the Eurasian primary investigator (PI); Dr. Don des Jarlais, Beth Israel Medical Center, is the U.S. PI. The investigators will examine the linkages between these two groups that might explain transmission and provide insight into observed increases in HIV infections among heterosexuals and women in Estonia. The second team will assess new trends in HIV-related risk patterns of injecting drug use and drug distribution in four Eurasian countries with substantial presence of alcohol, tobacco, and drug use. Former NIDA Humphrey Fellow Dr. Tomas Zabransky, Charles University, Czech Republic, is the Eurasian PI; Dr. Robert Booth, University of Colorado, is the U.S. PI. Other members of the five-country team include Dr. Zaruhi Beglaryan, United Nations Development Programme, Armenia; former NIDA Humphrey Fellow Dr. David Otiashvili, Union Alternative, Georgia; Dr. Oleksander Zeziulin, Vinnitsya Regional Narcological Dispensary, Ukraine; former WHO/NIDA/CPDD International Traveling Fellow Dr. Konstantyn Dumchev, Vinnitsya Regional Narcological Dispensary, Ukraine; former NIDA Humphrey Fellow Dr. Sergiy Dvoryak, Ukrainian Institute on Public Health Policy; Dr. Joseph E. Schumacher, University of Alabama at Birmingham, United States; and Dr. Shruti Mehta, Johns Hopkins University, United States. The multinational team will combine qualitative and quantitative techniques to develop data about HIV among drug users, recent developments in drug scenes that are associated with the transmission of blood-borne diseases, and the individual and social dynamics of HIV risks.

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Binational Agreements

US and Spain Sign Letter of Intent for Scientific Collaboration and Exchange

On October 18, 2008, NIDA and the National Plan on Drugs (PNSD), the government agency responsible for drug policy and programs in Spain, signed an agreement to pursue a program of scientific collaboration and exchange in the fields of biomedical and behavioral research related to drug abuse. Cooperation may include activities designed to further scientific and academic interactions between NIDA and PNSD's National Institute of Drug Research and Training (INIFD); to complement their respective areas of expertise; and to enhance their missions, particularly as they relate to the advancement of drug abuse research. The program for cooperation in research between NIDA-identified scientists and scientists identified by INIFD will include the exchange of scientists, information (including joint workshops), and research materials as well as other forms of research cooperation agreed upon and encouraged by both Institutes. The agreement has its roots in more than a decade of cooperation between NIDA and PNSD. The relationship began when the agencies cosponsored binational scientific meetings on drug abuse in 1997 and 1999 and has included additional workshops, scientific exchanges, and research training and exchanges since that time. A new INVEST Fellow, Marta Concheiro Guisan, is from Spain.

NIDA Supports Multinational Inhalant Abuse Research Efforts

NIDA is supporting a multinational working group of inhalant abuse researchers funded by the Social Sciences and Humanities Research Council (SSHRC) of Canada. The SSHRC grant was designed to bring together experts from Canada, the United States, Australia, and Mexico to develop an international research agenda on treating inhalant abuse among indigenous youth, and to share the success of Canadian Youth Solvent Addiction Committee (YSAC) models. The NIDA International Program is providing staff support, assistance in using the NIDA International Virtual Collaboratory (NIVC), and helping to coordinate a meeting in conjunction with the 2009 NIDA International Forum. To disseminate information about YSAC programs, the multinational team will hold a series of virtual seminars on NIVC. The first seminar, held December 11, 2008, featured a recorded presentation on treatment by YSAC Coordinator Debra Dell, and an online discussion forum question-and-answer session. The next seminar, tentatively scheduled for late February 2009, will focus on prevention programs in Canada and England. To develop a review paper for publication, the working group members are completing environmental scans about inhalant abuse in their own countries. The group will meet prior to the 2009 NIDA International Forum to finalize the paper and identify a research agenda. Principal Investigator Dr. Colleen Anne Dell, University of Saskatchewan, coordinates the team, which also includes NIDA grantee Dr. Matthew O. Howard, University of North Carolina; former NIDA INVEST Fellow Dr. Silvia Cruz, Cinestav, Mexico; and Dr. Sarah MacLean, Turning Point Alcohol and Drug Centre, Australia.

NIDA-Supported Meetings

Sino-US Symposium on Substance Abuse and HIV/HCV Co-morbidity

A NIDA and NIAAA jointly sponsored symposium was held in Xi'an, China during October 21-25, 2008. Dr. Jacques Normand, Director of NIDA AIDS Office and Dr. Max Goo, Deputy Director of Division of Metabolism and Health Effects/NIAAA co-chaired the roundtable discussion of this meeting. In addition, Dr. Yu (Woody) Lin, the NIDA program official of the symposium project coordinated interactive discussions throughout the conference among several top Chinese psychiatrists, practitioners in disease clinics, and basic HIV/HCV scientists from five prominent Chinese institutions. The goal of these discussions was to promote collaborative basic, clinical, and clinical trial

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research on, and prevention and treatment of HIV/HCV-substance abuse co-morbidity in China. As result of these discussions, a collaborative network has been initiated and several potentially collaborative research projects are actively under discussion. Dr. Johnny He, Professor and Director of Center for AIDS Research, Indiana University School of Medicine, will lead this consortium with assistance of Dr. Min Zhao of Shanghai Jiao tong University, Shanghai, China as the local coordinator in China. This consortium will primarily focus on western China and neighboring provinces, a geographical region where drug abuse is highly prevalent and has become the major contributing factor for new HIV/HCV infection.

NIDA Poster Session at SfN Features International Neuroscientists

NIDA organized an Early Career Investigators Poster Session on Friday, November 14, 2998 as part of NIDA's mini-convention on Frontiers in Addiction Research at the Society for Neuroscience Research meeting in Washington, D.C. The invited poster session showcased drug abuse and drug-related neuroscience research by:

- Brazil: Alline Cristina de Campos, Daniel Fraga, Sabrina F. deS. Lisboa, Leonardo Resstel Barbosa Moraes, and Ana Luisa Bernardes Terzian
- Canada: Stephanie L. Borgland
- China: Wenhua Zhou
- France: Amynah Pradhan
- India: Sharad Shashwat
- Iran: Pouya Tahsili Fahadan
- Italy: Michela Ferrucci
- Japan: Keiichi Niikura and Hideko Yamamoto
- Poland: Anna Golda
- Portugal: Frederico Pereira
- Spain: Alejandro Higuera Matas
- Thailand: Rasmon Kalayasiri
- United Kingdom: Tomasz Schneider

The international poster presenters were supported, in part, by NIDA and the International Union of Pharmacology, International Brain Research Organization, International Narcotics Research Conference, College on Problems of Drug Dependence, International Cannabinoid Research Society, and International Drug Abuse Research Society.

NIDA Shares Research Priorities and Funding Mechanisms with United Kingdom

The Medical Research Council (MRC), a publicly funded organization charged with coordinating addiction research throughout the United Kingdom, is developing a strategy to make better use of existing expertise and infrastructure, build U.K. research capacity, increase coordination among stakeholders, and conduct interdisciplinary studies on addiction to alcohol, nicotine, illicit drugs, and gambling. At the request of MRC officials, NIDA IP Director Dr. Steven W. Gust participated in a workshop in London on November 4, 2008, to identify thematic priorities for new addiction research clusters. Dr. Gust summarized NIDA research priorities in prevention among children and adolescents, new targets and strategies for treatment interventions, and HIV/AIDS and mechanisms the Institute uses to support research and develop research infrastructure at the individual, institutional, and inter-institutional levels.

International Scientists Explore Role of Neuroimmunomodulation in Drug Abuse and HIV/AIDS

NIDA supported the International Symposium on Biotechnological Approaches

to Neuroimmunomodulation and Infectious Diseases, held December 11-13, 2008, in Nagar, India. The meeting featured speakers from India, Germany, and the United States, including NIDA grantee Dr. Robert Donahoe, an expert in how abused drugs affect the progression of AIDS. The National Institute on Pharmaceuticals and Educational Research of India sponsored the conference, with support from NIDA, Roche Pharmaceuticals of India, and the University of Utah.

REDLA Identifies Worrisome Trends in Latin American Drug Use

Fourteen members of REDLA (the Latin American Epidemiological Network known more commonly by its Spanish name, la Red Latinoamericana de Investigadores en Drogas) met prior to the June 2008 NIDA International Forum to analyze the drug situation in each country, identify knowledge gaps that could be closed through secondary analysis of existing databases, and create a work plan to analyze cross-national databases in Argentina, Brazil, Canada, Chile, Colombia, Costa Rica, Guatemala, Mexico, Peru, and the United States, including Puerto Rico. REDLA is a network of academic researchers coordinated by the Inter-American Drug Abuse Control Commission (CICAD) and supported by NIDA. Participants noted increased drug use in almost all countries, particularly regarding the use of marijuana and cocaine. Perception of risk appeared to be decreasing in all countries. Attendees reported that prescription drug use without a prescription or medical supervision is now widespread across Latin America and culturally accepted, as with the use of benzodiazepines among Brazilian women. REDLA members noted that national and multinational surveys do not clearly identify which pharmaceuticals are most commonly misused and suggested that future CICAD surveys include a more precise breakdown of pharmaceuticals misused and better classification of abused inhalants. In addition, discussion revealed a series of patterns of substance use that were previously unknown or rarely observed in Latin America:

- Binge drinking.
- Jarra Loca--mixing strong liquor with pharmaceuticals, which had been previously reported in Paraguay, has recently been reported in Argentina, Peru, and Brazil.
- Merla--the combination of cocaine or crack with cannabis is growing in popularity among Brazilians.
- Heroin mixed with Xylazine--Puerto Rican injection drug users have been reported to add Xylazine, an animal tranquilizer, to heroin, believing that the mixture mimics or extends the effects of heroin.

Fellowships

NIDA Welcomes Humphrey Fellows

Ms. Dale Weiss, program analyst from the NIDA IP, met with Hubert H. Humphrey (HHH) Fellows at two fall meetings to introduce NIDA opportunities available during their fellowships. Ms. Weiss met with NIDA-supported Humphrey Fellows in Substance Abuse Education, Treatment, and Prevention at Virginia Commonwealth University (VCU) on September 19, 2008. Ms. Weiss introduced NIDA resources, including the NIDA International Virtual Collaboratory (NIVC), a password-protected tool to support geographically distant partners in collaborative research, discussion, and education, and met individually with the fellows to discuss their research affiliations. During a 4-day Global Leadership Forum sponsored by the U.S. Department of State and the Institute of International Education, Ms. Weiss met October 20 and 21, 2008, with HHH Fellows in Drug Abuse and Public Health from Johns Hopkins University, HHH Fellows in HIV/AIDS Policy and Prevention from Emory University, and HHH Fellows in Public Health Policy and Management from Tulane University. She discussed NIH opportunities open to the fellows, the international research priorities of NIDA Divisions, and the NIDA IP's role in

strengthening research networks outside the United States by creating opportunities for global research collaboration, training, and scientific exchange. The NIDA-supported Humphrey Fellows at VCU include:

- **Mr. Daniel Akwasi Amankwaah**, Ghana, obtained his bachelor's degree in political science and French in 1994 and his LL.B. degree in 2007 from the University of Ghana. He is currently the head of the Legal Liaison Unit of the Ghana Narcotics Control Board. Prior to that, he was the head of the Demand Reduction Department and was responsible for United Nations Office on Drugs and Crime demand reduction activities in Ghana. He has worked extensively with nongovernmental organizations in substance abuse prevention and education. During his fellowship, Mr. Amankwaah will focus on substance abuse policy, criminal justice, and designing substance abuse prevention, treatment, and rehabilitation programs.
- **Dr. Muna H. Sawwaf**, Saudi Arabia, obtained her medical degree with honors from King Saud University in 1989 and completed her fellowship in general psychiatry in 1994. Dr. Sawwaf's postgraduate training includes studies at the University of London in women's mental health and drug addiction, and a postgraduate diploma in psychological medicine from University College Dublin. She is a consultant psychiatrist and head of the Department of Psychiatry at King Fahd General Hospital in Jeddah, and a member of the scientific advisory board of Mentor Arabia and Mentor International, a nongovernmental organization that deals with drug abuse prevention programs. In 2007, she was awarded an International Fellowship from the American Psychiatric Association. Her fellowship goals are to learn more about managing drug addiction in women, behavioral and pharmacological drug treatments, and prevention programs.
- **Dr. Munir Ahmed**, Bangladesh, obtained his medical degree in 1989, a master's degree in public health in 2003, and a diploma in health economics degree in 2004 from Dhaka University. From 1991-2002, he worked in the tribal tea plantation area of Bangladesh where malaria, tuberculosis, leprosy, and alcohol addiction are endemic. In 2004, he joined CARE's harm reduction program for injection drug users and heroin smokers. Since early 2006, he has led operations for CARE's HIV program. During his fellowship year, Dr. Ahmed will focus on drug treatment modalities, including self-help groups and treatment for drug overdoses, prevention programs, and drug control policy and legislation.
- **Mr. Oleksii Smirnov**, Ukraine, is a senior program officer for the International HIV/AIDS Alliance, coordinating HIV prevention projects in southern Ukraine. He has master's degrees from Warsaw University and the Central European University in Budapest. Mr. Smirnov organized three waves of Participatory Site Assessments (PSA) that identified subgroups of injecting drug users (IDUs), locations where they congregate, and their migration. As a result of the PSAs, local nongovernmental organizations have implemented evidence-based practices in different regions of Ukraine. Since HIV/AIDS is spread mostly among IDUs in Ukraine, during his fellowship, Mr. Smirnov wants to learn new strategies for harm reduction, rehabilitation, and substitution therapy for this vulnerable group. He is also interested in substance abuse policy and drug control legislation.
- **Dr. Petr Popov**, Czech Republic, received his medical degree from Charles University Prague in 1987, where he also completed his specialty in psychiatry in 1991 and his postgraduate specialty in drug abuse in 1997. He is head of the Division of Substance Abuse Services of the General Faculty Hospital Prague and head of the Department of Addictive Disorders at the Czech Institute of Postgraduate Study in Medicine. Dr. Popov is chairman of the Czech Society of Addictive Medicine and has attended psychiatry and addictions conferences and training workshops throughout Europe and the United States. During his fellowship year, Dr. Popov will study drug treatment modalities, policies, prevention, drug control legislation, and

professional training programs.

- **Dr. Tekendra Kumar Rai**, India, obtained his bachelor of medicine and surgery from Marathwada University in 1990. After completing his doctoral degree in pharmacology in 1996, he joined the Drugs Cell in the Indian State of Sikkim Department of Health, where he was responsible for the enforcement of the Drugs and Cosmetics Act. Currently, he oversees the Sikkim State Anti-Drugs Unit, where he framed legislation to control abuse and trafficking of prescription drugs. During his fellowship, Dr. Rai will focus on policy, prevention, and drug control legislation regarding prescription drug abuse and the relationship between HIV/AIDS and injection drug use, particularly among adolescents and women.
- **Dr. Adrian Octavian Abagiu**, Romania, graduated from the Bucharest University of Medicine in 1987 and earned a Ph.D. in medical science in 2000. He has been a senior doctor in infectious diseases since 1994 and was head of the Infectious Diseases Department of the Bucharest Prison Hospital until 2000. Currently, he is working as senior doctor in infectious diseases at the National Institute for Infectious Diseases in Bucharest and as medical coordinator for the ARENA Center, the first Romanian low-threshold center for methadone maintenance treatment. During his fellowship, Dr. Abagiu hopes to learn more about substance abuse prevention and treatment, especially for multidrug use, and about program development and evaluation of direct clinical services for patients with co-occurring disorders.

INVEST Fellow Ends Year with Scientific Presentations

Dr. Adhi Nurhidayat, Indonesia, chaired one session at the Pre-Pacific Rim College of Psychiatrists (PRCP) meeting and presented on Indonesia's mental health policy during the meeting, which was held in Tokyo, Japan, October 29-November 2, 2008. A 2007-2008 NIDA INVEST Fellow, Dr. Nurhidayat was awarded a travel scholarship from PRCP to participate in the meeting. He also received a travel scholarship from the World Health Organization and the International Society of Addiction Medicine (ISAM) to present on addiction medicine in Indonesia during the ISAM Annual Scientific Meeting in Cape Town, South Africa, November 17-20, 2008. Earlier, Dr. Nurhidayat was awarded a travel scholarship to the Society for Prevention Research conference held in San Francisco, May 27-31, 2008, where he presented a poster on evaluation of HIV prevention programs in Indonesia. With his mentors, Dr. David Metzger and Dr. George Woody of the University of Pennsylvania, Dr. Nurhidayat has submitted one research grant proposal that is under review, and he is preparing a second grant application and two articles.

NIDA Selects New INVEST Fellows

Dr. Marta Concheiro Guisan, University of Santiago de Compostela, Spain, has been selected as a NIDA INVEST Fellow. Working with Dr. Marilyn Heustis, NIDA IRP, Dr. Concheiro aims to develop and validate an analytical method to quantify the level of buprenorphine in the oral fluid and sweat of pregnant, opioid-dependent women receiving buprenorphine maintenance treatment. Although maternal plasma concentrations provide actual levels of free buprenorphine and metabolites that can cross the placenta and reach the fetus, plasma is rarely collected for monitoring purposes. Oral fluid and sweat testing both offer promising, noninvasive alternatives to plasma collection. Drs. Concheiro and Heustis will develop and validate a liquid chromatography tandem mass spectrometry method to measure the concentration of buprenorphine and its metabolites, and then correlate that data with administered dose; maternal and neonatal outcomes; and data from maternal urine and plasma specimens and infant placenta, umbilical cord, and meconium specimens. A pharmacist and forensic toxicologist, Dr. Concheiro has been a researcher at the University of Santiago de Compostela, CIENTISOL S.L., and Cienytech. Her postdoctoral fellowship at the NIDA IRP was supported by the Spanish Fundacion Espanola de Ciencia y Tecnologia.

Dr. Albeart Moriggia, University of Pavia, Italy, is a new INVEST Fellow who will work with Dr. David L. Thomas of the Johns Hopkins School of Medicine to investigate the role of HIV in the progression of HCV-related liver diseases among injection drug users (IDUs). His work will focus on defining the role of injection drug use in liver damage as well as clinical and biological markers for liver disease among IDUs. In the United States and Europe, HCV-related liver disease is one of the leading causes of death among IDUs who are infected with HIV. Yet the degree to which HIV increases HCV-related liver disease among this group and the mechanisms of how HIV and injection drug use affect liver disease are largely unknown. The major limitation of liver disease research and therapy among IDUs today is the measurement of liver disease stage and prediction of liver disease progression. Dr. Moriggia and Dr. Thomas will investigate the accuracy of elastography and surrogate markers in different situations of immunosuppression, liver damage, HCV-RNA values, biochemical parameters, and drug use. They also will study the role of microbial translocation in the progression of liver disease. Results from this study should contribute to an increase in the number of HCV-infected IDU candidates for HCV therapy, thus prolonging their lives and reducing the reservoir of HCV infection the United States and Europe. After receiving his degree in Medicine and Surgery from the University of Milan, Dr. Moriggia began his current residency in Infectious and Tropical Diseases at the University of Pavia. He also served internships in pediatrics at the University of Milan and in tropical medicine and pediatrics at Mnazi Mmoja Hospital in Zanzibar, Tanzania.

International Visitors

On October 15, 2008 Mr. Piotr Jabloski, Director of the National Bureau for Drug Prevention Poland and Mr. Krzysztof Brzozka Director of the State Agency for Prevention of Alcohol-Related Problems in Poland visited NIDA. This visiting scholars tour was organized by Dr. Robert Zucker under the auspices of the International Clinical, Operational and Health Services Research and Training Award (ICOHRTA). While at NIDA the visitors met with Dr. Liz Ginexi, DESPR, Dr. Larry Stanford and Ms. Debbie Grossman, DCNBR and Ms. Dale Weiss, IP.

As part of the U.S. Department of State's International Visitor Leadership Program three visitors from Venezuela came to NIDA on November 4, 2008. Objectives of the visit included providing an overview of U.S. policy regarding drug demand reduction efforts in general, presenting a substantive view of drug education and prevention programs, strategies and methodologies in the U.S. and familiarizing the group with the latest trends in treatment of drug addiction. While at NIDA the visitors met with Drs. Liz Ginexi and Dionne Jones, DESPR, Dr. Ivan Montoya DPMCDA and Ms. Ana Anders, SPO.

Mrs. Gayle Hamilton an Information Specialist from the Bahamas National Drug Council visited NIDA December 4, 2008. The purpose of the visit was to learn more about NIDA's information dissemination efforts. Mrs. Hamilton met with Mr. Brian Marquis, OSPC during her visit.

Other International Activities

Wilson M. Compton, M.D., M.P.E., Director, DESPR, participated in the Joint World Health Organization-American Psychiatric Association DSM-ICD Harmonization Committee Meeting, Geneva, Switzerland, December 3, 2008.

Wilson M. Compton, M.D., M.P.E. presented on Epidemiology of Methamphetamine in a panel at the Pacific Rim College of Psychiatrists Scientific Meeting, Tokyo, Japan, October 31, 2008.

Dr. Steven Grant, DCNBR, gave the opening address entitled "Dopamine and Glutamate Dysfunction in Addiction" at the 7th Charity Conference on Psychiatric Research: Emotional Neuroscience held at Charity -

Universitaetsmedizin in Berlin, Germany on August 28-31, 2008.

Dr. Rao S. Rapaka, DBNBR, co-organized an "International Symposium on Organic Synthesis and Drug Development 2008" (ISODD) at Nanjing University, Nanjing, October 14-17, 2008.

Dr. Rapaka's co-organizers were Dr. Yi Pan (Nanjing University) and Dr. Guo-Qiang Lin (Shanghai Institute of Organic Chemistry).

Dr. Yu (Woody) Lin, represented DCNBR at the NIDA-NIAAA jointly sponsored symposium entitled "Sino-US Symposium on Substance Abuse and HIV/HCV Co-morbidity", which was held in conjunction with the 10th Chinese National Biennial Conference on Drug Dependence at Xi'an, China on October 21-25, 2008.

Dr. Ivan Montoya, DPMCDA, co-chaired with Francisco Cumsille from the Organization of American States (OAS) a 1-day meeting of the Latin American Network of Drug Abuse Epidemiology (REDLA). The meeting took place at the OAS headquarters in Washington DC, on September 30, 2008. The panel included drug abuse epidemiology experts from 10 countries of the Americas and Puerto Rico.

Dr. Ivan Montoya was invited to chair a symposium and present at the annual meeting of the Colombian Psychiatric Association in Bogota, Colombia, on October 8-12, 2008. The topic of the symposium was "Advances in the Treatment of Drug Abuse". It included presentations by Dr. Ricardo Restrepo from Columbia University in New York, Dr. Ximena Sanchez from Harvard University, and Dr. Sergi Ferre from the NIDA IRP.

Dr. Ivan Montoya attended and chaired a symposium at the annual meeting of the International Society of Addiction Medicine in Cape Town, South Africa. The title of the symposium was "Addiction and Post Traumatic Stress Disorder (PTSD)". It included presentations by Dr. Carlos Blanco and Dr. Nathilee Caldeira from Columbia University, Dr. Sudie Back from Medical University of South Carolina, and Dr. R. Kjosnes from the Addiction Research Center of Norway.

Dr. Ahmed Elkashef, DPMCDA, organized a one-day pre-congress workshop at the annual meeting of the International Society of Addiction Medicine in Cape Town, South Africa. The title was: Methamphetamine - New Knowledge from Research Findings. The co-chairs were Dr. Salomon Rataemane from South Africa and Dr. Tim Condon from NIDA. There were presentations by Drs. W. Ling, C. Grella, R. Rawson, B.Myers, N. Ntlhe, M. Brecht, C.J. Reback, R. Sodano and A. Elkashef.

Dr. Jag Khalsa, DPMCDA, has been invited by Laila Pharmaceutical Ltd., Chennai, India, Jan 18-20, 2009, to give a special lecture on medical consequences of drug abuse and infections (HIV/AIDS, HCV, TB, and others) at the International Conference on Molecular Medicine. The conference is planned to be inaugurated by the former President of India. Dr. Khalsa will receive an award from the President for his contributions in the field of substance abuse and infections.

David A. Gorelick, M.D., Ph.D., IRP, visited the Israel Anti-Drug Authority in Jerusalem, Israel on October 26, 2008, where he gave a presentation on pharmacological treatment of substance dependence.

See our **Contact Information**.

Director's Report to the National Advisory Council on Drug Abuse - February, 2009

Meetings/Conferences

The Friends of the National Institute on Drug Abuse hosted its eleventh congressional briefing titled **Developing New Tools to Prevent and Treat Addiction: Vaccine Development on the Horizon** on July 29, 2008. NIDA Director, Dr. Nora Volkow opened the briefing with an overview of the Institute's research portfolio as it relates to medications development and vaccine treatments for addiction. Other panelists addressed the potential use of vaccines for methamphetamine, cocaine and nicotine addiction. The event drew a crowd of 125, at least half of whom were congressional staff representing over 52 House and Senate Member offices. The incredible attendance and depth of questions from the audience during the panel discussion following the presentations demonstrated a strong interest in the topic.

For the first time ever, three award winning high school students were recognized at the NIH for their exemplary projects in addiction science. The awardees presented their science projects to Dr. Elias Zerhouni, Dr. Nora Volkow and a roomful of NIDA staff members in Bethesda, MD on August 11, 2008. The students were selected at the world's largest science competition for high school students - the **Intel International Science and Engineering Fair (ISEF)** in Atlanta, Georgia last May. The new **Addiction Science award** is co-sponsored by NIDA and Scholastic, and is the first series of Intel awards given exclusively for projects that advance addiction science.

NIDA Deputy Director, Dr. Timothy Condon was featured as a panelist for **SAMHSA's 2008 Recovery Month webcast** held on September 3, 2008 entitled **Recovery in the United States: Past, Present, and Future** together with other federal officials and representatives from recovery organizations. The program will look back at some of the successes the recovery movement has enjoyed as well as current policy initiatives to increase and enhance treatment services. It will also look forward, focusing on what remains to be done to ensure that all persons with a substance abuse and/or mental health condition get the sustained, comprehensive treatment they need. The taped webcast was posted at recoverymonth.gov.

NIDA's Dr. Steve Gust and David Anderson attended the annual meeting of the **International Society of Addiction Journal Editors (ISAJE)** in Bar Harbor, Maine, September 4-6, 2008. Dr. Gust spoke to attendees about NIDA's international program, which has collaborated with ISAJE on numerous projects, including a manual aimed at helping researchers worldwide, especially young researchers, navigate the publishing process. Mr. Anderson, editor of NIDA Notes and NIDA's Journal, Addiction Science & Clinical Practice, chaired a panel discussion on PubMed Central, the free-to-the-public literature database into which all publications based on NIH research are now deposited. According to meeting participants representing Elsevier Press, the journal Addiction, and the organization Substance Abuse Librarians and Information Specialists, the

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public is taking great advantage of the database.

The **Eighth Annual Meeting of the National Hispanic Science Network (NHSN) on Drug Abuse** was held in Bethesda, Maryland, October 1-3, 2008. The conference addressed vital issues of Latino drug use research, and included participants from 10 countries. Two international initiatives of the NHSN, in partnership with NIDA, were brought together at the conference. The first, the RED Latino Americana de Investigadores en Drogas (REDLA), is an epidemiology network of eight countries conducting coordinated epidemiological research on drug abuse, and bringing governments and scientists together. The second, the Central American Research Network on Addictions, known as RECIA for its initials in Spanish, was created to help Central American countries develop a research infrastructure to improve their drug abuse treatment programs.

The **Buprenorphine Treatment for Young Adults Blending Team** met in Gaithersburg, Maryland on November 5, 2008 to discuss the results of the CTN protocol: Buprenorphine/ Naloxone-Facilitated Rehabilitation for Heroin Addicted Adolescents/Young Adults. This Blending Team is part of the NIDA/SAMHSA Blending Initiative which promotes the use of evidence-based treatment by professionals in the drug abuse treatment field. "Blending Teams" are composed of staff from the Addiction Technology Transfer Center (ATTC) Network and NIDA/CTN researchers, who work together to develop innovative "products" that will be disseminated to the field at nearly the same time that the research results are published in peer-reviewed journals. This Blending Team is being coordinated by Dr. Denise Pintello (NIDA) and is led by Dr. Tom Freese (Pacific Southwest ATTC). Team members include: NIDA/CTN: Drs. Michael Bogenschutz Laura McNicholas, and Geetha Subramanian; ATTC: Thomas Durham, Beth Rutkowski and Pamela Waters. Future efforts will focus on updating current Buprenorphine products and developing new training and dissemination products in 2009.

On November 6-7, 2008, Dr. Nora Volkow, Dr. Timothy P. Condon and Dr. Frank Vocci helped educate nearly 75 judges on the neuroscience of substance abuse. Their presentations were part of a seminar on "Addiction Treatment Technologies" offered by the **Advanced Science and Technology Adjudication Resource (ASTAR) Program** - a national program designed to prepare judges to preside over cases involving complex scientific issues. After Dr. Condon's talk, which touched on addiction as a brain disease and recommended treatment principles for drug addicts within the criminal justice system, he was presented with ASTAR's "Distinguished Science and Technology Fellow" Award.

NIDA convened a one-day mini-convention on November 16, 2008, at the **Society for Neuroscience Annual Meeting** in Washington, D.C. NIDA scientists, including Director, Dr. Nora Volkow, presented recent findings and discussed future directions in neuroscience.

NIDA participated in a **Methamphetamine Summit: The National Summit to Promote Health, Partnerships, and Safety for Critically Affected Populations**, hosted by SAMHSA in Washington, D.C. on November 16-19, 2008. The Summit brought together representatives from states and territories with the goal of strengthening partnerships, and developing strategies to address the methamphetamine problems in their localities, especially those affecting women, GLBT, and justice-involved populations. Dr. Lucinda Miner spoke at the welcoming event and Dr. Susan Weiss was part of a Federal panel to provide information on future funding opportunities.

On December 11, 2008, NIDA convened an advanced press briefing for NIDA constituent representatives as well as a press conference in Washington, D.C. to announce the **2008 Monitoring the Future** survey results. The results received national, local and trade press coverage.

Activities

Planned Meetings

Publications

Staff Highlights

Grantee Honors

The Prevention Research Branch (DESPR, NIDA) in collaboration with the Behavioral Integrative Treatment Branch, (DCNBR, NIDA), the U.S. Army Medical Research and Materiel Command, the Department of Defense Health Affairs, the Army Center for Substance Abuse Programs, the Department of Veteran Affairs, the National Institute of Mental Health, the National Institute on Alcohol Abuse and Alcoholism, the National Heart, Lung, and Blood Institute, and the National Cancer Institute, sponsored a meeting on January 6-7, 2009, at the Bethesda Hyatt, Bethesda, Maryland entitled **Addressing Substance Abuse and Comorbidities Among Military Personnel, Veterans and Their Families: A Research Agenda.** The goals of this 2-day meeting were to: 1) gain an understanding of the intervention needs of military personnel, veterans, and their families regarding substance abuse and associated difficulties; 2) discuss current prevention and treatment approaches being used with these populations and their evidence base; 3) review existing efficacious prevention interventions and drug abuse treatments that may be appropriate for adapting and testing within military and veteran populations and their families; 4) understand how to successfully conduct research in military and veteran settings; and 5) formulate a research agenda for conducting addictions prevention and treatment research with military and veteran populations and their families.

Dr. Allison Hoffman, DBNBR, co-organized a workshop on **Drug Abuse Vulnerability and Neurodevelopmental Effects of Early Exposure to Secondhand Tobacco Smoke: Methodological Issues and Research Priorities**, held in the Neuroscience Center on January 13, 2009. The meeting's organizing committee also included Nicolette Borek (DCNBR), Cora Lee Wetherington (DBNBR), Michele Block (NCI) and Cathy Backinger (NCI).

Dr. Nicolette Borek organized a meeting on **Adolescent Development Following Prenatal Drug Exposure: Research Progress, Challenges, and Opportunities** which was held November 20 & 21, 2008 in Bethesda, MD. The meeting was sponsored by the Office of Science Policy and Communications (OSPC) and received co-funding from NIAAA. The purpose of the meeting was to bring together prenatal substance exposure researchers with researchers and NIH program staff from various areas including adolescent development and substance abuse in order to facilitate research advances. Session topics included adolescent brain development, neuroimaging, substance abuse, mental health, HIV risk behavior, sex/gender differences, and genetics. Several NIDA staff served as scientific experts at the meeting including Drs. Kevin Conway and Kathy Etz (DESPR), Drs. Joni Rutter and Cora Lee Wetherington (DBNBR), Pamela Goodlow (SPO/OD), Dr. Marilyn Huestis (IRP) and Drs. Jim Bjork, Joseph Frascella, Larry Stanford, Steven Grant, and Karen Sirocco (DCNBR). In addition, Dr. Vincent Smeriglio served as expert consultant. Drs. Jay Giedd, Judy Rumsey and Shelli Avenevoli (NIMH) and Dr. Ellen Witt (NIAAA) also contributed their scientific expertise to the meeting.

The Special Populations Office, NIDA, supported the members of the **"Native to Native"** mentoring program to attend the Annual Native Health Research Conference, in Portland Oregon, on August 25-28, 2008. The "Native to Native" mentoring program was developed by members of NIDA's American Indian/Alaskan Native external workgroup to provide career development support to American Indian/Alaskan Native post-doctoral fellows, graduate students and undergraduate students interested in pursuing research careers in the field of substance abuse and addiction. Kathy Etz, Ph.D. of DESPR attended the meeting to support NIDA's interest in American Indian/Alaska Native research and researchers.

The Special Populations Office held the **NIDA Researchers and Scholars Joint Workgroup Meeting** on September 29-30, 2008 in Bethesda, MD. The meeting convened members of the African American, American Indian-Alaskan Native, Asian American/Pacific Islander, and National Hispanic Science Network

workgroups, and NIDA staff. Individual workgroups provided updates on their initiatives that focused on training and mentoring early/new investigators pursuing research careers in the field of substance abuse and addiction. Recent activities included research and technical assistance training workshops, a mentoring program, and a mini medical school. NIDA Director, Dr. Nora Volkow, provided an opening address and discussed NIDA's research priorities. NIDA Division Directors and representatives provided updates on their research portfolios and current funding opportunities.

The Special Populations Office, NIDA, chaired a two-day **Research Development Seminar Series workshop** in Bethesda, Maryland on October 27-28, 2008. The workshop convened new underrepresented investigators seeking independent research careers through NIDA and the NIH. Topics included: overviews of the NIH grant application process and the NIH peer review system, one-on-one and small group mentoring sessions, and research presentations by NIDA-funded investigators. Members of the Special Populations Office and other NIDA staff participated.

The **National CTN Steering Committee Meetings** were held October 21-23, 2008 in Rockville, MD. The following meetings/committees convened:
CTP and PI Caucuses
Steering Committee
Executive Committee
Research Utilization Committee
Research Development Committee
Node Coordinator Workgroup
Pharmacotherapy Special Interest Group
CTN 0031 - STAGE-12 Study Team
CTN 0033 - Meth Use among American Indians Study Team
CTN 0044 - Web-based Study Team

Two workshops were held during the CTN Steering Committee Meetings:
Applying New Technology in Drug Treatments: Present and Future
This CTN workshop addressed a number of issues related to the present status and future prospects for adoption of e-technology innovations in substance use treatment. The major topics included: 1) current use of e-technology in community-based substance use treatment programs, 2) implementing a web-based Therapeutic Education System in the CTN, 3) evaluating readiness of substance use treatment programs to adopt e-technology innovations, 4) what does the future hold? Opportunities in the substance use treatment field for adoption of e-technology innovations and policy issues for implementation. The addiction treatment system in the United States is composed of about 12,000 treatment centers, most of which are small, free-standing, non-profits with few resources for building effective electronic information systems. The addiction treatment field needs to catch up with regard to adoption of e-technology innovations - there are many examples of e-technology that have not been adopted.

E-technology treatment strategies may be especially appealing to adolescents and young adults. Health care reform in states can change the role of the state as a payer of health care, and change the state's influence on control of addiction treatment services. The alcohol and drug confidentiality regulations (42 CFR Part 2) remain a substantial barrier to the implementation of electronic medical record systems (EMRs). State systems of care are changing. There is increasing emphasis on continuing care, which requires long-term periodic contact with clients. There is an evolution of payment and regulatory systems away from the acute care system of periodic admission and discharge. E-technology is an important facet of the evolving health care systems in the United States, but most addiction treatment programs fail to exploit relatively accessible and easy to use e-technology to manage these administrative tasks. Drug abuse treatment programs and clinicians need to begin to embrace the

available technology and to explore the potential in emerging technologies. Application of these technologies can enhance the quality and effectiveness of care and may contribute to reductions in the cost of care.

Conducting Research with American Indian/Alaska Native Communities in the CTN: Challenges, Opportunities and Collaborations
This workshop was designed to address a number of issues related to conducting community-based participatory research in American Indian/Alaska Native communities. The major topics included: 1) health disparities/substance abuse issues; 2) history of research in American Indian communities; 3) building relationships within the community; 4) ethical and regulatory issues; 5) study implementation issues; 6) publication and dissemination of the research; and 7) future research directions and funding opportunities. Almost 100 individuals from American Indian tribes and Alaska Native communities, the Clinical Trials Network, NIH Institutes and Centers, the Centers for Disease Control and Prevention, Office of Minority Health and the Indian Health Service attended the workshop and participated in the discussion.

Dr. Timothy P. Condon, Deputy Director, NIDA, presented "Neurobiology of Addiction: What Difference Does It Make?" at the 16th Annual International Community Corrections Association's Research Conference on What Works in Community Corrections: "Risk, Resilience and Reentry" on October 20, 2008, in Saint Louis Missouri.

Dr. Timothy P. Condon presented "The Science of Addiction: Implications for Prevention and Treatment" at the Hazelden Foundation's Meeting the Challenge: Treating Addiction in the 21st Century Conference on October 24, 2008, in Honolulu, Hawaii.

Dr. Timothy P. Condon presented "The State of Addiction Treatment Technologies" at the Advanced Science and Technology Adjudication Resource (ASTAR) Program Judge's Science School on November 7, 2008, in Bethesda, Maryland.

Dr. Timothy P. Condon presented "Addiction Medicine - From Research to Practice" at the International Society of Addiction Medicine's 10th Annual Scientific Meeting on November 17, 2008, in Cape Town, South Africa. He also co-chaired the pre-congress workshop on "Methamphetamine - New Knowledge from Research Findings" on November 16, 2008.

Dr. Timothy P. Condon presented "The Neurobiology of Nicotine Addiction: An Overview" at the Interagency Committee on Smoking and Health on December 8, 2008, in Washington D.C.

Dr. Cindy Miner, Deputy Director, OSPC, participated in a Grantwriting Workshop and Mock IRG Panel at the American Academy of Child & Adolescent Psychiatry on October 30, 2008. in Chicago, Illinois.

Dr. Cindy Miner, Deputy Director, OSPC, presented "The Science of Addiction" at the 2008 ASAP Statewide Prevention Conference on November 18, 2008, in Saratoga Springs, New York.

Dr. Ruben Baler, OSPC, delivered a lecture on the "Neuroscience of Drug Addiction" at the George Washington University's School of Public Health Drug Awareness course, Mount Vernon Campus on September 23, 2008.

Dr. Ruben Baler, OSPC, delivered the Keynote address entitled "How Can Science Help Us Navigate Around the Dangers of Abuse and Addiction?" and presented three youth and adult workshops at the 2008 Washington State Prevention Summit on Oct 16-18, 2008, in Yakima, Washington.

Dr. Lula Beatty, Chief, Special Populations Office (SPO), attended the meeting

of the Committee on Women in Psychology, American Psychological Association, September 19-20, 2008 in Washington, DC.

Dr. Lula Beatty was a member of the planning committee for the NIH Summit: The Science of Eliminating Health Disparities, December 15-18, 2008, in National Harbor, MD. In addition, she served as a review team leader and session moderator.

Dr. Lula Beatty presented opening remarks at the annual conference of the Hispanic Science Network on Drug Abuse, October 1, 2008, in Bethesda, MD.

Dr. Lula Beatty presented an overview of NIDA and the Special Populations Office and served as a faculty advisor at the SPO sponsored technical assistance workshop held for early career researchers, October 27-28, 2008, in Bethesda, MD.

Dr. Lula Beatty served as a moderator and presenter at the SPO sponsored Joint Expert Work Groups on Racial/Ethnic Minority Populations meeting, September 29-30, 2008, in Bethesda, MD.

Dr. Lula Beatty chaired two sessions at the annual meeting of the International Society of Addiction Medicine, November 17-20, 2008 in Capetown, South Africa. The sessions were titled "Lessons Learned from U. S. Health Disparity Research: Improving Addiction and HIV Interventions and Services for Underserved Populations" and "Lessons Learned from U. S. Health Disparity Research: Improving Drug Abuse and HIV Treatment for Underserved Populations."

Dr. Lula Beatty participated in a consultation meeting for the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP), CDC, December 8 -10, 2008 in Atlanta, GA.

Ana Anders, M.S.W., SPO, participated and represented NIDA in a leadership program to train Latino women at an international meeting of the Pan American Health Organization (PAHO) in September 2008 in Washington, D.C.

Ana Anders represented NIDA at the Latino Behavioral Health Institute annual conference in Los Angeles, September 15-17, 2008.

Ana Anders participated in the National Hispanic Science Network on Drug Abuse annual conference in Washington, D.C. September 1-3, 2008.

Ana Anders, current president of the NIH Hispanic Employee Organization, along with the EEODM Office, planned the Hispanic Heritage Month Observance for NIH, which took place at the Lister Hill Auditorium at NIH on October 8, 2008.

Ana Anders was appointed to the NIH Hispanic Employment Committee, which advises the NIH Director on health issues relevant to Hispanics.

Pamela Goodlow, SPO, presented a talk on "Research Training Opportunities at the National Institute on Drug Abuse," in a topic workshop at the American Psychological Association (APA) Convention in Boston, MA on August 15, 2008.

Pamela Goodlow gave a brief overview of the NIDA Diversity Supplements program to investigators at the NIDA sponsored "Adolescent Development Following Prenatal Drug Exposure Meeting" at NSC in Bethesda, MD on November 20, 2008.

Flair Lindsey, SPO, and Pamela Goodlow provided an overview and update of the "DIDARP" and "Diversity Supplements" programs to NIDA staff in Bethesda, MD on December 2, 2008.

Dr. Betty Tai, Director, Director, CCTN, co-chaired with Dr. Sergio Aguilar-

Gaxiola, professor from the University of California at Davis a symposium titled: "Translational Research and How to Accelerate it by Engaging Communities: Goals and Milestones of the NIH CTSA Consortium" at the 8th annual conference of the National Hispanic Science Network on Drug Abuse, October 1, 2008 in Bethesda, MD.

Dr. Betty Tai, a voting member from NIH attended the NIH CTSA Consortium Oversight meeting on October 6-7, 2008 in Rockville, Maryland. The meeting was on strategic planning for the Consortium together with the milestones that will allow for programs to be evaluated.

Dr. Betty Tai was an invited speaker at the 14th Regional Occupational Health Conference (ROHC) in the Washington DC, Virginia, and Maryland area, the Institute for Johns Hopkins Nursing (IJHN), The Johns Hopkins Center for Occupational Safety and Health. Her presentation was titled: "Treatment for Prescription Opioid Analgesic Abuse." The conference was held on October 25, 2008 in INOVA, Alexandria, Virginia.

Dr. Betty Tai represented NIDA at the National Methamphetamine Summit meeting on November 18, 2008 and served as one of three panel members on the panel titled: "Considerations in Identifying and Replicating Best Practices: Mechanics or Science of Evidence-Based Practices." The meeting was held in Washington DC.

Dr. Harold Perl, CCTN, gave a presentation describing opportunities for research career development at the NIDA Special Populations Research Development Seminar Series workshop on October 27-28, 2008 in Bethesda, Maryland. Along with Carmen Rosa, M.S., Dr. Perl met individually with workshop attendees to provide more personalized research development advice.

Dr. Raul Mandler, CCTN, was the keynote speaker in a Web Telecast Program on "Drug Abuse in the Workforce" at the VIII World Congress of Labor Medicine at the National Academy of Medicine in Buenos Aires, Argentina, on October 30, 2008.

Dr. Paul Wakim, CCTN, co-planned and co-chaired the November 2008 face-to-face meeting of the Biostatistics, Epidemiology, and Research Design (BERD) Key Function Committee of the Clinical and Translational Science Award (CTSA) Consortium.

Dr. Petra Jacobs, CCTN, attended the Conference on Co-Ingestion of Alcohol with Prescription Opioids (Opioid Risk Management Program) organized by Tufts Health Care Institute, November 20-21, 2008, in Boston, MA.

On November 19, 2008, Dr. Steve Sparenborg, CCTN, attended the annual AMSUS (Society of the Federal Health Agencies) meeting in San Antonia Texas to establish communication with military and VA personnel regarding PTSD and to learn about their practices in treating PTSD.

Carmen Rosa and Quandra Scudder, CCTN, attended NIH's first Research Summit on "The Science of Eliminating Health Disparities" on December 16-18, 2008 at the Gaylord National Resort and Convention Center, National Harbor, Maryland.

Carmen Rosa participated as reviewer and moderator for the session titled "Fostering Diversity in Clinical and Community Research Participation to Eliminate Health Disparities."

Dr. David Shurtleff, Director, DBNBR, gave an invited presentation to The University of Minnesota students and faculty at the Fall PharmacoNeuroImmunology Retreat, Minneapolis, MN, October 3, 2008 entitled: "What's Going on at NIDA: Research and Funding Opportunities".

Dr. Minda Lynch, DBNBR, chaired a Scientific Panel at the Winter Conference on Brain Research, January 2009, in Copper Mountain, Colorado. The session, entitled "The Behavioral Genetics of Co-Morbidity: More Than Just Overlapping Phenotypes", included presentations from Alexander B. Niculescu, III, M.D., Ph.D. from Indiana University School of Medicine, Gregory M. Miller, Ph.D. from Harvard Medical School, Edgardo Falcon (from Dr. Colleen McClung's program at UT Southwestern Medical Center) and Elissa J. Chesler, Ph.D. from Oak Ridge National Laboratory.

Dr. Susan Volman, DBNBR, organized and chaired a panel entitled "VTA Dopamine Neuron Heterogeneity: Can it Help Us Understand Addiction and Other Psychiatric Disorders?" at the 42nd Winter Conference on Brain Research, January 26, 2009, in Copper Mountain, Colorado. Talks were presented by Dr. Stephan Lammel (Stanford University), Dr. Elyssa Margolis (Gallo Research Institute), Dr. Gary Aston-Jones (MUSC), and Dr. Wenlin Sun (University of Tennessee).

Dr. Susan Volman organized the Early Career Investigators Poster Session for the NIDA satellite miniconvention at the Society for Neuroscience Annual Meeting in Washington, DC, November 14, 2008. The poster session showcased research by NIDA-supported and other young investigators, including international investigators co-sponsored by IUPHAR, IBRO, INRC, CPPD, ICRS, and IDARS.

Dr. Cora Lee Wetherington, DBNBR, represented NIDA at the NIH Office of Research on Women's Health (ORWH) annual meeting of the principal investigators and directors of the ORWH-sponsored K-12 program, "Building Interdisciplinary Research Careers in Women's Health (BIRCWH)," November 18, 2008, Rockville, MD. Dr. Wetherington serves on the ORWH oversight committee for this program.

Dr. Cora Lee Wetherington served as moderator for the session on sex/gender differences in substance abuse at the NIH Office of Research on Women's Health meeting, Fifth Annual Interdisciplinary Women's Health Research Symposium, November 19, 2008, Bethesda, MD. Several NIDA grantees made either oral or poster presentations.

Dr. Cora Lee Wetherington represented NIDA at the NIH Office of Research on Women's Health annual meeting of the principal investigators of the ORWH-sponsored program, "Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health," held November 20, 2008. The program consists of 11 center grants of which NIDA co-funds the three that focus on drug abuse: Kathleen Brady, PI (MUSC), Rajita Sinha, PI (Yale), and Emmalee Bandstra, PI (Miami). Dr. Wetherington serves on the ORWH oversight committee for this program.

Dr. Cora Lee Wetherington gave a talk, "Prenatal Drug-Exposed Cohorts: Gold Mines for Studying Sex/Gender Differences in Drug Abuse," at the NIDA meeting, Adolescent Development Following Prenatal Drug Exposure: Research Progress, Challenges, and Opportunities, November 20-21, 2008, Rockville, MD.

Dr. Cora Lee Wetherington was a session chair in the "Expert Panel Meeting of Federal Collaboration on Tobacco and Young, Low SES-Women," December 1, 2008 at the DHHS Humphrey Building. Dr. Wetherington and Debbie Grossman, DCNBR, represent NIDA on this DHHS-led collaborative effort to identify mutual interests and opportunities to develop initiatives and collaborations among various federal entities including AHRQ, CMS, CDC, HRSA, ORWH, SAMHSA, Medicare, ACF, etc. to reduce smoking among low SES women.

Dr. Cora Lee Wetherington represented NIDA at the meeting. "Posttraumatic

Stress Disorder (PTDS) in Women Returning from Combat," sponsored by the Society for Women's Health Research, December 8, 2008, Washington, DC.

Dr. Allison Hoffman, DBNBR, and Dr. Cindy Miner, Deputy Director, OSPC, were formally given the responsibilities of Co-coordinators of Nicotine and Tobacco Research and Outreach Activities for NIDA.

Dr. Allison Hoffman served on the planning committee for "Working Group on Smoking Cessation in Hospitalized Patients", held at the Hilton DC/Rockville Executive Meeting Center on September 17, 2008. Other members of the planning committee included Drs. Jared Jobe (NHLBI), Gail Weinmann (NHLBI) Michele Bloch (NCI), Xingzhu Liu (FIC), Patricia Mabry (OBSSR), and Ann Malarcher (CDC).

Dr. Allison Hoffman organized the "New Directions in Smoking Cue-Reactivity and Cue Exposure Research" Cutting Edge seminar, held on September 18, 2008 which involved collaboration between the NIDA Neuroscience Consortium and the NIDA Nicotine/Tobacco Interest Group.

Dr. Allison Hoffman served on the planning committee for the Nicotine Addiction Briefing for Acting U.S. Surgeon General, Admiral Steven Galson, December 8, 2008.

Dr. Allison Hoffman served as co-organizer for the "Drug Abuse Vulnerability and Neurodevelopmental Effects of Early Exposure to Secondhand Tobacco Smoke: Methodological Issues and Research Priorities" workshop, held in the Neuroscience Center on January 13, 2009. The Organizing Committee included Drs. Nicolette Borek (DCNBR), Cora Lee Wetherington (DBNBR), Jeffrey Schulden (DESPR), Michele Block (NCI) and Cathy Backinger (NCI).

Dr. Samia Noursi, DBNBR, Deputy Coordinator, Women and Sex/Gender Differences Research Program, represented NIDA at the "Connecting Agendas," Think Tank meeting, September 12-13, 2008 in San Diego, CA. The meeting was held prior to the 13th International Conference on Violence, Abuse and Trauma, September 14-17, 2008. The Think Tank included representatives from various organizations and academic institutes and was convened to initiate next steps as a follow up on the American Psychological Association Summit on Violence and Abuse in Relationships: Connecting Agendas and Forging New Directions which occurred February 28-29, 2008, in Bethesda, MD.

Dr. Samia Noursi and Dr. Tom Brady, DESPR organized and chaired the symposium "Girls in the Juvenile Justice System: Health Disparities in Substance Abuse and HIV/Sexually Transmitted Infection Risk," at the annual meeting of the American Academy of Child and Adolescent Psychiatry (AACAP), October 29, 2008 in Chicago Illinois. Panelists were: Linda A. Teplin (Feinberg School of Medicine, Chicago, IL), Steven Belenko (Temple University), Angela Bryan (University of New Mexico), Angela A. Robertson (Mississippi State), and Lisa Saladana (Center for Research to Practice, Eugene, OR). The presentations were discussed by Mina K. Dulcan (Northwestern University, Feinberg School of Medicine, Children's Memorial Hospital, Chicago, IL).

Dr. Roger Sorensen, DBNBR, represented NIDA and the NIH at the NIH Mini-Regional on Program Funding and Grants Administration held at the University at Albany, NY, on October 28, 2008. He gave two presentations; "A Peer into the NIH Review Process & Grant Writing for Success", and "Budget Basics for Investigators."

Dr. Roger Sorensen represented NIDA and the NIH at the US - Ireland R&D Partnership Steering Group Member and Researcher Visit to the NIH, Bethesda, held on November 5, 2008. He presented an overview and helpful suggestions of the NIH grant application process titled: "Grant Writing for Success: Application Tips."

Dr. Roger Sorensen represented NIDA and the NIH during participation with other agencies and institutions at the Decision Sciences Institute Miniconference on Successful Grantsmanship, Baltimore, MD, held on November 23, 2008. The title of his presentation was: "Successful Grant Proposals from the NIH Perspective."

Drs. Da-Yu Wu and Tom Aigner, DBNBR, as workgroup members, organized the NIH Neuroscience Blueprint Workshop: "Challenges and Opportunities in Non-Invasive Human Brain Imaging: From Molecules to Circuits", held September 23, 2008.

Drs. Geraline Lin, DBNBR, Tom Aigner and Da-Yu Wu co-organized and co-chaired NIDA SFN Mini-convention Session on "Multimodal Imaging of Gene Expression, Cells, Neurons and Circuitry", November 14, 2008.

Drs. Da-Yu Wu and Jonathan Pollock, DBNBR, co-chaired and co-organized the NIDA SFN Mini-convention Session on "Cortical Development and Substances of Abuse", November 14, 2008.

Dr. John Satterlee, DBNBR, gave an invited presentation to the International Drug Addiction Research Society, Washington, DC, November 15, 2008 entitled: "Addiction at NIDA: Genetics, Epigenetics, and Innovation".

Dr. John Satterlee and Dr. Christine Colvis, Office of the Director, co-organized and co-chaired a session entitled "Epigenetics, Brain Function, and Addiction" at 2008 NIDA Frontiers in Addiction Research Mini-convention.

Dr. John Satterlee attended miRNA and Epigenetic Regulations of the Immune System, December 11-12, 2008, Bethesda, MD.

Dr. John Satterlee attended Dynamic Epigenome and Homeostatic Regulations in Health and Disease, November 13-14, 2008, Bethesda, MD.

Dr. John Satterlee attended Operational Planning Meeting: Roadmap Epigenomics Program Mapping Centers November 3-4, 2008.

Dr. John Satterlee attended the Fourth Annual NIH Director's Pioneer Award Symposium September 23, Bethesda, MD, 2008.

Dr. John Satterlee attended the Mammalian Gene Collection Executive Steering Committee Meeting, September 22, 2008, Bethesda, MD.

Dr. Joni L. Rutter, DBNBR, organized and chaired a symposium entitled, "The Brain Connection: Obesity and Addiction" at the National Hispanic Research Network meeting in Bethesda, MD, October, 2008.

Drs. Joni L. Rutter, NIDA, Andrea Beckel-Mitchener, NIMH, and Robert Riddle, NINDS, co-chaired and Dr. Satterlee co-organized a symposium on "Epigenetics in the Nervous System" at the Society for Neuroscience Annual Meeting, November 2008.

Dr. Jonathan D. Pollock and Beth Babecki co-organized and co-chaired the satellite meeting "Addiction Genetics Workforce Development and Collaboration" at the 2008 Annual Meeting of the American Society for Human Genetics. November 16, 2008.

Dr. Jonathan D. Pollock gave two seminars, entitled, "It's the Addiction, Stupid:" one at Mt. Sinai Medical Center in New York City on December 4, 2008 and the other at Rockefeller University in New York on December 5, 2008.

Dr. Jonathan D. Pollock serves on the NIH Knockout Mouse Project (KOMP) Steering committee and attended the KOMP Annual Research Network Meeting, October 8, 2008 held in Rockville, MD.

Dr. Jonathan D. Pollock attended the Mammalian Gene Collection Executive Steering Committee Meeting, September 22, 2008 in Bethesda, MD.

Dr. Jonathan D. Pollock conducted a web-based Webex meeting with Dr. Joni Rutter and Mark Caulder on "Rare Genetic Variants in Drug Addiction: Recommendations for Identification and Prioritization". This meeting was convened to assess the new opportunities that have emerged in genetics as a result of new sequencing technologies that permit the identification of copy number variants and rare variants.

Dr. Jonathan D. Pollock at the NIDA Genetics Consortium Meeting, December 2-3, 2008 at NIDA Headquarters in Rockville, MD presented issues and recommendations from the web-based meeting in a presentation entitled "Rare Genetic Variants in Drug Addiction: Recommendations for Identification and Prioritization."

Dr. Jonathan D. Pollock attended the Scientific Advisory Board meeting of Dr. Katze's NIDA Center for Functional Genomics of Hepatitis C and HIV infection, October 5, 2008 at the Marriott Rivercenter Hotel in San Antonio, TX.

Dr. Jonathan D. Pollock attended the 15th International Symposium on Hepatitis C Virus and Related Viruses, October 6-7, 2008 at the Marriot Rivercenter Hotel in San Antonio, TX.

Dr. Jonathan Pollock serves on the NIH GTex (Genotype-Tissue Expression (GTEx) Resource Roadmap steering committee. The Genotype-Tissue Expression (GTEx) project aims to provide to the scientific community a resource with which to study human gene expression and regulation and its relationship to genetic variation. This project will collect and analyze multiple human tissues from donors who are also densely genotyped, to assess genetic variation within their genomes. By analyzing global RNA expression within individual tissues and treating the expression levels of genes as quantitative traits, variations in gene expression that are highly correlated with genetic variation can be identified as expression quantitative trait loci, or eQTLs.

Dr. Elena Koustova, DBNBR, established the NIDA workgroup "Bridging Science & Business," and co-chairs the workgroup. Two meetings have been conducted since September 2008.

Drs. Elena Koustova and David Shurtleff actively participated in establishing the framework of the Neurodegeneration Blueprint initiative and preparation for its presentation to ICs Directors.

Dr. Elena Koustova attended the NIH Science of Science Management Meeting, October 2-3, 2008, Bethesda, MD.

Dr. Elena Koustova attended the FNIH Summit, December 16-18, 2008.

Dr. David Shurtleff was as an invited participant to the Parkinson's Disease Foundation meeting on "Impulse Control Disorder in Parkinson-Treated Patients" held on November 7, 2008 in New York, NY.

Drs. David Shurtleff, Rita Liu, OEA, and Cathrine Sasek, OSPC, co-coordinated and co-chaired the 2008 NIDA Frontiers in Addiction Research Mini-convention satellite meeting held on November 14, 2008 as a satellite to the Society for Neuroscience(SfN) Annual meeting in Washington, DC.

Dr. David Shurtleff gave introductory remarks on the challenges and opportunities for data sharing, and participated in the DESPR workshop "Crossroads: Sharing Social Environment and Genetic Data held at the Embassy Suites Hotel, Washington, DC, December 8 - 9, 2008.

Dr. Mary Kautz, DCNBR, served as the NIDA representative for a series of NIH-NASA collaboration meetings to gather information and help gauge NASA's

interest in participating in an cross-NIH FOA seeking Investigator-initiated applications for implementation on the International Space Station to benefit human health on Earth, August-November 2008.

Dr. Steven Grant, DCNBR, served as a NIDA representative for the joint Department of Energy Trans-NIH workgroup on radiochemistry.

Dr. Steven Grant served as a NIDA representative for the joint trans-NIH collaboration with the Uniformed Health Sciences University Center for Neuroscience and Regenerative Medicine.

Dr. Steven Grant represented NIDA at the Center for Neuroscience and Regenerative Medicine Trans-Federal Conference on Traumatic Brain Injury held at the Marriott Bethesda North Conference Center in Rockville, Maryland on September 17, 2008.

Drs. James Bjork and Woody Lin of DCNBR represented NIDA at the 2008 Annual Conference of the Society for Neuroeconomics, held in Park City, Utah on September 25-27, 2008.

Dr. James Bjork presented a talk entitled: "Rewards, Risk, and the Teenage Brain: Insights from brain imaging research conducted at the NIH Clinical Center" at the NIH main campus on October 27, 2008 as an invited speaker for NIH's "Fall in Love with NIH" presentation series. This series is devoted to new support staff hires at the NIH, to illustrate the end research result of the combined efforts of NIH researchers and the staff who support them.

Dr. Steven Grant presented a seminar titled "Relationships between Addiction and Traumatic Brain Injury" at Wells College in Aurora, NY on October 29, 2008.

Drs. James Bjork and Steven Grant organized and chaired a symposium entitled: "Willpower: What Really Governs our Choices?" which was held as part of the NIDA's Frontiers in Addiction Research, held on November 14, 2008 in Washington D.C. This symposium featured talks by: 1) Patrick Haggard of University College-London, 2) Brian Knutson of Stanford University, 3) Paul Glimcher of NYU, and 4) Alan Sanfey of the University of Arizona. All are renowned experts on the neuroimaging of behavior control in human subjects.

Dr. Steven Grant and Dr. Rita Goldstein (Brookhaven National Laboratory) co-chaired a symposium titled "Functional Neuroimaging Evidence for a Brain Network Underlying Impaired Insight (into illness) in Drug Addiction" at the annual meeting of the Society for Neuroscience held in Washington, DC on November 15-29, 2008. The speakers were AD "Bud" Craig (Barrow Neurological Institute), Antoine Bechara (University of Southern California), Hugh Garavan (Trinity College), and Anna Rose Childress (University of Pennsylvania).

Drs. James Bjork, Harold Gordon, Steven Grant, Mary Kautz, and Woody Lin of DCNBR, represented NIDA in the Annual Meeting of the Society for Neuroscience in Washington D.C., November 15-19, 2008.

Dr. Steven Grant represented NIDA at the annual meeting of the American College of Neuropsychopharmacology in Scottsdale, Arizona, December 6 - 11, 2008.

Dr. Steven Grant represented NIDA at the Air Force Office of Scientific Research (AFOSR) conference on "A Roadmap to Define the Neurobiological Mechanisms of Political Conflict" held at the FDIC Seidman Conference Center in Arlington, Virginia on December 16-17, 2008.

Dr. Cecelia Spitznas, DCNBR, moderated a symposium at the Addictions Health Services Research Conference held in Boston, MA, October 21, 2008. The

symposium, Developing a Skilled Practitioner Workforce Using Lower-Cost Training Interventions, included findings from the first ever nationwide attempt to train community treatment providers to conduct evidence based behavioral treatment over the internet developed by NIDA grantee Dr. Mary Joe Larson at New England Research Institute and included investigators and supervisor perspectives.

Dr. Lisa Onken led a luncheon roundtable at the NIH Office of Behavioral & Social Sciences (OBSSR) Retreat on November 12, 2008.

Dr. Karen Sirocco, DCNBR, moderated a workshop on October 12, 2008 at the Annual American Academy of Pediatrics Meeting in Boston, MA with presentations by Jay Giedd, MD: "Inside the Teenage Brain"; B.J. Casey, Ph.D: "What Have we Learned about Cognitive Development from Brain Imaging: Risk Taking and the Adolescent Brain"; Krista Medina, Ph.D.: "Neuroimaging Marijuana Use and its Effects on Cognitive Function"; Yasmin Hurd, Ph.D.; "Assessing the Impact of Drug Exposure on Brain Development in Utero"; and Mary Lou Behnke, M.D.: Prenatal Drug Exposure and Brain Development Outcomes from a Prospective longitudinal study of Prenatal Cocaine Exposure."

Drs. Nicolette Borek and Joseph Frascella of DCNBR presented a workshop on "Exposure to Drugs of Abuse During Development: Implications for Adolescent Vulnerability to Substance Abuse" at Healthy Brain Development: Key Impacts & Interventions on October 22, 2008 in Eugene, OR.

Drs. Nicolette Borek and Joseph Frascella served as mentors for Addiction Science Fair Award winner Shelby Raye at the Frontiers in Addiction Research: 2008 NIDA Mini-Convention, November 14, 2008 in Washington, DC. Shelby was one of three winners for her project "What's In and What's Out: High Schoolers' Perceptions of Coolness". Shelby is currently a sophomore at Manatee High School in Bradenton, Florida.

Dr. Nicolette Borek chaired the Maternal Lifestyles Study Annual Meeting on November 19, 2008 in Bethesda, MD. MLS is a multisite study of prenatal drug exposure and developmental outcomes. This cooperative agreement is co-sponsored by NICHD and NIMH.

Dr. Wilson M. Compton, Director, DESPR, chaired a plenary session on Drug Abuse and Criminal Justice and presented in a breakout session on Drug Courts at the Annual Meeting of the American Academy of Addiction Psychiatry, Boca Raton, FL, December 4-7, 2008.

Dr. Wilson M. Compton participated in a panel called Funders' Response to the Research Agenda at the Robert Wood Johnson Foundation Substance Abuse Policy Research Program Annual Grantee Meeting, December 16, 2008, Tucson, AZ.

Dr. Wilson M. Compton participated in the NIDA meeting on Sharing Social Environment and Genetic Data, December 8, 2008, Washington, D.C.

Dr. Wilson M. Compton presented to the meeting of the Lung Cancer Modeling Group of the NCI Cancer Intervention and Surveillance Modeling Network (CISNET), November 19, 2008, Bethesda, MD.

Dr. Wilson M. Compton presented on Addiction as a Brain Disease as a plenary speaker at the Federal Judicial Magistrate's Workshop, Washington, D.C., November 13, 2008.

Dr. Wilson M. Compton participated in the Joint NIJ-NIDA meeting on Methamphetamine Drug Markets, November 5, 2008, Washington, D.C.

Dr. Wilson M. Compton presented on Addiction as a Brain Disease as a keynote speaker and as a discussant for a panel on Physical Activity and Drug Abuse at

the Clinical Translation Research Conference, University of Kentucky, Lexington, KY, November 28, 2008.

Dr. Wilson M. Compton participated in meetings of the DSM-V Task Force and the Substance Use Disorders Workgroup, Arlington, VA, September 15-16 and October 26-27, 2008.

Dr. Wilson M. Compton presented on Prevention Research At NIDA as a plenary at the CSAP Strategic Prevention Framework-State Incentive Grant (SPF-SIG) meeting, Bethesda, MD, October 23, 2008.

Dr. Wilson M. Compton presented on Addiction as a Brain Disease as a grand rounds speaker at Stamford Hospital, October 22, 2008, Stamford, CT.

Dr. Wilson M. Compton presented in a plenary on A Broader View: Innovation in Delivery of Behavioral Health Services at the Addiction Health Services Research meeting, Boston, MA, October 21, 2008.

Dr. Wilson M. Compton presented on Addiction as a Brain Disease as an Invited Speaker at the Institute on Psychiatric Services, October 2, 2008, Chicago, IL.

Dr. Wilson M. Compton presented on behalf of NIDA at the Healthy People 2010 Midcourse Review, Washington, D.C., October 1, 2008.

Dr. Wilson M. Compton presented on Screening and Brief Intervention for Illicit Substances at the White House Leadership Summit, Washington, D.C., September 5, 2008.

Dr. Redonna K. Chandler, Chief Services Research Branch, DESPR, presented "Treatment is Key: Addressing Drug Abuse in Criminal Justice Settings" at the National Association of Drug Court Professionals 14th Annual Conference, Saint Louis, MO, May 29, 2008.

Dr. Redonna K. Chandler presented "CJ-DATS: Criminal Justice Drug Abuse Treatment Studies" at the annual meeting for the National Association of Drug Court Professionals, Saint Louis, MO, May 28, 2008.

Dr. Redonna K. Chandler co-chaired Academy Health Behavioral Health Services Research Interest Group Meeting entitled "Embedding Services Research Questions into Comparative Effectiveness Studies from the Start," Washington, D.C., June 10, 2008.

Dr. Elizabeth Robertson, PRB, DESPR gave a presentation titled: NIDA's HIV Prevention Research: Recent Findings at the Center for Substance Abuse Prevention kick-off meeting for their Minority AIDS Initiative held on December 2-4, 2008 at the Gaylord Hotel in National Harbor, MD.

Drs. Bethany G. Deeds and Yonette F. Thomas, DESPR, convened a meeting of NIDA grantees to discuss their findings on "After Hurricane Katrina: Alcohol and Drug Abuse Research." The meeting was held on October 29, 2008 in Rockville, MD. Participants described their research findings on drug abuse and related risk behaviors among persons living in New Orleans and nearby areas most affected by the hurricane.

Dr. Dionne Jones, DESPR, planned and organized a panel on "Women in Violent Relationships: Trauma and HIV Risk" presented at the American Psychological Association Annual Meeting, Boston, MA, August 14-17, 2008.

Drs. Tom Brady and Richard Denisco, both of DESPR, coordinated a meeting sponsored by NIDA and the ONDCP titled "Identifying Prescription Drug Abuse in Medical Settings: Challenges and Opportunities", in Bethesda, MD on May 19, 2008.

Dr. Eve E. Reider, PRB, DESPR conducted a workshop on "Emerging Principles

of Prevention" at the 21st Annual National Prevention Network Prevention Research Conference on August 25, 2008, in Indianapolis, IN, at the Indianapolis Marriott Downtown.

Dr. Dionne Jones planned and organized a Grantsmanship Workshop for New Investigators, and presented on "Grant Writing; The Role of the Program Official; and NIH Funding Mechanisms" at the Addictions Health Services Research (AHSR) Annual Conference, Boston, MA, October 20-22, 2008.

Dr. Belinda Sims and Dr. Eve Reider of PRB/DESPR co-chaired a symposium at the 116th convention of the American Psychological Association on August 14, 2008 entitled "Potential of Universal Childhood Prevention to Reduce Later Criminal Behavior."

On November 13, 2008 Dr. Elizabeth Robertson, PRB, DESPR was the discussant for a panel on The Future of Prevention Science at the 10th Anniversary Meeting of the Prevention Research Center at Pennsylvania State University in State College, PA.

Dr. Sarah Q. Duffy of the Services Research Branch, DESPR, chaired a session entitled "Economic Analyses of Substance Abuse Consequences and Treatments" at the 2008 Addiction Health Services Meetings, October 20-22, in Boston, MA.

On November 14, 2008 Drs. Elizabeth Robertson and Aleta Meyer, PRB, DESPR were discussants for a panel on The Future of Prevention Science at the 10th Anniversary Meeting of the Prevention Research Center at Pennsylvania State University in State College, PA.

Marsha Lopez, Ph.D., of NIDA's Epidemiology Research Branch, DESPR, organized a field visit to NIDA's DESPR for predoctoral and postdoctoral trainees participating in the Johns Hopkins Drug Epidemiology T32 on November 4, 2008. The visit provided an opportunity for the T32 trainees to meet individually with DESPR Program Officials about their research interests and career goals, and to identify grant application mechanisms that might be most appropriate for them.

Dr. Peter Hartsock, DESPR, co-chaired a session on applications of mathematical modeling to real-world problems, including HIV/AIDS, at the national conference of INFORMS (Institute For Operations Research and Management Sciences), October 15, 2008, Washington, D.C.

Dr. Peter Hartsock participated in an Institute of Medicine Consultation on "Addressing the Threat of Drug Resistant TB: A Realistic Assessment of the Challenges," November 5, 2008, Washington, D.C.

Dr. Peter Hartsock participated in the organization and conduct of a PEPFAR (President's Emergency Program for AIDS Assistance) Consultation on Multiple and Concurrent Sexual Partnerships in Generalized HIV Epidemics, October 29-30, 2008, Washington D.C. Concurrent partnerships account for at least 50% of HIV transmissions through sexual contact, regardless of number of partners (which can be very small) and NIDA has led the field in this research.

Dr. Peter Hartsock organized and co-chaired a special invited session at the national conference of the APHA, San Diego, October 27, 2008. The session dealt with NIDA-supported research on the U.S.-Mexico border on drug abuse, HIV/AIDS, TB, STIs, and related problems.

Dr. Elizabeth Robertson presided over a Research Priorities and Funding Opportunities Breakout Session on prevention research at the National Hispanic Science Meeting on October 1, 2008 at the Hyatt Hotel in Bethesda, MD.

Dr. Tom Hilton, DESPR, presented a lecture at the NIDDK career development

workshop: "Career Development Symposium: Life After K" entitled "Leading from Behind: The Role of Leadership as a Researcher," in San Diego, CA, June 18-20, 2008.

Dr. Dionne Jones served as a mentor in "Speed Mentoring" sessions at the American Public Health Association Annual Meeting, San Diego, CA, October 25-29 2008.

Dr. Augie Diana, PRB, DESPR, served as a Panelist in the session, "Careers in Medical Sociology Role" at the American Sociological Association Annual Meetings in Boston, MA on August 2, 2008. Dr. Diana presided over 2 additional sessions at the conference, focused on the application of sociology in applied settings, including federal employment.

Dr. Richard Jenkins, PRB, DESPR presented a colloquium titled "Funding Opportunities & the Role of the NIDA Program Staff" at the Memorial-Sloan Kettering Cancer Center in New York, NY on September 12, 2008.

Dr. Augie Diana presented "Federal Funding Opportunities NIDA's Physical Activity Initiative" at the Association for Applied and Clinical Sociology Annual Meetings in Jacksonville, FL on October 12, 2008.

On October 14, 2008, Dr. Aleta Meyer gave a presentation at the Society for Prevention Research's workshop, Advancing Translation of Prevention Science into Practice: The Next Generation, on "Funding for Type II Translation Research at NIH" in Aurora, CO.

Drs. Aria Crump, Aleta Meyer and Belinda Sims of PRB, DESPR presented a NIH/NIDA Grant Writing Session at the SAMHSA Strategic Prevention Framework State Incentive Grant National Grantees' Meeting, on October 22, 2008 in Bethesda, MD.

Dr. Elizabeth Ginexi, PRB, DESPR participated in a Workshop on Statistical Methods in Drug Abuse and Health-Related Research on October 29, 2008 at the University of Kentucky in Lexington KY. Dr. Ginexi provided an "Overview from a NIDA Perspective."

Drs. Aria Crump and Belinda Sims presented on NIDA training opportunities for physician scientists at a W.T. Grant Foundation meeting entitled "Improving Adolescent Health and Well-being - Training the Next Generation of Physician Scientists in Transdisciplinary Research," on November 18, 2008 in New York, NY.

Dr. Aria Crump presented on DESPR Research Priorities at the NIDA Special Populations Office Research Development Seminar Series Meeting held on October 27-28, 2008 in Bethesda, MD.

Dr. Eve Reider is representing NIDA on a Joint Program Review Panel responsible for providing programmatic reviews of proposals for Psychological Health, Concussion, and/or Suicide Research, through the Military Operational Medicine Research Program, Department of the Army, U.S. Army Medical Research and Materiel Command.

Dr. Eve Reider, PRB, DESPR became a member of the Federal Interagency TBI Research (FITBIR) working group.

Dr. Jag Khalsa, DPMCDA, participated in the annual meeting of the American Association for the Study of Liver Diseases (AASLD), November 1-3, 2008, San Francisco, CA.

Dr. Ivan Montoya, DPMCDA, participated in the "Working Group on Smoking Cessation in Hospitalized Patients" meeting in Rockville, MD on September, 17th 2008. This meeting was sponsored by NHLBI, NCI and NIDA.

Dr. Ivan Montoya presented the topic entitled "Cancer Research at NIDA" at the Trans-NCI Extramural Awareness Group (TEAG) forum on September 16, 2008.

Dr. Ivan Montoya presented the areas of research priority in DPMCDA to the NIDA Researchers and Scholars Joint Workgroup meeting, on September 29, 2008 in Bethesda, MD.

Dr. Ivan Montoya attended the annual meeting of the National Hispanic Science Network (NHSN) on Drug Abuse. He also co-chaired a symposium with Ana Anders and Yonette Thomas to discuss the research priorities of NIDA and a led a session to discuss opportunities for clinical research in drug abuse. The meeting took place in Bethesda, MD on October 1-3, 2008.

Dr. Ivan Montoya participated in the Fall meeting of the TTURC grantees, in Bethesda, MD, on October 22-23, 2008.

Dr. Ivan Montoya attended and chaired a symposium at the annual meeting of the American Academy of Child and Adolescent Psychiatry. The title of the symposium was "Advances in the Treatment of Marijuana Dependence in Adolescents". It included presentations by Drs. Alan Budney, Jack Cornelius, Meg Haney, Frances Levin, and Danielle Piomelli. The meeting took place in Chicago, on October 28-31, 2008.

Mr. Lyle Furr, OEA, attended the 59th National Meeting of the American Association for Laboratory Animal Science, November 9-13, 2008 in Indianapolis, IN.

Dr. Teri Levitin, OEA, spoke at the National Hispanic Science Network on Drug Abuse 8th annual conference held in Bethesda, MD on October 3, 2008. She participated in a workshop on grant writing and described recent recommendations to enhance peer review at NIH.

Dr. Teri Levitin, OEA, served as a co-facilitator for one of the breakout sessions at the NIH-wide retreat for behavioral and social sciences on November 12, 2008.

Dr. Gerald McLaughlin, OEA, co-organized the 4th International Mitochondria Minisymposium 2008, The Interaction and Independence of Sirtuins and Mitochondria: A Few NIH Perspectives, November 19, 2008, with 9 NIH intramural scientist presentations dealing with diabetes, cancer, atherosclerosis, and neurological conditions related to Sirtuins.

Dr. Gerald McLaughlin, OEA, co-organized the NIH Director's Wednesday Afternoon Lectures Series (NIH WALS) presentation of Sirtuins, Aging and Disease, by Leonard Guarente, November 19, 2008.

Dr. Gerald McLaughlin, OEA, co-organized and moderated the Scientific Program and Review Interest Group innovative transformative research series, including "FOA Development for Innovative Transformative Research" session November 21, 2008.

Dr. Meena Hiremath, OEA, attended the Addiction Health Services Research Conference in Boston, MA and presented a session on peer review to junior investigators, October 20-23, 2008.

Dr. Meena Hiremath, OEA, participated in the review of abstracts for the NIH Research Summit on the Science of Eliminating Health Disparities and attended the meeting in Gaylord, MD on December 16-18, 2008.

Dr. Nadine Rogers, OEA, participated as Adjunct Faculty, Morgan State University, School of Community Health & Policy teaching a graduate course, "Strategies for Health Promotion, Planning, and Program Development."

Dr. Nadine Rogers, OEA, presented "The Top 10 Things You Should Know About NIDA Review" at the NIDA Research Development Seminar Series, October 27-28, 2008 Bethesda, MD.

Dr. Nadine Rogers, OEA, presented, "NIH Submission and Review Process" at the NIDA Researchers and Scholars Joint Workgroup Meeting, September 29-30, 2008, Bethesda, MD.

Dr. Amy Newman, IRP, was a featured speaker at the NIH National Graduate Student Research Festival in Bethesda, in September 2008. The title of her talk was Molecular Tools to Study Drug Addiction.

Dr. Amy Newman was invited to give a seminar at the St. John's University, in Queens, NY, entitled Dopamine D3 Receptor Antagonists as Potential Therapeutic Agents for Addiction in October 2008.

Dr. Noel Paul, IRP, was invited to give a NIDA-IRP Seminar entitled Exploring Dopamine D2/D3 Receptor Selectivity With Novel Tropine-Based Ligands in October 2008.

Dr. Jean Lud Cadet, IRP, presented Methamphetamine Self-administration Causes Dose-dependent Dopamine Depletion in Rat Striatum at the Society for Neuroscience Conference in Washington D.C. on November 17, 2008.

Irina Krasnova, IRP, presented Methamphetamine Self-administration-Induced Transcriptional Profiles in the Rat Striatum at the Society for Neuroscience Conference in Washington D.C. on November 17, 2008.

Subramaniam Jayanthi, IRP, presented The Dopamine D1 Receptor Antagonist, SCH23390, Causes Suppression of the Methamphetamine-induced Endoplasmic Reticulum (ER) Stress Response at the Society for Neuroscience Conference in Washington D.C. on November 18, 2008.

Ning Cai, IRP, presented Methamphetamine Administration Causes Significant Increases in the Expression of the Morphogenesis Gene, Involucrin, in the Rat Hippocampus at the Society for Neuroscience Conference in Washington D.C. on November 18, 2008.

Fidelis Atianjoh, IRP, presented Analysis of Superoxide-mediated Transcriptional Changes Underlying Amphetamine Toxicity in the Cortex at the Society for Neuroscience Conference in Washington D.C. on November 15, 2008.

Mike McCoy, IRP, presented Attenuation of Methamphetamine-induce Toxicity by the Dopamine D1 Receptor Antagonist, SCH23390, Involves Inhibition of Multiple Transcription Factors at the Society for Neuroscience Conference in Washington D.C. on November 19, 2008.

Director's Report to the National Advisory Council on Drug Abuse - February, 2009

Media and Education Activities

Press Releases

July 1, 2008 - **Broad Differences in Alcohol, Tobacco and Illegal Drug Use Across Countries.** A survey conducted by the World Health Organization (WHO) research consortium found that the United States had among the highest lifetime rates of tobacco and alcohol use and led in the proportion of participants reporting cannabis (marijuana) or cocaine use at least once during their lifetime. The study, led by Dr. Louisa Degenhardt of the University of New South Wales, Sydney, Australia and colleagues, looked at patterns in the use of alcohol, tobacco, cannabis and cocaine in 17 countries representing all six WHO regions (the Americas, Europe, Asia, the Middle East, Africa and Oceania). The study, funded in part by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health (NIH) is published in the July 1, 2008 issue of the open access journal *PLoS Medicine*.

July 31, 2008 - **A Long Lasting Impression: New Study Finds Persistent Brain Changes in Response to Cocaine Depend on the Expectation of Reward.** Drug addiction dramatically shifts a person's attention, priorities, and behaviors towards a focus almost entirely on seeking out and taking drugs. Now, an animal study funded by NIDA has identified some of the specific long-term adaptations in the brain's reward system that may contribute to this shift. These long-lasting brain changes may underlie the maladaptive learning that contributes to addiction and to the propensity for relapse, even after years of abstinence from the drug. The study was published in *Neuron* on July 30, 2008.

August 1, 2008 - **Experts Encourage More Research into Drugged Driving: New Study Guidelines Released.** *(Note to Reporters)*. Driving under the influence of drugs, also known as drugged driving, is a growing problem in many countries. Researchers studying drugged driving use a wide range of different measurements and test for a variety of drugs that differ among studies, making comparisons between studies that could advance the science difficult. To overcome these barriers, the International Council on Alcohol, Drugs and Traffic Safety (ICADTS) convened a 4-day meeting in 2006 to develop formal guidelines for research on drugged driving, which was supported by international organizations including the National Institute on Drug Abuse. The final guidelines, including 32 recommendations for behavioral research, 40 recommendations for epidemiology, and 64 recommendations for toxicology, were published in the August 2008 issue of the journal Addiction.

August 6, 2008 - **Anti-HIV "Drug Cocktails" Equally Effective in Patients with or without History of Injection Drug Use.** Highly active antiretroviral therapy (HAART) has been extremely effective at slowing the progression of HIV infection to AIDS as well as extending the lives and improving the quality of life for those with HIV. However, some doctors have been reluctant to

Activities

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prescribe HAART to HIV-infected injection drug users because of concern that they may not fully benefit from the therapy. A new study by investigators funded by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health, and led by the British Columbia Centre for Excellence in HIV/AIDS in Canada, suggests that this is not the case: in their large, community-based study of HIV-infected people, injection drug users and people who did not inject drugs had equivalent survival rates seven years after initiating HAART. These results were published August 6 in the *Journal of the American Medical Association*.

August 8, 2008 - **NIDA Study Reveals Dopamine Receptors' Surprising Flexibility.** Neurotransmitters, or brain chemicals, play a key role in the long-term changes that allow a brain to continuously adapt in response to experience. This hinges on the ability of neurotransmitters to change the efficiency with which neurons talk with one another. In the striatum, a brain region critically involved in certain types of learning, dopamine is the main chemical responsible for tuning the efficiency of this communication up and down. Two types of dopamine receptors (D1 and D2) were previously thought to have completely opposite functions in this process, whereby D1 and D2-expressing neurons could only tune the strength of the connections either up or down, respectively. The present study dispels that notion, demonstrating that conditions in the local brain environment can make it possible for both cell types to carry out either function, thereby resolving a long-standing scientific puzzle posed by conflicting experimental evidence. These findings were reported in an article in the August 8, 2008 issue of *Science* by NIH-funded investigators Paul Greengard, Ph.D. of Rockefeller University and James Surmeier of Northwestern University and their colleagues.

September 5, 2008 - **NIDA Announces Recipients of New Avant-Garde Award for Innovative HIV/AIDS Research.** NIDA today announced the first three recipients of its new Avant-Garde Award. This award is intended to stimulate high-impact research that may lead to groundbreaking opportunities for the prevention and treatment of HIV/AIDS in drug abusers. Award recipients will receive $500,000 per year for five years to support their research.

September 18, 2008 - **NIDA Unveils "Innovations" in Addiction Research.** The first annual *NIDA Notes* "Innovations" issue, released September 18th, features examples of benchmark NIDA research advances, all of which have profound implications for addiction science. Highlights include deep-brain exploration made possible by new optical technologies; remote control of animal behavior in real time; and novel approaches to pain treatment. Articles in this issue shed light on mechanisms underlying neurodegenerative diseases such as Alzheimer's and Lou Gehrig's and will explore the role of memory in addictive behavior.

September 22, 2008 - **NIDA Launches New Research Dissemination Center - Drug*Pubs*.** NIDA launched its new Research Dissemination Center (Drug*Pubs*), designed to distribute the latest scientific materials and information on drug abuse and addiction to virtually all audiences: drug abuse researchers, health professionals, teachers, advocacy groups, teenagers and the general public. In its first month, NIDA Drug*Pubs* sent out 145,000 NIDA publications. Callers to 1-877-NIDA-NIH or visitors to www.drugabuse.gov can receive scientific information on drug abuse in a timely and effective manner.

October 1, 2008 - **World-Renowned Hispanic Scientists Gather to Address Disparities in Hispanic Drug Use, Treatment and Prevention.** The National Hispanic Science Network (NHSN) on Drug Abuse held its eighth annual conference, "Community, Behavioral and Molecular Sciences in Addictive Disorders," October 1-3, 2008 at the Hyatt Regency Bethesda, Maryland. NIDA Director Dr. Nora Volkow presented the keynote address,

"Imaging Obesity and Addiction." In her address, Dr. Volkow examined the links between obesity and addiction from the basic biological, the epidemiologic, and the treatment perspective.

October 31, 2008 - **Top NIH Neuroscience Experts to Discuss the Latest in Neurological and Psychiatric Research.** *(Media Advisory)*. Find out the latest news about the brain and its complexity from the world's top experts. Several institute directors and program leaders from the National Institutes of Health will be available to discuss success stories and new directions in neuroscience research during this year's Society for Neuroscience meeting. This is a rare opportunity to meet and interact with several NIH directors and other leading neuroscientists. Topics include mental health, substance abuse, brain issues related to aging, eye health, as well as stroke and neurological disorders.

November 4, 2008 - **Extended Suboxone Treatment Substantially Improves Outcomes for Opioid-Addicted Young Adults.** In the first clinical trial of a medication that was used for an extended time to treat opioid addiction in young adults, participants who received counseling and Suboxone (buprenorphine-naloxone) for 12 weeks had substantially better outcomes than those who received the standard treatment of short-term detoxification and counseling. The study, published November 5 in the Journal of the American Medical Association, was conducted through the National Drug Abuse Treatment Clinical Trials Network supported by NIDA. Opioids include heroin, morphine and prescription pain killers such as Vicodin and Oxycontin.

November 10, 2008 - **NIDA's Frontiers in Addiction Research Mini-Convention.** *(Media Advisory)*. NIDA will convene a one-day mini-convention at the Society for Neuroscience Annual Meeting in Washington, D.C. NIDA scientists will present recent findings and discuss future directions in neuroscience. Concepts to be discussed include: how the environment can alter gene function (epigenetics) in addiction and brain development; what determines free will or "free won't"; and how ground-breaking imaging technologies can reveal gene activation in the living brain, and/or control neurons and behavior.

December 11, 2008 - **Downward Trend in Teen Marijuana Use Slows; Prescription Drug Abuse Remains High.** There are signs that the ongoing decline in teen marijuana use in recent years has stalled; however the downward trend in cigarette and alcohol use continues, according to the 2008 Monitoring the Future (MTF) Survey. Results were announced at a news conference on this date.

Research News

Full NewsScans can be seen at http://www.nida.nih.gov/NIDANews.html.

August 4, 2008 - **NIDA NewsScan #54** - Research News

- Increase in Heart Infection Caused by Injection Drug Use Observed
- Positive Emotions Linked to Smoking May Contribute to Difficulty Quitting in Dual-Smoker Couples
- Hemopressin Binds to Cannabinoid Receptor and Reduces Perception of Pain
- Anti-Inhalant Messages Targeting Young Adolescents Vary in Ability to Influence Future Use
- Therapeutic Playgroup May Help Foster Children with School Success Skills
- Motivational Interviewing Reduces Marijuana Use in At-Risk Adolescents
- Pain Management with Virtual Reality - Exploring the Underlying Neurobiology

Chaperone Protein Sig-1R Helps Cells Regulate Calcium Levels Under Stress

September 29, 2008 - **NIDA NewsScan #55** - Research News

- Children's but Not Adolescents' Behavior Improves With Parents' Sobriety Counseling
- Methadone Maintenance Before Prison Release Increases Participation in Community-Based Treatment
- Chromosome Region Involved in the Development of Dopaminergic Neurons Identified
- Onsite 12-Step Meeting at Treatment Program Improves Odds of Sustained Abstinence
- Linked Gene Variations Associated With Nicotine Dependence
- Adolescents Allowed to Smoke at Home Have Higher Level of Nicotine Dependence
- Cigarette Reduction in Adolescent Smokers Does Not Reduce Toxin Exposure
- Effects of Drugs of Abuse on the Aging Brain Explored

October 30, 2008 - **NIDA NewsScan #56** - Research News

- Graphic Warnings Change Viewers' perception of Tobacco Advertisements
- Disulfiram and Naltrexone May Help Adherent Patients Abstain from Cocaine and Alcohol
- Smokers' Brains Ignore Error Messages
- Nicotine Receptor Subunit Alters Postsynaptic Signaling
- Computerized Cognitive-Behavioral therapy Plus Standard Therapy Helps Reduce Drug Use
- Computer Therapy for Opioid Addiction Effective at Promoting Abstinence
- Nonmedical Use of Prescription Stimulants Among First-year College Students
- Parental Monitoring Reduces High School Drinking, Leading to Reduced College Drinking
- "Good Behavior Game" Improves Early Classroom Behavior and Leads to Impact in Young Adulthood
- Experts Encourage More Research into Drugged Driving: New Study Guidelines Released
- Dialing Up or Down: The Surprising Versatility of Dopamine Receptors
- Frontiers in Addiction Research: NIDA to Hold Mini-Convention at Society of Neuroscience Annual Meeting (Meeting of Interest)
- NIDA Announces DrugPubs - A New Research Dissemination Center (Other NIDA News)

November 30, 2008 - **NIDA NewsScan #57** - Research News

- First-Year College Students Show High Rate of Cannabis Use Disorders
- Factors Associated with Detectable HIV Viral Load in a Vulnerable Population
- Adolescents Who Work for Pay More Likely to Use Tobacco
- MDMA Use Does Not Appear to Cause Depression in Most People
- Starting Middle-School in Sixth Grade Increases Behavior Problems
- Ovarian Hormones May Play a Role in Smoking Cessation for Women
- Researchers Estimate Number of Injection Drug Users in the United Sates 1992-2002.

Interviews & Articles of Interest

September 9, 2008, *Los Angeles Times* -- Interview with Nora Volkow, M.D., about prescription drug addiction.

September 9, 2008, BBC -- Interview with Dr. Linn Goldberg about marijuana.

September 9, 2008, *MSN Health and Fitness* -- "Predicting Addiction: Why some people go from trying to requiring." Dr. Steven Grant, DCNBR was interviewed by Tina Adler for MSN.com / Health and Fitness.com.

September 11, 2008, ABC On-line -- Interview with Dr. Wilson Compton about opioid addiction.

September 11, 2008, *LA Times* -- Interview with Dr. Bennett Fletcher and Dr. Lisa Onken about effective length of treatment for drug addictions.

October 3, 2008, *Men's Vogue* -- Interview with Dr. Elizabeth Robertson about methamphetamine programs in U.S.

October 9, 2008, *The Washington Post* -- Interview with Dr. David McCann about new treatments.

October 9, 2008, *O (Oprah) Magazine* -- Interview with Nora Volkow, M.D., about relapse from weight loss.

October 17, 2008, *Newsweek* -- Interview with Nora Volkow, M.D., about BNL study on obesity and dopamine.

October 22, 2008, AP -- Interview with Nora Volkow, M.D., about study on obesity and dopamine.

October 24, 2008, *Alcoholism and Drug Abuse Weekly (Vol 20(45) November 24, 2008, pp. 1 ,6-7)* -- "Scientists: Brain Circuitry Research Could Alter Course Of SA Treatment." Dr. Steven Grant, DCNBR, was interviewed by Gary Enos of Alcoholism and Drug Abuse Weekly for an article regarding the findings presented at Society for Neuroscience.

November 10, 2008, *LA Times* -- At addiction centers, longer treatment programs are proving key to ending the relapse-rehab cycle. Lisa Onken of DCNBR was interviewed on the topic of drug addiction treatment and length of treatment.

November 19, 2008, *USA Today* -- Interview with Dr. John Satterlee about epigenetics.

December 11, 2008, Channel 8 News -- Interview with Dr. Wilson Compton and Dr. Nora Volkow about Monitoring the Future Survey Results.

December 12, 2008, *Behavioral Health Care* -- Interview with Dr. Nora Volkow about Monitoring the Future Survey Results.

December 12, 2008, *Newsday* -- Interview with Dr. Nora Volkow about Monitoring the Future Survey Results.

December 12, 2008, ABC Radio -- Interview with Dr. Nora Volkow about Monitoring the Future Survey Results.

Additional Highlights

August 7, 2008 -- The PILB press team coordinated a press event at **International AIDS Conference**, held in Mexico City. The press event featured Drs. Nora Volkow and Jacques Normand highlighting HIV/AIDS portfolio and public awareness campaigns, as well as taking questions from the participants. Reporters from fifteen international print media outlets, four

broadcast outlets and three wire agencies attended. In conjunction with the Conference, Dr. Volkow was interviewed on CNN en Espanol and on two separate Univision news programs. She participated in four one-on-one radio interviews as well as nine interviews for Hispanic print media outlets. Dr. Normand also participated in a newspaper interview. Dr. Volkow was also interviewed at the end of July for the PBS program "To the Contrary," an all-female news analysis series that provides an important, timely forum for women to discuss national and international issues and policies. Dr. Volkow discussed drug abuse and women, why women over 40 have high rates of lifetime drug abuse, and approaches to treatment for women with drug addictions.

Outreach Activities

October 7, 2008 -- More than 30 NIDA researchers and science writers answered a record total of 1,300 questions from close to 100 schools nationwide at NIDA's second annual **Drug Facts Chat Day**. Although NIDA limited the number of schools that could participate this year, we still received 11,000 questions, underscoring how much teens (and their teachers) want to learn real facts about drug use. For the first time, the event was covered by the *Associated Press (AP)*. AP Reporter Kevin Freking, along with an AP video crew, attended the event at both Chat Day headquarters and at Rockville High School to glean perspectives from both sides of the computer. NIDA's Dr. Nora Volkow and Dr. Joe Frascella were interviewed for the story, which was published in more than 20 print and online publications including *The Washington Post, The Los Angeles Times, Education Week* and CBSNews.com.

Learn the Link Campaign. "After the Party," the Spanish portion of NIDA's drugs + HIV > Learn the Link campaign was one of five nominees for a special Emmy award bestowed each year for national public service announcements.

Awards

NIDA's Science Education Drug Abuse Partnership Award Program (SEDAPA) project, **"Drug Abuse, Addiction, and the Adolescent Brain,"** has received a **Bronze Telly Award**. This project, developed by Anne Westbrook of BSCS (who also developed the high school curriculum project, "The Brain: Understanding Neurobiology through the Study of Addiction"), includes DVD and print curriculum materials for middle school teachers and students on drug abuse and the brain. Founded in 1979, the Telly Awards honor the finest video and film productions, outstanding local, regional, and cable TV programs and commercials, and groundbreaking web commercials, videos and films. This year there were 13,500 entries from around the world. Winners represent the best work of the most respected advertising agencies, production companies, television stations, cable operators, corporate video departments, and SEDAPA grantees.

Recent and Upcoming Conference Exhibits

NIH Summit: The Science of Eliminating Health Disparities
National Harbor, MD -- December 16-18, 2008

Addressing Substance Abuse and Comorbidities Among Military Personnel, Veterans and Their Families: A Research Agenda
Bethesda, MD -- January 6-7, 2009

Community Anti-Drug Coalitions of America (CADCA) National Leadership Forum XIX
National Harbor, MD -- February 9-12, 2009

National Association of School Psychologists (NASP) 40th Annual Convention
Boston, MA -- February 24-28, 2009

National Science Teachers Association (NSTA) 57th Annual National Conference
New Orleans, LA -- March 19-21, 2009

American Society of Addiction Medicine (ASAM) 40th Annual Medical-Scientific Conference
New Orleans, LA -- April 30-May 3, 2009

American Psychiatric Association (APA) 162nd Annual Meeting
San Francisco, CA -- May 16-21, 2009

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Planned Meetings

The National Institute on Drug Abuse (NIDA) will participate in a number of sessions at the **Community Anti-Drug Coalitions of America (CADCA) annual National Leadership Forum in National Harbor, Maryland, February 9-12, 2009.** NIDA Deputy Director, Dr. Timothy P. Condon, will participate in a plenary session. Also, two workshops will be conducted: one on the topic of *Translating Research Findings to the Field: How Mass Media Prevention Findings Can Inform Practice,* and the other on *The Real Inside Scoop on What Teens Want to Know About Drug Abuse,* which will discuss some of the interesting findings from NIDA's Drug Facts Chat Day, a youth-friendly online chat between NIDA scientists and teens first held in October 2007, and repeated in 2008.

The National Institute on Drug Abuse (NIDA) is organizing a program at the **American Psychiatric Association (APA) Annual Meeting in San Francisco, May 16-21, 2009.** A number of NIDA staff and NIDA researchers will participate in several symposia and workshops at the upcoming meeting on a wide range of topics such as, *Diversion of Prescription Stimulants; Imaging Insight: Basic Definitions, Measures, and Relevance to Psychopathology; Older Adults and the Neurobiology of Substance Abuse; Clinical Challenges Identifying and Treating Unpresented Co-morbidity; Integrating Treatment for Substance Use and Post-Traumatic Stress Disorders in Patients with Co-Occurring Conditions; and Genetic Vulnerabilities for Drug Abuse and Co-Morbid Mental Health Disorders.* This program will build on previous tracks NIDA has been conducting at the APA Annual meeting since 1998.

NIDA is organizing a program at this year's **American Psychological Association (APA) Annual Meeting in Toronto, Canada, August 6-9, 2009.** A number of NIDA staff throughout the Institute are involved in organizing symposia on a wide range of 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 (NIAAA) as part of the two Divisions' Social Hour.

NIDA and the Office of Dietary Supplements (ODS) will co-sponsor a gathering of experts at its Headquarters in the Neurosciences Building, in the Spring of 2009, entitled **"Caffeine: Is the Next Problem Already Brewing?"**, which will explore the prevalence, patterns of use and the potential deleterious (and/or beneficial) health effects of caffeine, particularly in younger people. The ultimate goal of the symposium is to identify some of the most pressing research questions that need to be addressed in order to assess the latent or emerging threats to public health posed by new beverage recipes with unprecedented high concentrations of caffeine or that combine caffeine with other substances like nicotine or alcohol.

Dr. Harold Gordon of DCNBR organized a symposium titled **Sleep**

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Disturbances and Circadian Disruptions Affecting, and Affected by, Addiction to Drugs which will be held as part of the **American Psychiatric Association Annual Meeting** to be held in May, 2009 in San Francisco. The meeting is sponsored by the Office of Science Policy and Communications (OSPC). The purposes of the meeting are to learn 1) sleep physiology and recognize how it is altered by abused drugs and how to identify signs and symptoms of drug-abuse-related insomnia and cognitive deficits, 2) that disruptions by cocaine in normal circadian clock function increase risk for depression and bipolar disorder, among others, 3) the reciprocal interactions between sleep and the immune system in substance dependence, and 4) treatment issues related to sleep disturbances in cocaine and opiate dependents.

Dr. Steven Grant of DCNBR organized a workshop titled **Imaging Insight: Basic Definitions, Measures, and Relevance to Psychopathology** which will be held as part of the **American Psychiatric Association Annual Meeting** to be held in May, 2009 in San Francisco. The meeting is sponsored by the Office of Science Policy and Communications (OSPC). This workshop will combine presentations from basic cognitive, neuropsychological and clinical investigators on the definition and measurement of insight. The panel will address the following basic questions: What is insight? How is it defined/measured? Are there individual differences (e.g., age, sex) in insight? What is its relevance to psychopathology (especially to disorders of impulse control)? What are the underlying neurobiological substrates of impaired insight in these disorders? Evidence for newly developed behavioral and functional neuroimaging measures as potential biomarkers of impaired insight will be presented.

Dr. Joni Rutter, DBNBR, and Dr. Minda Lynch, DBNBR, will co-chair a symposium at the American Psychiatric Association's Annual Meeting in San Francisco, May, 2009. The symposium, **Genetic Vulnerabilities for Drug Abuse and Co-Morbid Mental Health Disorders** will feature presentations from Harriet de Wit, Ph.D., Caryn Lerman, Ph.D., Teresa R. Franklin, Ph.D., Howard J. Edenberg, Ph.D. and Joel Gelernter, M.D.

Drs. Cora Lee Wetherington, DBNBR, and Wendy Lynch, University of Virginia, co-organized and will co-chair the symposium, **Biological Basis of Sex Differences in Drug Abuse: A Translational Perspective**, at the annual meeting of the American Psychiatric Association, May 16-21, 2009 in San Francisco, CA. Presenters will be Wendy Lynch, Ph.D. (University of Virginia), Jill Becker, Ph.D. (University of Michigan), Karen Berman, M.D. (NIMH), Marc Potenza, M.D., Ph.D. (Yale University School of Medicine), and Larry Cahill, Ph.D. (UC Irvine).

Dr. Allison Hoffman organized an upcoming symposium at the **World Conference on Tobacco OR Health**, March 2009. The symposium, **The Future of Smoking Cessation Treatment** will feature presentations by Drs. Taylor Hays, Dorothy Hatsukami, Marcus Munafo and Rachel Tyndale, and will be moderated by Dr. Cindy Miner, OSPC.

Dr. Allison Hoffman organized an upcoming symposium at the **World Conference on Tobacco OR Health**, March 2009. The symposium, **Smoking and Co-Morbid Diseases** will feature presentations by Drs. Suchitra Krishnan-Sarin, Janice Blalock, Eden Evins, and Judith Brook, and will be moderated by Dr. Cindy Miner, OSPC.

As a Team Leader the NIH Roadmap Science of Behavior Change initiative, Lisa Onken of DCNBR is organizing a preliminary Planning Meeting to inform a trans-NIH effort on the science of behavior change. The Planning Meeting is tentatively scheduled for February 17 and 18, 2009 (place to be determined).

The next National CTN Steering Committee Meetings is planned for March 24-26, 2009 in Bethesda, MD.

A Mini Symposium entitled **HIV Risk Prevention in the CTN** has been accepted for presentation at the 2009 CPDD meeting June 20-25, 2009 in Reno, Nevada. Dr. Raul Mandler will chair this event.

A NIDA-OSPC supported symposium entitled **Integrating Treatment for Substance Use and Post-Traumatic Stress Disorders in Patients with Co-occurring Conditions** has been accepted for presentation at the 2009 American Psychiatric Association Annual Meeting May 16-21, 2009 in San Francisco, California. Dr. Udi Ghitza will chair this event. At the conclusion of this symposium, participants should have increased knowledge of: (1) prevalence of co-occurring post-traumatic stress disorder (PTSD) and substance use disorders (SUD) in both civilian and returning veteran populations, (2) psychotherapy treatment programs developed for patients with co-occurring SUD and PTSD, (3) pharmacotherapy treatment programs for these patients, (4) challenges and opportunities for advancing an integrated medical care approach concurrently treating functional impairments associated with each disorder.

A NIDA-OSPC supported meeting entitled **Narrowing Research-Practice Divide in Evidence-Based Medicine with Adoption of Electronic Health Record Systems: Present and Future Directions** will be held in Bethesda, Maryland in July 2009. Dr. Udi Ghitza will co-chair this event. This meeting is designed to explore the potential health and financial benefits of adoption of electronic health record systems (EHR) in behavioral health treatment and primary care settings, the current status of EHR implementation in health care settings, and future prospects, including opportunities and challenges to the adoption of interoperable EHR that have the potential to narrow the research-practice divide in evidence-based medicine.

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Publications

NIDA Publications

Research Report Series: Comorbidity of Drug Abuse and Mental Illness
NIH Pub. No: 08-5771
When two disorders or illnesses occur simultaneously in the same person, they are called comorbid. This new research report addresses the comorbidity of drug abuse and addiction and other mental disorders. It explores the complex ways in which genetic, developmental and environmental factors appear to interact to predispose individuals to develop both diseases or to have a greater risk of the second disorder after the first appears. The report describes the prevalence of, as well as the diagnostic and treatment challenges posed by, comorbid conditions that involve drug abuse, addiction and other mental disorders.

Research Report Series: Cocaine and Addiction
NIH Pub. No.: 08-4166
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
NIH Pub. No.: 08-4342
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)
NIH Pub. No.: 09-4180
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 conditions--all 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.

Epidemiologic Trends in Drug Abuse Highlights and Executive Summary, January 2008 ***[pdf, 3.4 MB]***
NIH Pub. No.: 09-6200
This publication highlights data reported at the January 2008 meeting of the CEWG.

NIDA NOTES

***NIDA NOTES,* Vol. 22, No. 2**
NIH Pub. No. 08-6457
The lead story describes imaging studies that elucidate the neurobiology of cigarette craving. They show that when smokers resist cravings, they engage brain areas that focus attention and regulate emotion and that heavy smokers can stave off cravings only by keeping virtually all the brain's nicotinic receptors filled. Also included in the issue are features reporting that both methadone and a medication prescribed for schizophrenia prevents rats from resuming cocaine seeking; that long-term cocaine self-administration depresses monkeys' neural activity in regions linked with cognition and emotion; and that close judicial supervisions can increase the effectiveness of drug treatment for high-risk offenders. The Director's Column evaluates progress on the development of vaccines to fight drug addiction.

NIDA Journal of Addiction Science and Clinical Practice

Addiction Science and Clinical Practice Volume 5, Number 1
NIH Pub. No.: 08-6453, January, 2009
This issue features two articles on drug abuse and criminal justice. In the first, Dr. Michael Prendergast describes how correctional drug treatment can improve outcomes for offenders upon release and stresses the importance of community aftercare for reducing relapse and recidivism. In the second, Ms. Melody Heaps and her colleagues at Treatment Alternatives for Safe Communities (TASC) of Illinois posit a recovery-oriented system of care for drug-abusing criminal offenders that exists outside of the justice system, co-manages offender treatment, and provides other services to promote successful outcomes as well as public health and safety. Addressing some of the medical complications of illicit drug use are Dr. Shenghan Lai, who explores cocaine abuse and its involvement in atherosclerosis and other cardiovascular problems, and Drs. Kristy Hendricks and Sherwood Gorbach, who describe the nutrition issues of chronic drug users living with HIV. Finally, Dr. Michael S. Robbins and colleagues investigate the process of implementing an evidence-based practice, Brief Strategic Family Therapy, in a community treatment setting.

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 16 CTN trials are now available on the CTN Data Sharing Web Site http://www.nida.nih.gov/CTN/Data.html. Currently more than 150 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.

The CTN flyer/poster on Improving Recruitment and Retention - R & R Tips has

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been published. This document includes many suggestions and hints from the staff at participating CTPs in CTN trials. Topics covered include:

- How to improve outreach efforts
- How advertising dollars can be maximized
- How incentives can help a study
- Best practices

International Program-Related Publications

NIDA International Program E-News Letter
December 2008 - This issue reported on trends in Latin American drug use as identified by REDLA; NIDA's new Research Dissemination Center, DrugPubs; a NIDA poster session at SfN that featured international neuroscientists; and other achievements of NIDA Fellows or alumni. The issue also announced three new funding initiatives, the reissue of the international research collaboration PAs, new Huber H. Humphrey Fellows, and a new letter of intent for scientific collaboration between NIDA and Spain.

Other Publications

Volkow, N., Rutter, J., Pollock, J.D., Shurtleff, D., and Baler, R. One SNP Linked to Two Diseases-Addiction and Cancer: A Double Whammy? Nicotine Addiction and Lung Cancer Susceptibility. Mol. Psychiatry. 13(11), pp. 990-992, 2008.

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Bjork, J.M., Knutson, B., and Hommer, D.W. Incentive-Elicited Striatal Activation in Adolescent Children of Alcoholics. Addiction, 103(8), pp. 1308-1319, 2008.

Recent functional neuroimaging research of DCNBR's Dr. James Bjork was featured in the news section of the BHC Journal (www.bhcjournal.com). The BHC Journal is an on-line resource of psychiatry research findings for behavioral health care practitioners. Dr. Bjork found that compared to healthy controls, substance-dependent patients have exaggerated nucleus accumbens (NAcc) activation by receiving general (nondrug) rewards, but also showed an exaggerated NAcc deactivation by both denial and deferral of expected rewards. These findings indicate a possible biological signature of the lack of willpower characteristic of refractory addiction, where notifications of a delay to receiving a reward are processed by the patient's motivational neurocircuitry as though they were outright denials of reward.

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Staff Honors and Awards

The National Hispanic Science Network on Drug Abuse (NHSN) presented its National Award of Excellence in Public Service to NIDA IP Director **Dr. Steven W. Gust** on October 2, 2008. The NHSN National Award of Excellence in Public Service recognizes an individual whose work in public service has promoted the development of Hispanic substance abuse researchers and research on drug abuse among Hispanic populations. NHSN cited Dr. Gust's instrumental role in establishing the group's International Subcommittee, attracting more international members and expanding NHSN activities to Latin America.

Dr. Jag Khalsa, DPMCDA, received an award for his contributions in the field of substance abuse and infections from the former President of India at a special reception during the International Conference on Molecular Medicine, Chennai, India, January 19, 2009.

Dr. Jag Khalsa was recently appointed as the member of the Editorial Board of the Journal of HIV/AIDS Research and Palliative Care.

Dr. Amy Newman, IRP, was named the NIDA-IRP Associate Director of Translational Research.

Dr. Rao Rapaka, DBNBR, was awarded the 2008 ISODD Achievement Award in Organic Synthesis and Drug Development. He was cited for his original contributions in research in peptide chemistry/medicinal chemistry, lipidomics, leadership, administrative excellence and foresight.

Dr. George Uhl, IRP, founded the new journal *Addiction Reviews*, an annual volume that is part of the *Annals of the New York Academy of Sciences* series.

Staff Changes

Dr. Will Aklin joined the Behavioral and Integrative Treatment Branch, DCNBR at NIDA in October 2008. He received his Ph.D. in Clinical Psychology from the University of Maryland, and clinical internship at Yale University. He later went on to complete a post-doctoral fellowship at Johns Hopkins University. Dr. Aklin has received numerous awards and honors, including Early Career Investigator Awards from the College on Problem of Drug Dependence (CPDD) and the Association of Behavioral and Cognitive Therapies (ABCT). Dr. Aklin's research interests include the development of treatments targeting specific processes (e.g., impulsivity, risk-taking), behavioral/combined behavioral and pharmacological treatments, and the transportability of treatments in community settings.

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Dr. Scott Chen has joined OEA as Scientific Review Officer. Prior to joining NIDA, he was a Research Fellow at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), studying the effects of corticotrophin-releasing hormone receptor type 1 blockade on stress responses and stress-induced alcohol consumption, using genetic, physiological, and behavioral assays. Collaborations with researchers at American University examined effects of genetic differences, early-life stress, sex differences, and nicotine on alcohol response. Prior to the NIAAA, Dr. Chen was a NIDA NRSA-funded Research Associate at The Scripps Research Institute, focusing his work on motivational aspects of opiate dependence. Dr. Chen received his B.S. in biological sciences from the University of California-Irvine and his M.S. and Ph.D. in applied biopsychology from the University of New Orleans.

Jessica H. Cotto joined OSPC as an Epidemiologist in January 2009. Her primary responsibilities include providing briefings to the Director and other high-level government officials on the use of prescription medications among young and aging populations including, geographical prescription patterns, physician prescribing habits, patient demographics, and prescription medication trends. During the past 6 years, Ms. Cotto has been engaged in a variety of basic science research including the study of heat shock proteins in cardiovascular disease and the signaling pathways of Human IFN-a. She has over 4 years of experience in statistical analysis, procedures and methods, and database management. Prior to NIDA, Ms. Cotto served as a Clinical Research Associate for The Children's National Medical Center, The National Institute of Allergy and Infectious Diseases, and The National Cancer Institute. She is also a co-author on several published scientific manuscripts, some of which have been published in the Journal of Biological Chemistry and The Journal of Interferon and Cytokine Research. She holds a Bachelors Degree in Cellular and Molecular Biology from San Diego State University and a Master of Public Health in Epidemiology and Biostatistics from George Washington University.

Dr. Lori Ducharme joined NIDA in September 2008. Prior to joining NIDA, Dr. Ducharme was on the research faculty at the University of Georgia, where she was part of a collaborative investigator team studying the organization, delivery, and quality of addiction treatment services in the nation's specialty behavioral health care system. At NIDA, Dr. Ducharme manages a portfolio of research studies that focus on the organization and management of addiction treatment programs; practice improvement in community-based organizations; and implementation research.

Dr. Minna Liang has joined OEA as a Scientific Review Officer. Dr. Liang has worked as a research scientist in several scientific disciplines including neuroscience, medical genetics and virology/immunology, and her peer-reviewed publications can be found in a number of journals including the Journal of Neuroscience, Molecular and Cellular Biology and the Journal of Biological Chemistry. Prior to joining OEA, Dr. Liang was a project director with a biotechnology consulting firm in Gaithersburg, Maryland, and prior to that position, she worked as a staff fellow/associate at the National Institute of Mental Health (NIMH). She completed her post-doctoral training in human molecular genetics at Children's Hospital of Los Angeles and Georgetown University Medical Center. Dr. Liang holds a Ph.D. in cell and molecular biology from Tulane University.

Dr. Jacqueline Lloyd recently joined the staff in DESPR's Prevention Research Branch as a Health Scientist Administrator. Dr. Lloyd received a Ph.D. in public health from Johns Hopkins Bloomberg School of Public Health and a Master in Social Work from the University of Connecticut School of Social Work. She completed a post doctoral fellowship with the Treatment Research Institute in conjunction with the University of Pennsylvania and the Center for Substance Abuse Treatment. Dr. Lloyd came to NIDA from Temple University, where she was an Assistant Professor in the School of Social Administration. Dr. Louise

Wideroff recently joined DESPR's Epidemiology Research Branch. Dr. Wideroff is an epidemiologist who earned her doctorate in epidemiology from the University of Michigan and was a post-doctoral fellow in the intramural program at NCI. Prior to coming to NIDA, Dr. Wideroff was on assignment at the National Human Genome Research Institute, assisting with management of the GENEVA cooperative agreements in GEI. For the past 11 years, she has been a Program Director at the National Cancer Institute, specializing in assessment of genetic and molecular risk factors for cancer, and the adoption of emerging cellular, molecular, and genomic technologies in clinical care.

Dr. Rita Liu, OEA, retired from Government service in November 2008 after 20 years at NIDA. She served as the NIDA Referral Officer, the Referral Liaison to the NIH Center for Scientific Review and as Scientific Review Officer for the NIDA Centers Review Committee and conducted reviews of many complex activities. Dr. Liu was co-chair of the NIDA Neuroscience Consortium Working Group that promotes cutting-edge neuroscience and coordinates NIDA activities at the Society for Neuroscience annual meetings. She co-edited the Special Issues of Neuropharmacology in 2004 commemorating NIDA's 30th and, in 2008, the 35th anniversaries. Prior to joining NIDA in 1988, she held faculty positions at Georgetown University and the Uniformed Services University of the Health Sciences. She was trained as a dentist in the National Taiwan University Medical College and received a M.S. in Oral Pathology and Anatomy from Emory University. While working in the Neuroanatomy laboratory of Dr. Muriel Ross at the University of Michigan, she decided to pursue research in neuroscience and obtained a Ph.D. from Georgetown University. Dr. Liu received numerous honors from NIDA and NIH, and she was recognized with the Michael J. Morrison Award, presented at the 2008 of the CPDD, for outstanding contributions in the area of scientific administration related to drugs of abuse.

Dr. Charlie Sharp, DBNBR, announced his retirement on October 31, 2008. Charlie has had a major impact on the field of drug abuse and addiction in many areas. He leaves a lasting influence on the field through his contributions to the training of young scientists and to the development and support of basic AIDS and inhalant research. Charlie Sharp has a long and distinguished history at NIDA starting with the Institute's inception in 1974. He is currently Special Assistant to the Division Director and DBNBR Training Coordinator wherein he directs and oversees the DBNBR NRSA program. Training the next generation of scientists is Charlie's passion - fellowships, traineeships and career development awards have comprised a major focus of his career. For many years, Charlie has developed and overseen DBNBR's research portfolio on HIV/AIDS and neuroimmunology, and as the programs grew to include other program officers, Charlie continued to contribute his wisdom and leadership to the success of these programs. Also, he along with several extramural researchers organized the first conferences in 1989 and 1992 dedicated specifically to an exploration of the role of drugs of abuse in modulating immune function.

Dr. Frank Vocci, Director, DPMCDA, retired from NIDA effective January 2, 2009, after more than 30 years of Government service. Dr. Vocci was responsible for instituting research and development activities for medications targeted for the treatment of marijuana, cocaine, methamphetamine, nicotine and opiate dependence. Frank Vocci began his career working in the Clinical Neurophysiology Laboratory in the Department of Neurology at the University of Maryland while pursuing his graduate degree. After receiving his doctoral degree and post-graduate training in pharmacology, Dr. Vocci was employed from 1978 to 1989 by the Food and Drug Administration in the Division of Neuropharmacological Drug Products. In addition to his duties as an FDA reviewer, Dr. Vocci was also a guest researcher in the Clinical Neurosciences Branch of the National Institute on Mental Health, and an ad hoc consultant to the NIDA and the World Health Organization. Beginning in July 1989, he was

affiliated with the Medications Development Program (now the DPMCDA) at NIDA where he then served as Director. During his years at NIDA, Dr. Vocci has authored and co-authored over 50 articles in the field of neuropharmacology and substance abuse. He has conducted more than 100 presentations at professional conferences and meetings, and has been interviewed by hundreds of national and local print and broadcast media outlets on behalf of the Institute, including the *New York Times, the Washington Post, Time, Newsweek, Wall Street Journal,* and *National Public Radio.* Beginning January 1, 2009, Dr. Vocci became President of the Friends Research Institute (FRI), which promotes health and well-being through research, grants administration, education and treatment. Researchers at FRI receive federal, state, county, and private funding to conduct studies in the fields of substance abuse, health, HIV/AIDS, mental health, and criminal justice.

Dr. David McCann has been appointed as Acting Director of DPMCDA. A national search is underway to fill the position on a permanent basis.

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Dr. Benjamin F. Cravatt, professor of Chemical Biology at the Scripps Research Institute, has been awarded the 2008 Tetrahedron Young investigator award (Tetrahedron publications) in Bioorganic and Medicinal Chemistry. His work involves chemical proteomics and the characterization of enzymatic pathways in mammalian biology, including those that regulate the cellular levels and signaling of the endocannabinoids 2-arachidonylglycerol and anandamide. Dr. Cravatt is a NIDA grantee and principal investigator on an NIH/NIDA Eureka grant award.

Dr. Victor Hruby was awarded the 2009 Arthur C. Cope Scholar Award of the American Chemical Society. Professor Hruby is being recognized for his outstanding work in pioneering the use of chemical synthesis, conformational constraint, design and structural analysis of synthetic molecules with lasting impact in chemical biology. The Arthur C. Cope Scholar Award is one of the top ACS awards. Established in 1984, the award recognizes outstanding achievement in the field of organic chemistry, the significance of which has become apparent within the five years preceding the year in which the award is considered. Professor Hruby will accept the Award at the National ACS Meeting in Salt Lake City, Utah in March of 2009 and will deliver the Award address at the Arthur C. Cope Symposium at the ACS Meeting in Washington, D.C. in August of 2009.

Dr. Laura E. O'Dell of the University of Texas, El Paso received the 2007 Presidential Early Career Award for Scientists and Engineers (PECASE) for her insights into the neurobehavioral mechanisms that mediate adolescent tobacco use, as well as for her mentorship of minority students interested in pursuing careers in science. Selection for this award is based on the combination of innovative research and community service demonstrated through scientific leadership and community outreach. Laura and the other PECASE awardees were honored in a ceremony at the White House with President George W. Bush on Friday, December 19, 2008.

Dr. Johnny He, Indiana University, was awarded the "Excellence in Public and Community Service" Award from China National Society on Drug Dependence, China National Society for Pharmacology and Toxicology, and China National Committee on Drug Abuse, Prevention and Treatment.

Dr. Margaret Brandeau of Stanford University was presented with the President's Award during the national conference of INFORMS (Institute for Operations Research and Management Sciences), October 13, 2008, in Washington, D.C. Dr. Brandeau has played a central role in advanced HIV/AIDS modeling research, including expanded HIV testing.

Dr. Maziak and the Syrian Center for Tobacco Studies have been selected as the winner of the 2008 Hamdan Award for the Best Medical College/Institute or

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Centre in the Arab World. This very prestigious award is presented by the Deputy Ruler of Dubai, for research excellence and training that is now broadening its outreach to train researchers in the Arab region. The center was initiated in 2002 with a grant from the National Institutes of Health to the University of Memphis (UM), in collaboration with the Syrian Society Against Cancer, Aleppo University, and Virginia Commonwealth University (VCU).

Dr. Barbara Gerbert, Professor and Director of the Center for Health Improvement and Prevention Studies at the University of California San Francisco, received the 2008 UCSF School of Dentistry, Research and Clinical Excellence Day, Faculty Research Award. As part of this honor, Dr. Gerbert presented a lecture entitled "Research and Clinical Excellence."

Dr. William Stoops, Assistant Professor in the Department of Behavioral Science at the University of Kentucky, was the recipient of the "2008 Wyeth Young Psychopharmacologist Award" from Division 28 of the American Psychological Association (August 2008).

Dr. Daniel R. Kivlahan, (Pacific Northwest Node) University of Washington Associate Professor of Psychiatry & Behavioral Sciences and the Director of the Center of Excellence in Substance Abuse Treatment and Education (CESATE) for the Department of Veterans Affairs located at the VA Puget Sound Health Care System in Seattle, was selected as the recipient of the 2008 Award for Distinguished Scientific Contributions to Public Interest by Division 50 (Addictions Division) of the American Psychological Association. This award is conferred on a Division 50 member who has made "distinguished contributions to the advancement of public interest in the addictions field. This contribution might include research or advocacy leading others to view national policies differently, research demonstrating the importance of the application of scientific methods and theory to public policy, or research clarifying the ways scientific knowledge of human behavior informs public interest about the addiction field." The award was officially presented at the APA's conference in Boston in August 2008.

Three CTN-affiliated CTPs were named recipients of the 2008 SAMHSA (Substance Abuse and Mental Health Services Administration) Science and Service Awards: **Maryhaven in the Ohio Valley Node, Residence XII in the Pacific Northwest Node, and Western Psychiatric Institute and Clinic - Addiction Medicine Services in the Appalachian Tri-State Node.** There were only 5 recipients in each of the two categories in which the CTPs were included.

Dr. Shelly F. Greenfield, (Northern New England Node Co-PI) was recently appointed to the newly created position of Chief Academic Officer at McLean Hospital. Dr. Greenfield was also the recipient of the first annual Jack H. Mendelson Memorial Research Award at McLean Hospital on October 6th for her contributions to substance abuse research and addiction psychiatry.